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Coronary Artery Calcium Density and Cardiovascular Events by Volume Level: the Multi-Ethnic Study of Atherosclerosis

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Abstract

Background—The Agatston coronary artery calcium (CAC) score provides robust cardiovascular disease (CVD) risk prediction, but upweights plaque area by a density factor. Density, however, has been shown to be inversely associated with events. Using CAC volume and density separately improves risk prediction, but it is unclear how to apply this method clinically. We aimed to evaluate the association between CAC density and CVD across the spectrum of CAC volume to better understand how to incorporate these metrics into a single score.

Methods—We performed an analysis of Multi-Ethnic Study of Atherosclerosis (MESA) participants with detectable CAC to evaluate the association between CAC density and events by level of CAC volume using multivariable Cox regression models.

Results—In a cohort of 3,316 participants, there was a significant interaction ($p<0.001$) between CAC volume and density for coronary heart disease (CHD) risk (myocardial infarction, CHD death, resuscitated cardiac arrest). Models using CAC volume and density resulted in improvement in the C-index (0.703, SE 0.012 versus 0.687, SE 0.013) and a significant net reclassification improvement (NRI, 0.208, 95% CI 0.102–0.306) compared with the Agatston score for CHD risk prediction. Density was significantly associated with lower CHD risk at volumes ≤130 mm^3 (HR 0.57 per unit of density, 95% CI 0.43, 0.75) but the inverse association at volumes >130 mm^3 was not significant (HR 0.82 per unit of density, 95% CI 0.55, 1.22).

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Disclosures

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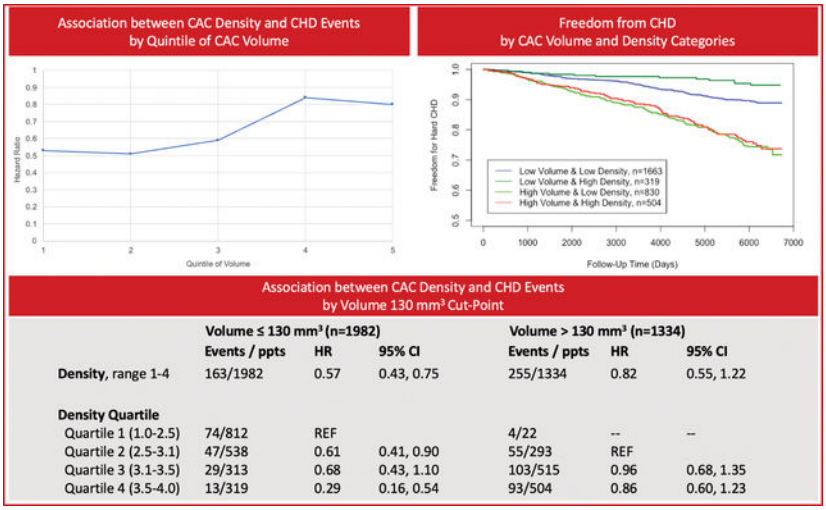
Supplemental Material:

Tables S1–S5

Figure S1

Conclusions—The lower risk for CHD associated with higher CAC density varied by level of volume, and volume ≤ 130 mm^3 is a potentially clinically useful cut-point. Further study is needed to integrate these findings into a unified CAC scoring method.

Graphical Abstract



	Volume ≤ 130 mm³ (n=1982)			Volume > 130 mm³ (n=1334)		
	Events / ppts	HR	95% CI	Events / ppts	HR	95% CI
Density, range 1-4	163/1982	0.57	0.43, 0.75	255/1334	0.82	0.55, 1.22
Density Quartile						
Quartile 1 (1.0-2.5)	74/812	REF		4/22	--	--
Quartile 2 (2.5-3.1)	47/538	0.61	0.41, 0.90	55/293	REF	
Quartile 3 (3.1-3.5)	29/313	0.68	0.43, 1.10	103/515	0.96	0.68, 1.35
Quartile 4 (3.5-4.0)	13/319	0.29	0.16, 0.54	93/504	0.86	0.60, 1.23

Keywords

coronary disease; cardiovascular disease; heart disease risk factors; primary prevention; computed tomography scanner

Introduction

Coronary artery calcium (CAC) scoring is well established as a robust tool for cardiovascular disease (CVD) risk prediction in asymptomatic individuals.[1] Current guidelines for the management of blood cholesterol[2] and primary prevention[3] endorse the use of CAC scoring to assist clinical decision making in individuals with intermediate estimated 10-year CVD risk. Clinically, the Agatston score is currently the standard CAC scoring method, but there is potential for improvement of this scoring method.

