Associations of cardiovascular disease risk factors with abdominal aortic calcium volume and density: The Multi-Ethnic Study of Atherosclerosis (MESA)

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Abstract

Background and aims—Abdominal aortic calcium (AAC) predicts future cardiovascular disease (CVD) events and all-cause mortality independent of CVD risk factors. The standard AAC score, the Agatston, up-weights for greater calcium density, and thus models higher calcium density as associated with increased CVD risk.

We determined associations of CVD risk factors with AAC volume and density (separately).

Methods—In a multi-ethnic cohort community living cohort, we used abdominal computed tomography scans to measure AAC volume and density. Multivariable linear regression was used to determine the period cross-sectional independent associations of CVD risk factors with AAC volume and AAC density in participants with prevalent AAC.

Results—Among 1413 participants with non-zero AAC scores, the mean age was 65 ± 9 years, 52% were men, 44% were European-, 24% were Hispanic-, 18% were African-, and 14% were Chinese Americans (EA, HA, AA, and CA respectively). Median (interquartile range, IQR) for AAC volume was 628 mm^3 (157–1939 mm^3), and mean AAC density was 3.0 ± 0.6. Compared to EA, each of HA, AA, and CA had lower natural log (*ln*) AAC volume, but higher AAC density. After adjustments for AAC density, older age, ever smoking history, higher systolic blood pressure, elevated total cholesterol, reduced HDL cholesterol, statin and anti-hypertensive

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medication use, family history of myocardial infarction, and alcohol consumption were significantly associated with higher *ln*(AAC volume). In contrast, after adjustments for *ln*(AAC volume), older age, ever smoking history, higher BMI, and lower HDL cholesterol were significantly associated with lower AAC density.

Conclusions—Several CVD risk factors were associated with higher AAC volume, but lower AAC density. Future studies should investigate the impact of calcium density of aortic plaques in CVD.

Keywords

Abdominal aortic calcium; Agatston calcium score; Cardiovascular disease risk factors; Coronary artery calcium; Density calcium score; Volume calcium score

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Introduction

Abdominal aortic calcium (AAC) and coronary artery calcium (CAC) scores similarly predict future cardiovascular disease (CVD) events independent of CVD risk factors, but only AAC predicts all-cause mortality in mutually adjusted models.[1–3] The Agatston method, used as the standard for AAC and CAC scores, up-weights plaque for higher calcium density, and thus models density as positively associated with CVD risk. However, evidence exists that more densely calcified coronary artery plaques may pose a lower CVD risk than less densely calcified plaques.[4–6] Researches have reported that among patients with plaque measured from coronary computed tomography angiography (CTA), incident CVD was lowest among patients with only calcified plaques, compared to those with both calcified and non-calcified, and those with only non-calcified plaques.[4,5] Researches have also reported that for a given CAC volume, higher CAC density was protective for CVD events.[6] To date, most studies quantifying AAC and CAC for CVD risk prediction have used the Agatston score, which models a positive association between CVD risk factors and calcium density. We investigate this model by determining independent associations of CVD risk factors with AAC volume and density (separately).

Materials and methods

Study sample

The Multi-Ethnic Study of Atherosclerosis (MESA) is a multi-center, prospective cohort study designed to investigate the prevalence, risk factors, and CVD outcomes of individuals without clinical CVD at baseline. A detailed description of the study design, recruitment methods, examination components, and data collection has been published.[7] In brief, participants included 6,814 men and women (age 45–84) of Caucasian, Hispanic-, African-, and Chinese-American descent, recruited between July 2000 and August 2002 from 6 U.S field centers; New York, NY; Baltimore, MD; Winston-Salem, NC; St Paul, MN; Chicago IL; and Los Angeles, CA. Signed informed consent was obtained for all participants, and institutional review board approval was obtained for all participating institutions. During follow up visits between August 2002 and September 2005, a randomly selected subsample of 2,202 MESA participants were invited to participate in an ancillary study that aimed to determine the presence and extent of AAC. Of these, 2,172 agreed to participate. Individuals

were excluded if they were pre-menopausal, or had a recent (within prior 6 months) abdominal computed tomography (CT) scan. This left 1,970 participants who underwent abdominal CT scans to measure AAC. Since a density score only has meaning in those with non-zero calcium volume, this study was limited to 1,413 participants with prevalent AAC (Agatston scores > 0).