The Agatston score represents plaque area weighted upward by a density factor.[4] However, increased plaque density is associated with greater plaque stability[5,6] which translates into an inverse association with coronary heart disease (CHD) and CVD events.[7,8] In particular, very dense plaque is associated with reduced events.[9] Additionally, CVD risk factors such as body mass index and diabetes are inversely associated with plaque density, while age, high-density lipoprotein-cholesterol (HDL-C),[5] statin use[10] and physical activity[11,12] are positively associated with plaque density. This underlying pathophysiology of plaque density and its inverse association with CVD risk factors and CVD events illustrate why the Agatston score weighting plaque area upward for density is suboptimal. Using the volume score with adjustment for the density score instead provides superior risk assessment compared to the Agatston score or volume score alone.[7,8] The method described in these

studies allows calculation of the density score from data that are already available with the standard Agatston scoring methodology.

Despite the improved predictive value of the volume and density method, this has not been adopted for widespread clinical use. This is likely due, in part, to the fact that the optimal method for integrating the volume and density scores into a unified clinical assessment has not been established. There is a need to better understand the relationship between CAC volume and density, and how to apply these measures clinically. In particular, the inverse association of density with events may vary by CAC score,[6] and this may be due plaque burden being a more significant predictor of CVD events than focal stenoses.[13]

We aimed to evaluate the relationship between CAC density and CHD events across the range of CAC volume to understand how the inverse association of density with risk varies by level of volume, and how to better integrate these tools. The ultimate goal was to provide information to guide a new CAC scoring methodology that makes use of existing technology and currently available measurements.

Methods

Study Population

The Multi-Ethnic Study of Atherosclerosis (MESA) is a prospective, multi-ethnic cohort study of participants free of known cardiovascular disease at baseline. The design of the MESA has been described previously [14]. In brief, initial recruitment was conducted for the first examination between 2000–2002 at six centers across the United States with a total of 6,814 participants. The study was approved by the institutional review boards at each center, and all participants provided written informed consent. All data and materials are available through MESA. For this study, all participants without baseline CAC were excluded as detectable CAC is necessary to assess density. Additionally, participants without follow-up for adjudication of events or with pre-baseline events were excluded.

CAC Measurement

All participants underwent baseline CAC measurement with electrocardiogram-gated non-contrast cardiac computed tomography (CT) at exam 1. Three centers (Chicago, Los Angeles, New York) utilized electron-beam CT (EBCT) with slice thickness of 3 mm, while the other three centers (Baltimore, St. Paul, Winston-Salem) used multi-detector CT (MDCT) with slice thickness of 2.5 mm. Exams were interpreted centrally at the MESA CT Reading Center and were brightness adjusted with a standard phantom control to adjust for differences between clinical sites.

Calcified lesions were defined as having at least four contiguous pixels with a density of 130 Hounsfield units (Hu) or higher. Agatston scores were calculated for each participant by measuring the area of each discrete lesion, multiplying the area by a density factor of 1, 2, 3 or 4 depending on the maximum density within each lesion, and summing these lesion-specific scores. Volume scores (total of lesion areas multiplied by CT scanner slice thickness) were also reported. Density scores were not provided as part of the MESA database and were thus calculated for each participant for this study. The density score was

calculated by dividing the volume score by the CT scanner slice thickness to derive an area score. The density score is equal to the Agatston score divided by the area score. In the MESA protocol, Agatston scores were adjusted for differences in slice thickness.[15] In order to obtain density scores of 1–4 for both EBCT and MDCT scans, a correction was applied to MDCT density scores by multiplying the score by the ratio of slice thickness for EBCT to MDCT (3 / 2.5).

Risk Factors and Outcomes

MESA participants answered standardized questionnaires at baseline which were used to gather information on demographics, medical comorbidities, smoking history and medication use. Cigarette smoking was defined as current, former, or never, and also quantified in pack years. Three seated systolic and diastolic blood pressure measurements were taken, and the last two measurements were averaged. Hypertension was defined by the 6th Joint National Committee criteria. Fasting blood samples were taken for laboratory analysis including total and high-density lipoprotein cholesterol measurements. Low-density lipoprotein cholesterol was calculated by the Friedewald equation. The presence of diabetes was defined as fasting glucose ≥126 mg/dL or the use of medications for diabetes.