Calcium measurement

The methodology for acquisition and interpretation for AAC has previously been described.[8] Abdominal images were obtained using multi-detector CT scanners at Columbia University, Wake Forest University, and University of Minnesota field centers (Sensation 64 [Siemens, Malvern, Pennsylvania] and GE Lightspeed [GE Healthcare, Waukesha, Wisconsin], Siemens S4 Volume Zoom, and Siemens Sensation 16, respectively). Electron-beam CT scanners were utilized at Northwestern University and University of California, Los Angeles (Imatron C-150, Imatron Inc., South San Francisco, California). Images were reconstructed in a 35 cm field of view with a slice thickness of 3 mm (EBCT scanners) or 2.5mm (multi-detector scanners). For equal comparisons among participants with different abdominal aortic length, an 8cm segment proximal to the aortic bifurcation was used to quantify AAC.

AAC Agatston scores were quantified from abdominal CT scan slices by identifying an area of plaque defined by density Hounsfield Units (HU) greater than 130.[9] The plaque area (mm^2) was then multiplied by 1, 2, 3, or 4, depending on the plaque's maximum density. Plaques with maximum density of 130 to 199 HU were multiplied by 1, those with 200 to 299 HU were multiplied by 2, those with 300 to 399 HU were multiplied by 3 and those with 400 HU or greater were multiplied by 4. AAC scores for all CT slices were then summed to produce the total plaque-specific scores. AAC volume (mm^3) scores were the sum of all plaque areas multiplied by the CT slice thickness. The AAC density scores were calculated as: density = [Agatston] / [area, in mm^2]. Where area, in mm^2 = [volume, in mm^3] / [CT scan slice thickness, in mm]. Thus density from these calculations represents a participant's average multiplicative density factor (1–4 scale) derived from their original Agatston score.

Risk factor assessments

Participants were given standardized questionnaires at baseline, which were used to obtain information on demographics, medical history, family history of myocardial infarction (FHMI), ever smoking history, and alcohol use (#drinks/week). A medication inventory was also performed, and medications were grouped based on use to treat high blood pressure, elevated blood glucose or abnormal cholesterol. Standard measurements for height and weight were obtained, and body mass index (BMI) was calculated from weight (kg) over height (cm^2). Systolic blood pressure (SBP) was measured 3 times in the seated position with a Dinamap model Pro 100 automated oscillometric sphygmomanometer after at least 5 minutes of rest. The average of the last 2 measurements was used. Blood samples were obtained after a 12 h fast for measurements of total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, and glucose. Diabetes was defined as fasting plasma glucose 126 mg/dL, or use of hypoglycemic medications.

Statistical analysis

This is a period cross-sectional analysis of 1,413 participants with prevalent AAC measured from CT scans obtained between 2002 and 2005 and CVD risk factors measured at the baseline examination in MESA approximately 18 and 36 months previously. Descriptive statistics for the study cohort were presented across AAC density quartiles as means (SD) and medians (interquartile ranges, IQR) for normally distributed and skewed continuous variables (respectively), and frequencies for categorical variables. Pearson's correlation coefficient was used to determine the univariate associations of the AAC volume, and density scores. Backwards deleting multivariable linear regression ($p < 0.10$ for inclusion) was used to determine independent associations of CVD risk factors of age, sex, ethnicity, diabetes and ever smoking history, SBP, TC and HDL cholesterol, BMI, FHMI, use of alcohol, hypertension medications, and statin therapy with AAC volume and AAC density (separately). Models investigating correlates of AAC volume were additionally adjusted for AAC density, and vice versa. A multiplicative interaction term ethnicity X AAC volume (ethnicity*AAC volume) and ethnicity X AAC density (ethnicity*AAC density) was tested in models investigating correlates of AAC volume and density respectively. As AAC volume scores were skewed, natural log (*ln*) was used. All analyses were conducted using PSAW Statistics 20 (IBM, Corp., 2011 Amronk, NY).*p*-value 0.05 (two-sided) was considered significant for all analyses.

Results

Among the 1413 participants, the mean age was 65 ± 9 years, 52% were men, 44% were European-, 24% were Hispanic-, 18% were African-, and 14% were Chinese Americans (EA, HA, AA, and CA respectively). Median (IQR) for AAC volume, was 628 mm^3 (157–1939 mm^3), and mean AAC density was 3.0 ± 0.6 (Table 1). Compared to the lowest AAC density quartile, participants in the highest quartile had more AAC volume, were older, more likely to be male, less likely to be EA, and had a higher prevalence of statin use. Also, AAC density was correlated with *ln*(AAC volume) (correlation coefficient=0.65, *p*-value < 0.01) (not shown).