Participants in MESA have been followed prospectively for adjudication of events. Cardiovascular events are reported through 2018. For this analysis, the primary outcome was coronary heart disease (CHD), which was defined as myocardial infarction (MI), resuscitated cardiac arrest or CHD death. CVD was also evaluated and defined as the components of CHD plus fatal and non-fatal stroke.

Statistical Analysis

Baseline characteristics were compared across quartiles of baseline CAC volume and quartiles of density using analysis of variance (ANOVA) testing for continuous variables and Chi square tests for categorical variables. We performed time to event analyses using Cox proportional hazards models to assess the associations between CAC volume quartile and CHD and CVD events and CAC density quartile and CHD and CVD. Models with volume quartile were also adjusted for a standard set of covariates (age, sex, race/ethnicity, total cholesterol, HDL-C, systolic blood pressure, diabetes history, smoking pack years, treatment for hypertension and statin use) and density score. Models with density quartile were also adjusted for the standard covariates and ln-transformed volume score. Statin use was adjusted for due to the known associations between statins, density, and cardiovascular events.

We evaluated the potential interaction between volume score and density for CHD events in Cox proportional models with adjustment for the standard covariates. We then used Cox models with adjustment for the standard covariates and ln-transformed volume score to evaluate the association between density score and CHD events by level of volume. Volume was stratified by quartiles and quintiles to best determine potential levels of volume which could serve as clinically relevant cut-points which would differentiate the effect of density on CHD events. We then assessed the association between density and CHD events above

and below these volume cut-points in Cox models with the same standard covariates as above.

In a sensitivity analysis, we performed the same analysis with adjustment for the composite 10-year ASCVD risk score based on the ACC/AHA pooled cohorts equation (PCE). We also tested the interactions between CAC density and race/ethnicity and CAC density and sex to determine if further stratified analyses were necessary. Given the association between statin use and density, we also performed a sensitivity analysis using similar Cox proportional hazards models as above to assess the association between density and CHD events, stratified by volume of 130 mm^3, in statin naive participants (those who were never recorded as taking a statin during the follow-up period). To evaluate for improvement in predictive value for CHD events with the use of CAC volume and density, we calculated Harrell's C-index for models including the PCE alone, the PCE + ln-transformed Agatston score, and the PCE + ln-transformed Volume score + Density score. We also calculated the continuous NRI (net reclassification improvement) of the PCE + Volume + Density model compared with the PCE + Agatston model at the median follow-up (16.7 years) with confidence intervals estimated using 200 bootstrap samples.

Finally, we categorized participants into four volume / density categories: low volume – low density, low volume – high density, high volume – low density, and high volume – high density. High or low volume was based on the cut-point determined in previous analyses, and high or low density was defined as the top quartile of density versus all other quartiles (based on analyses using different combinations of density quartiles). We constructed Cox proportional hazards models using the standard covariates as above for CHD and CVD events based on combined volume and density group. We also constructed Kaplan-Meier Curves for freedom from CHD and CVD by combined volume and density group.

Analyses were performed using R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS Statistics v26.0 (IBM, Armonk, New York, USA). A two-tailed p-value of <0.05 was considered statistically significant. HSB had full access to all data and takes responsibility for its integrity and the data analysis.

Results

At baseline, the MESA enrolled 6,814 participants. Of these, 3,398 had detectable CAC. After excluding those without follow-up (n=16) and with missing covariates (n=66), the final analytic cohort was 3,316 participants. Characteristics for the study participants are shown in Table 1 by volume and density levels. In general, there was a greater prevalence of cardiovascular risk factors with higher CAC volume level including higher age, more male participants and more participants with hypertension and diabetes, and higher smoking pack years. Statins were more common and LDL-C and total cholesterol were lower with increasing volume quartile. White ethnicity was more common with higher volume level. Density score was higher with higher levels of volume. Similarly, risk factors, including higher age, male sex, hypertension, and smoking pack years also had higher prevalence with higher density level. LDL-C was lower, and HDL-C was higher with increasing density level. Volume score was also higher with increasing density level.

The distribution of participants by volume and density groups is shown in Figure 1. Within volume quartile 1, most participants were in quartile 1 of density. Similarly, within volume quartile 4, most participants were in quartile 4 of density. However, within quartiles 2–3 of volume, the distribution of density quartiles was more heterogeneous.