After adjustments for AAC density, compared to EA, each of HA, AA, and CA, had significantly lower *ln*(AAC volume) (Table 2 and Fig. 1). After similar adjustments, older age, ever smoking history, higher SBP, elevated TC, but reduced HDL cholesterol, FHMI, higher alcohol use, and Statin and antihypertensive medication use were significantly associated with higher *ln*(AAC volume). Finally higher BMI showed a borderline association (*p*=0.07) with higher *ln*(AAC volume). In contrast, after adjustments for *ln*(AAC volume), compared EA, each of HA, AA, and CA had significantly higher AAC density (Table 3 and Fig. 1). After similar adjustments, ever smoking history, higher BMI, and reduced serum HDL cholesterol were significantly associated with lower AAC density. Test for ethnicity**ln*(AAC volume), and ethnicity*AAC density in models with AAC volume and AAC density as the outcome (respectively) was positive (*p*<0.01 for both).

Discussion

In our study, compared to EA, each of HA, AA, and CA had lower AAC volume but higher AAC density. Also, older age, ever smoking history, reduced serum HDL cholesterol were independently associated with higher *ln*(AAC volume) but lower AAC density. To the best of our knowledge, this study is the first to investigate correlates of calcified plaque composition (volume and density) separately.

While ethnic differences in the prevalence CAC have been reported, few studies have investigated AAC. In both a clinical and community cohort, CAC was more prevalent in EA, compared to other minority groups.[10,11] In MESA, AAC was also more prevalent for EA.[8] To date, most studies investigating calcified atherosclerotic plaques have used the Agatston method which up-weights for density, thus ethnic differences in calcium density in calcified plaques are unknown. In our study, compared to EA, each of HA, AA, and CA had less AAC volume but more AAC density, and CA had the strongest association with AAC density. Other MESA researchers have reported the lowest CVD event rates in CA, after adjustments for CVD risk factors.[6]

In our study, traditional atherosclerotic risk factors[12] of older age, ever smoking history, higher BMI, and reduced HDL cholesterol, were positively associated with increased AAC volume, but lower AAC density. Furthermore, other known atherosclerotic risk factors such as; higher SBP and hypertension treatment, elevated total cholesterol and statin medication use, and FHMI were associated with higher AAC volume, but had no significant association with AAC density, and their associations tended to be inverse. Taken together, these results suggest that AAC density in contrast to AAC volume may not be independently associated with increased CVD risk, and further studies are needed to determine the impact of AAC density (in contrast to AAC volume) in CVD.

Supportive of our results are prior studies suggesting density of calcified plaque may be inversely associated with incident CVD. In two clinical cohorts of patients being evaluated for coronary artery disease by coronary CTA, the lowest CVD event rate was observed in participants with only calcified plaque, followed by those with mixed calcified and non-calcified plaques, while the highest rate was observed in those with non-calcified plaques.[4,5] Furthermore, in MESA, after adjustments for CVD risk factors, higher CAC volume was associated increased CVD risk, while CAC density was protective.[6] Studies of the differential association of AAC volume and density with CVD events are warranted.

The strengths of our study include a community-living, geographically and ethnically diverse cohort of both men and women who were free of clinically manifest CVD at recruitment. Our study, however, also has important limitations. First, the non-simultaneity of the predictor and outcome measures makes it problematic, even as a period cross-sectional study and we cannot assign temporality. However, it is unlikely that over a short period of time these measures would change systematically. Second, study sample was limited to participants with prevalent AAC, thereby limiting the generalizability of the results to individuals with calcified disease. Finally, AAC density was assessed using 4-point

scale rather than a continuous HU scale (130 – 3000), thereby limiting power and the ability to detect significant associations.

Several CVD risk factors were associated with increased AAC volume, but lower AAC density. Further studies are needed to determine the impact of calcium density in the aorta and other vascular beds in CVD.

The standard method used to score calcified plaque in arteries, the Agatston, up-weights plaque for higher calcium density, thus modeling density as a CVD hazard. While the Agatston is widely used in CVD risk prediction models, the appropriateness of up-weighting for density is controversial. We observed that a greater burden of CVD risk factors was associated with higher AAC volume but lower AAC density. Our novel study supports prior research showing that increased calcium density in calcified plaque may be protective for CVD.

The composition of calcified plaque (calcium density content) which can be measured non-invasively may improve CVD risk stratification for the early implementation of CVD prevention strategies. Further studies are needed to better understand the impact of calcium density in CVD risk, and how best to incorporate calcium density in our CVD risk prediction models.

Acknowledgments

Abbreviations

AA	African-Americans
AAC	abdominal aortic calcium
CA	Chinese-Americans
CAC	Coronary artery calcium
CVD	Cardiovascular disease
EA	European-Americans
HA	Hispanic-Americans.