There were 418 total hard CHD and 608 total hard CVD events over a median follow-up of 16.9 [IQR 9.9, 17.3] years. In multivariable adjusted models, increasing quartile of CAC volume was associated with increasing risk of CHD (HR 3.77 for quartile 4, 95% CI 2.48, 5.74, p<0.001) and CVD (HR 2.81 for quartile 4, 95% CI 2.01, 3.94, p<0.001, Figure 2A). Increasing quartile of CAC density was associated with decreasing risk for CHD (HR 0.47 for quartile 4, 95% CI 0.32, 0.69, p<0.001) and CVD (HR 0.58 for quartile 4, 95% CI 0.43, 0.79, p<0.001, Figure 2B). The interaction between density and volume with multivariable adjustment for the standard covariates was statistically significant (p<0.001). The association between CAC density and CHD by level of volume was then evaluated in both quartiles and quintiles of volume (Figure S1) with adjustment for the standard covariates and natural log(ln)-transformed volume score. Within quartiles of volume, a significant and inverse association with density was observed in the first and second quartiles of volume (up to 85 mm^3), with an inverse but non-significant association in quartiles three and four (Table 2). When quintiles of volume were used instead of quartiles, density was significantly associated with CHD events in the first 3 volume quintiles (up to 132.5 mm^3), but not the fourth and fifth quintiles (Figure S1B).

Based on the analyses of density by volume strata (Figure S1), a volume cut-point of 130 mm^3 was chosen for further analysis. In those with volume at or below 130 mm^3 (n=1,982), higher continuous CAC density was significantly associated with a reduction in CHD events when assessed continuously (HR 0.57 per unit of density, 95% CI 0.43, 0.75, p<0.001). In contrast, in those with volume above 130 mm^3 (n=1,334), CAC density was not associated with CHD events when assessed continuously (HR 0.92 per unit of density, 95% CI 0.55, 1.22, p=0.34, Table 3). When density was assessed in quartiles for those with volume score ≤ 130 mm^3, the second (HR 0.61, 95% CI 0.41, 0.90, p=0.013) and fourth quartiles (HR 0.26, 95% CI 0.16, 0.54, p<0.001) were associated with a significant reduction in CHD, while a non-significant trend towards a reduction in CHD was noted in the third quartile (HR 0.68, 95% CI 0.43, 1.10, p=0.12). In those with volume score > 130 mm^3, the second quartile of density was used as the reference level due to a low number of participants in quartile 1 of density with volume > 130 mm^3. Quartile 3 (HR 0.96, 95% CI 0.68, 1.35, p=0.80) and quartile 4 (HR 0.86, 95% CI 0.60, 1.23, p=0.41) of density were inversely, but not significantly associated, with CHD events in those with volume > 130 mm^3, in contrast to those with lower volume. Similar analyses of CVD events using the same cut-point were performed and similar results were obtained with a slightly less pronounced association with density (HR 0.74 per unit of density, 95% CI 0.60, 0.91, p=0.005 for volume ≤130 mm^3; HR 0.85, 95% CI 0.61–1.81, p=0.33 for volume >130 mm^3, Table S1). An additional analysis with adjustment for the ASCVD risk score rather than its components yielded similar results (HR 0.57 per unit of density, p<0.001 for volume ≤130 mm^3; HR 0.78, p=0.22 for volume >130 mm^3, Table S2). We also performed a sensitivity analysis of the association between density and CHD events by volume level in statin naïve patients (n=1,519), and the results were similar. For those with volume ≤130 mm^3, the HR for CHD per unit of density was

0.56 (95% CI 0.37, 0.83, p=0.004) and 0.78 (0.41, 1.48, p=0.448) for those with volume >130 mm^3. Additionally, there was not a significant interaction between statin use and density (p=0.62) in the fully adjusted Cox models.

For CHD risk prediction, CAC volume and density resulted in an improved C-index compared with the Agatston score (0.703, SE 0.012 versus 0.687, SE 0.013). Both scoring methods improved upon the PCE (0.666, SE 0.013). CAC volume and density also resulted in a significant continuous NRI compared with the Agatston score (0.2082, 95% CI 0.1020, 0.3064) with improvement among both those with events and without events (Table 4).

Finally, participants were categorized into 4 categories: 1) low volume-low density (n=1,663), 2) low volume-high density (n=319), 3) high volume-low density (n=830), and 4) high volume-high density (n=504). High volume was defined as >130 mm^3 and high density was defined as the top quartile of density. Kaplan-Meier curves comparing freedom from CHD and CVD are shown in Figures 3A and 3B. Low volume-high density had greater event-free survival than low volume-low density, and high volume-low density was similar to high volume-high density for CHD (p<0.001 for trend). Low volume-high density had significantly lower CHD risk than low volume-low density (HR 0.45, 95% CI 0.26, 0.80, p=0.006, Table S3) in Cox proportional hazards models adjusting for ASCVD risk factors and statin use. Both high volume categories had greater CHD risk than low volume-low density. However, high volume-high density was not significantly different than high volume-low density (HR 0.98, 95% CI 0.76, 1.27, p=0.90, Table S4). The fourth quartile of density was chosen as “high density” as the protective association of density was more apparent and significant using this scheme than when using quartiles 3–4 or quartiles 2–4 to represent “high density” (Table S5).

There was no interaction between density and race/ethnicity (p=0.67) or between density and sex (p=0.98).

Discussion

In this study of multi-ethnic participants with prevalent CAC and free of known cardiovascular disease at baseline, we found that the protective association of CAC density varies by level of volume, with more pronounced protection at lower levels of volume. Based on our analyses, 130 mm^3 (approximately the 60^{th} percentile) appears to be a clinically relevant cut-point; at volume below 130 mm^3, higher CAC density is significantly associated with a decrease in CHD risk, while the decreased risk with higher density was not significant at volume levels above 130 mm^3. Use of CAC volume with adjustment for density improves risk prediction but is not currently used clinically. Understanding the non-linear relationship between CAC density and volume is an important step towards developing a more accurate and predictive CAC score. We provide an example for how these findings may be implemented clinically by categorizing individuals based on their volume and density scores. Ideally, a new CAC score would involve a single metric incorporating both volume and density.

CAC volume and density have previously been shown to be superior to the Agatston method. This is likely because the Agatston score is upweighted for density though density is inversely associated with CVD events and using the volume score with adjustment for density improves predictive value.[7,8] In a case-control study of individuals with acute coronary syndrome who underwent coronary computed tomography angiography (CCTA), very dense (1K or 1000 HU) plaque was associated with a lower risk for acute coronary syndrome.[9] In a cohort study of individuals with serial CCTAs, statin use was associated with increased plaque density, supporting the notion that greater density is associated with lower risk.[10] The Agatston score has also been shown to be slightly less predictive of CHD and CVD events in statin-treated individuals, likely due to the treatment of density in the Agatston score.[16] CAC density has previously been shown to be less predictive of CVD mortality at higher CAC Agatston scores.[6] Our study expands on prior studies of CAC volume and density in MESA by incorporating significantly longer follow-up. Increased follow-up and increased accrual of CHD events allowed us the power to examine the non-linear relationship between CAC density, volume and events for the first time, which was not previously described in MESA. Demonstrating this non-linear relationship is an important step towards the development of a new CAC score. Another significant finding was that CAC density retained its significant inverse association with events, even with much longer follow-up. The differential association between CAC density and events by level of volume was also observed in statin naïve patients, which is important given the described association between statin use and density. Additionally, plaque burden is a more important predictor of CVD events than stenosis.[13] This may partly explain our findings – at higher levels of volume, plaque burden is the overwhelming predictor of risk, and the relative impact of plaque density, and, perhaps, plaque stability, may be lessened.

Additionally, a prior study from the CAC Consortium observed a differential association between mean plaque density and CVD mortality by CAC score, with an association observed at CAC <100 but not ≥100.[6] Our study adds multiple novel findings by evaluating CHD events and by evaluating the association between density and events across a continuum of volume. Rather than using cut-points previously determined to be clinically relevant, we evaluated the association between density and events within volume quartiles and quintiles. This allowed us to first demonstrate the non-linear relationship between density, volume and events, and to choose the optimal cut-point reflective of the data. Our study elucidates the relationship between density and volume across the spectrum of volume, which paves the way for clinical application of these scores.