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Highlights

- Older age was associated with higher abdominal aortic calcium (AAC) volume but lower AAC density

- Compared to European ethnicity, minorities had lower AAC volume, but higher AAC density

- A greater burden of cardiovascular (CVD) risk factors was associated with higher AAC volume but lower AAC density

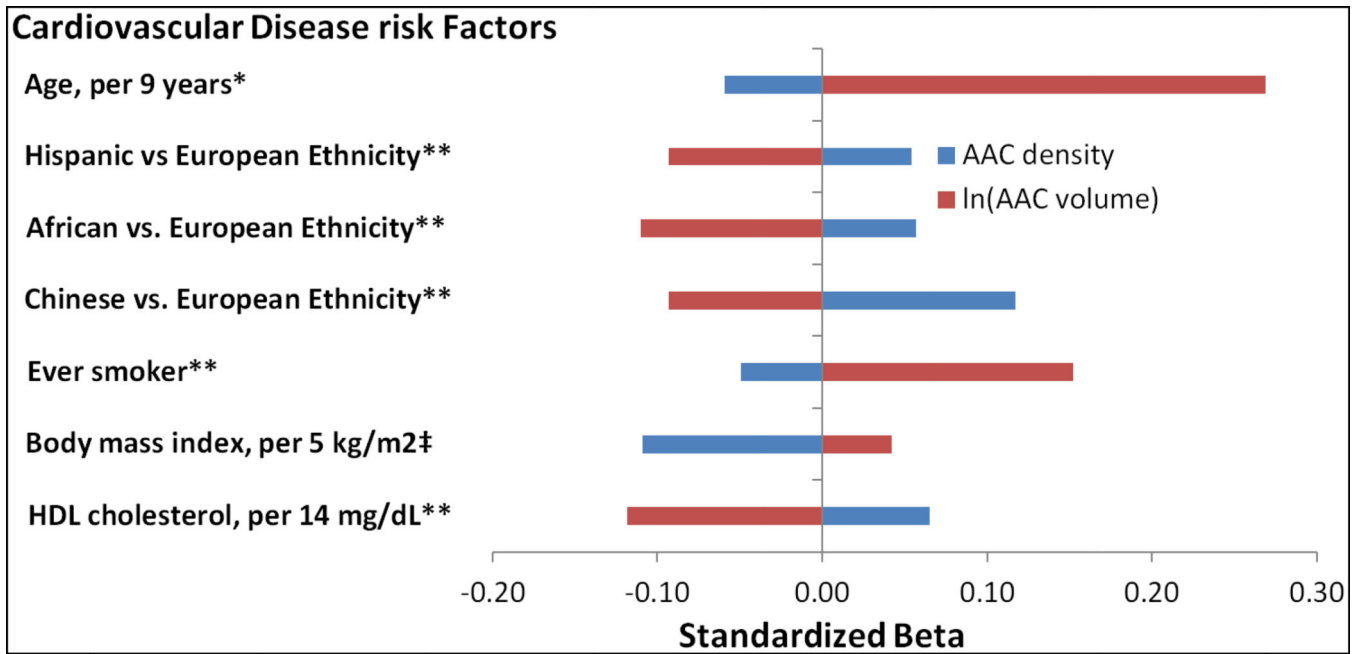**Fig. 1. Differential associations of cardiovascular disease risk factors with abdominal aortic calcium (AAC) density and AAC volume separately**

Model for AAC density additionally adjusted for natural log (*ln*) AAC volume and vice versa. **Indicates significance (*p*-value < 0.05) in both models. *Indicates significance in *ln*(AAC volume) model only. ‡Indicates significance in AAC density model only.

Table 1

Cohort characteristics for participants with non-zero abdominal aortic calcium (AAC) scores by quartiles of AAC density.