There are multiple potential ways to apply the findings from this study clinically, which require prospective study to evaluate further. The density score can easily be calculated by knowing the Agatston score, volume score and slice thickness. Importantly, the density score appears to have less relevance at high levels of plaque volume. If volume is above 130 mm^3, minimal adjustment based on density score may be necessary based on the present analysis. For lower levels of volume (60% of participants in this study), however, density adds important information regarding risk. Individuals can be categorized into one of four risk categories based on volume above or below 130 mm^3 and density quartile (4^{th} quartile versus all others) for assessment of CHD and CVD risk. For example, low volume-high density is associated with a 55% reduction in CHD risk compared with low volume-low

density. Alternatively, a reduction in estimated risk of 43% per unit of density may be applied using density continuously. It is important to note that the volume cutpoint of 130 mm^3 was derived from the MESA population and requires validation in an external population. Ultimately, the optimal use of this information would be development of a new method of calculating the CAC score which would integrate the volume score with adjustment in score based on continuous levels of density and volume.

Our study has notable limitations. While efforts were made to map the inverse association of risk with density across the range of volume, further granularity and refinement of cut-point selection may have been possible with a larger sample size. However, the volume cut-point of 130 mm^3 appears to distinguish the protective association of density well when density was assessed continuously. In addition, we utilized an average peak density score, which is based on a factor scoring system, for this study, while average mean density or continuous assessment of density may improve predictive value.[6,17] The current method also results in a large peak density range for a score of 4. However, the Agatston score is calculated using peak density, and peak density can be easily calculated from widely available information without a change in software or methodology, and is thus more clinically useful and easily applicable. The findings of this study apply only to those with detectable CAC; for those with CAC of 0, this study would not change clinical assessment. Finally, this is an observational study, and our findings are subject to residual confounding.

Conclusions

In conclusion, the protective association of plaque density varies by the level of calcified plaque volume and is more pronounced below a volume level of 130 mm^3. This study provides information for clinical applications of volume and density scoring, and suggests further study to develop new methodology integrating the CAC volume and density scores into a single metric.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Non-standard Abbreviations and Acronyms

ASCVD	Atherosclerotic Cardiovascular Disease
CAC	Coronary Artery Calcium
CCTA	Coronary Computed Tomography Angiography
CHD	Coronary Heart Disease
CT	Computed Tomography
CVD	Cardiovascular Disease
EBCT	Electron-Beam Computed Tomography
HDL-C	High-density lipoprotein cholesterol
Hu	Hounsfield units
LDL-C	Low-density lipoprotein cholesterol
MESA	Multi-Ethnic Study of Atherosclerosis
MDCT	Multi-Detector Computed Tomography
MI	Myocardial Infarction

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Clinical Perspective

Coronary artery calcium (CAC) volume and density scoring improves risk prediction over the Agatston score, but it is unclear how to apply these two metrics clinically in a unified assessment. In a prospective cohort study of Multi-Ethnic Study of Atherosclerosis participants with baseline CAC, we evaluated the association between CAC density and coronary heart disease (CHD) events across the spectrum of CAC volume. The lower risk for CHD associated with higher CAC density varied by level of volume, and we identified volume ≤ 130 mm^3 as a potentially clinically useful cut-point. At volume levels ≤ 130 mm^3, higher density was significantly and inversely associated with events, while it was not significantly associated at higher levels of volume. This information can be derived from a typical Agatston CAC score report and can be used to integrate an assessment for density into clinical decision making. Further study is needed to develop a new way of calculating the CAC score which integrates these findings into a single score.