	AAC density score, quartile				
	Q1 (0.88–2.75) N=354	Q2 (2.76–3.14) N=351	Q3 (3.15–3.46) N=355	Q4 (3.47–4.00) N=353	Cohort N= 1413
AAC density, mean (SD)	2.1 (0.5)	3.0 (0.1)	3.2 (0.1)	3.7 (0.2)	3.0 (0.6)
AAC volume, median (25–75th), mm³	92 (36–251)	627 (266–1450)	1259 (373–3202)	1623 (600–3038)	628 (157–1939)
Age, mean (SD), years	61 (8)	65 (9)	66 (9)	67 (9)	65 (9)
Men, N (%)	186 (53%)	197 (55%)	172 (49%)	175 (50%)	730 (52%)
Ethnicity, N (%)					
European	133 (38%)	181 (51%)	192 (54%)	120 (34%)	626 (44%)
Hispanic	100 (29%)	83 (23%)	72 (21%)	86 (24%)	341 (24%)
African	75 (21%)	68 (19%)	53 (15%)	59 (16%)	255 (18%)
Chinese	42 (12%)	26 (7%)	35 (9%)	88 (25%)	191 (14%)
Clinical characteristics					
Diabetes, N (%)	41 (1 2%)	50 (1 4%)	42 (1 2%)	44 (1 3%)	177 (13%)
Ever smoker, N (%)	184 (53%)	197 (55%)	206 (59%)	192 (54%)	779 (55%)
Body mass index, mean (SD), kg/m²	29 (6)	29 (5)	28 (5)	28 (5)	28 (5)
Systolic blood pressure, mean (SD), mmHg	127 (21)	131 (22)	131 (23)	131 (21)	130 (22)
Total cholesterol, mean (SD), mg/dL	195 (34)	198 (34)	198 (37)	196 (35)	197 (35)
HDL cholesterol, mean (SD), mg/dL	50 (14)	50 (13)	50 (14)	52 (15)	50 (14)
Hypertension treatment, N (%)	127 (36%)	140 (39%)	163 (46%)	163 (46%)	593 (42%)
Statin medication use, N (%)	48 (14%)	68 (19%)	62 (18%)	85 (24%)	263 (19%)
Family history of myocardial infarction, N (%)	127 (36%)	178 (50%)	163 (46%)	137 (39%)	605 (43%)
Alcohol use, median (25–75th), drinks/week	2 (0–7)	2 (0–8)	2 (0–7)	2 (0–7)	2 (0–7)

HDL, high density lipoprotein.

Table 2

Multivariable associations of *In*(AAC volume) adjusted for AAC density in participants with non-zero AAC scores.

	Beta	95% CI	Std. Beta[a]	p-value
AAC density	1.50	(1.39, 1.61)	0.58	<0.01 *
Age, years	0.05	(0.04, 0.06)	0.27	<0.01 *
Ethnicity (*vs.* European)				
Hispanic	−0.26	(−0.43, −0.09)	−0.07	<0.01 *
African	−0.47	(−0.66, −0.28)	−0.11	<0.01 *
Chinese	−0.44	(−0.66, −0.22)	−0.09	<0.01 *
Clinical characteristics				
Ever smoker	0.50	(0.36, 0.64)	0.15	<0.01 *
Body mass index, kg/m^2	0.01	(−0.001, 0.03)	0.04	0.07
Systolic blood pressure, mmHg	0.01	0.002, 0.01)	0.07	<0.01 *
Total cholesterol, mg/dL	0.004	0.002, 0.01)	0.08	<0.01 *
HDL cholesterol, mg/dL	−0.01	(−0.02, −0.01)	−0.12	<0.01 *
Hypertension treatment	0.16	(0.01, 0.30)	0.05	0.04
Statin medication use	0.38	(0.20, 0.55)	0.09	<0.01 *
Family history of myocardial infarction	0.22	(0.08, 0.35)	0.07	<0.01 *
Alcohol use, drinks/week	0.01	(0.003, 0.02)	0.06	<0.01 *

[a]Standardized Beta, backwards deletion model with *p*-value < 0.1 for inclusion.

p-value (2-tailed) < 0.05 significant.

p-value for interaction term ethnicity X *In*(AAC volume) <0.01.

Table 3

Multivariable associations of abdominal aortic calcium (AAC) density adjusted for *In*(AAC volume) in participants with non-zero AAC.

	Beta	95% CI	Std. Beta[a]	*p*-value
In(AAC volume)	0.27	(0.24, 0.29)	0.71	<0.01[*]
Age, years	−0.01	(−0.01, 0)	−0.07	<0.01[*]
Ethnicity (*vs.* European)				
Hispanic	0.0 8	(−0.01, 0.17)	0.0 5	0.0 4[*]
African	0.09	(−0.02, 0.19)	0.06	0.02[*]
Chinese	0.22	(0.14, 0.37)	0.12	<0.01[*]
Clinical characteristics				
Ever smoker	−0. 06	(−0.12, −0.003)	−0. 05	0.0 4[*]
Body mass index, kg/m^2	−0.01	(−0.02, −0.01)	−0.11	<0.01[*]
HDL cholesterol, mg/dL	0.003	(0, 0.01)	0.07	<0.01[*]

[a]Standarized Beta, backwards deletion model with *p*-value < 0.1 for inclusion.

[*]*p*-value (2-tailed) < 0.05 significant.

p-value for Interaction term ethnicity X AAC density < 0.01.