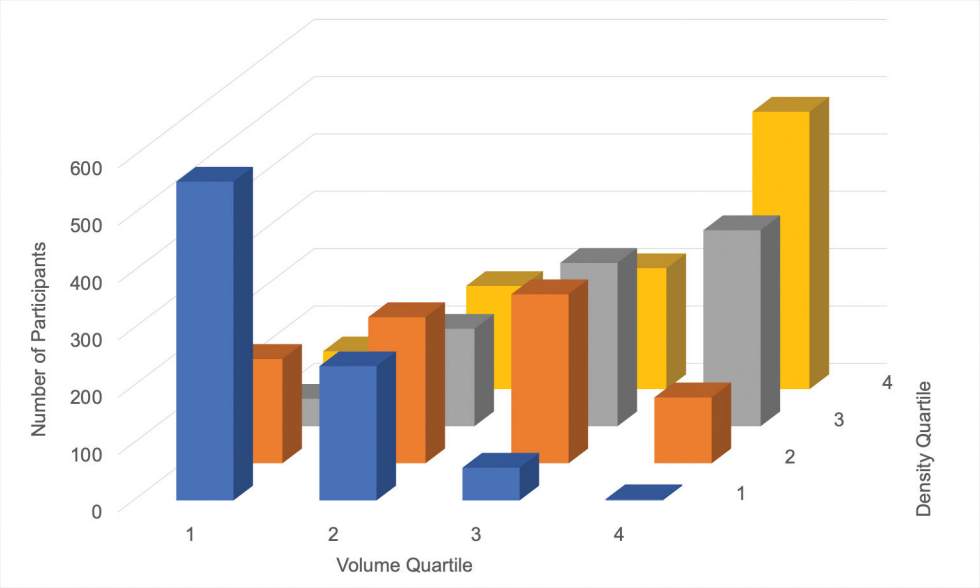

Figure 1.

Distribution of Participants by CAC Volume and Density Quartiles

Most participants in volume quartile 1 are in the first quartile of density, while most participants in the fourth quartile of volume are in the fourth quartile of density. For quartiles 2 and 3 of volume, there is a more heterogenous spread of participants across density quartiles.

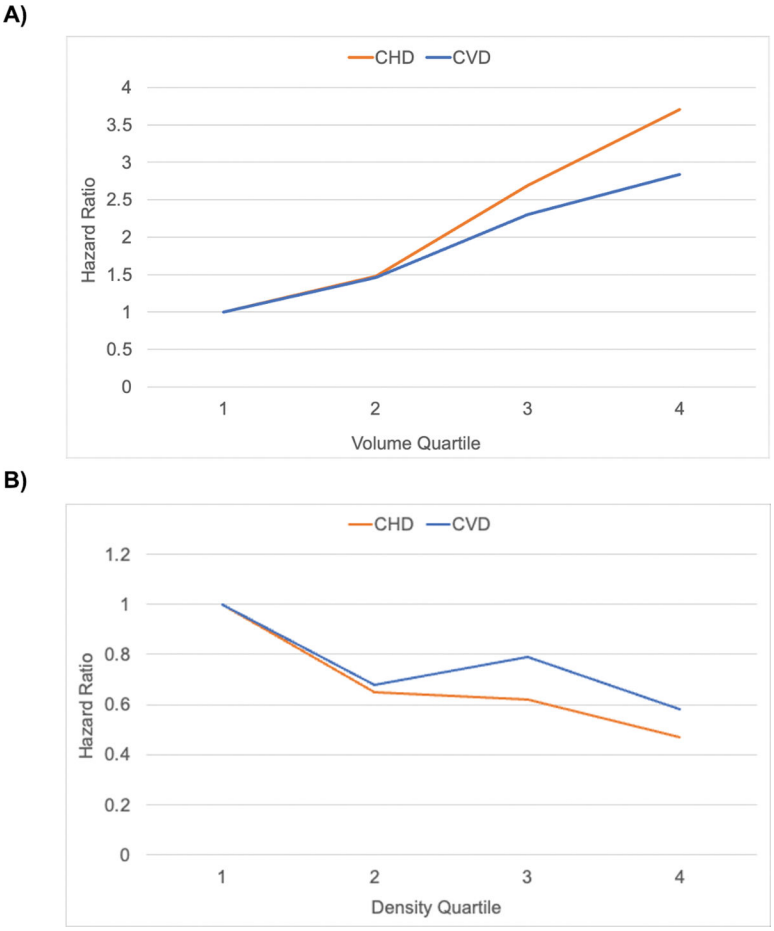

Figure 2.

Association of Volume and Density with CHD and CVD Risk.

A) Volume Quartiles. Increasing quartile of volume is associated with increased risk of CHD (p-values: Q1: REF, Q2: 0.045, Q3 and Q4: <0.001) and CVD (p-values: Q1: REF, Q2: 0.015, Q3 and Q4: <0.001).

B) Density Quartiles. Increasing quartile of density is associated with decreased risk of CHD (p-values: Q1: REF, Q2: 0.009, Q3: 0.008, Q4: <0.001) and CVD except for quartile 3 (p-values: Q1: REF, Q2: 0.006, Q3: 0.108, Q4: <0.001).

Multivariable models adjusted for age, sex, race/ethnicity, total cholesterol, HDL-C, systolic blood pressure, diabetes history, smoking pack years, treatment for hypertension and statin use. Volume analysis adjusted for density score and density analysis adjusted for ln-volume.

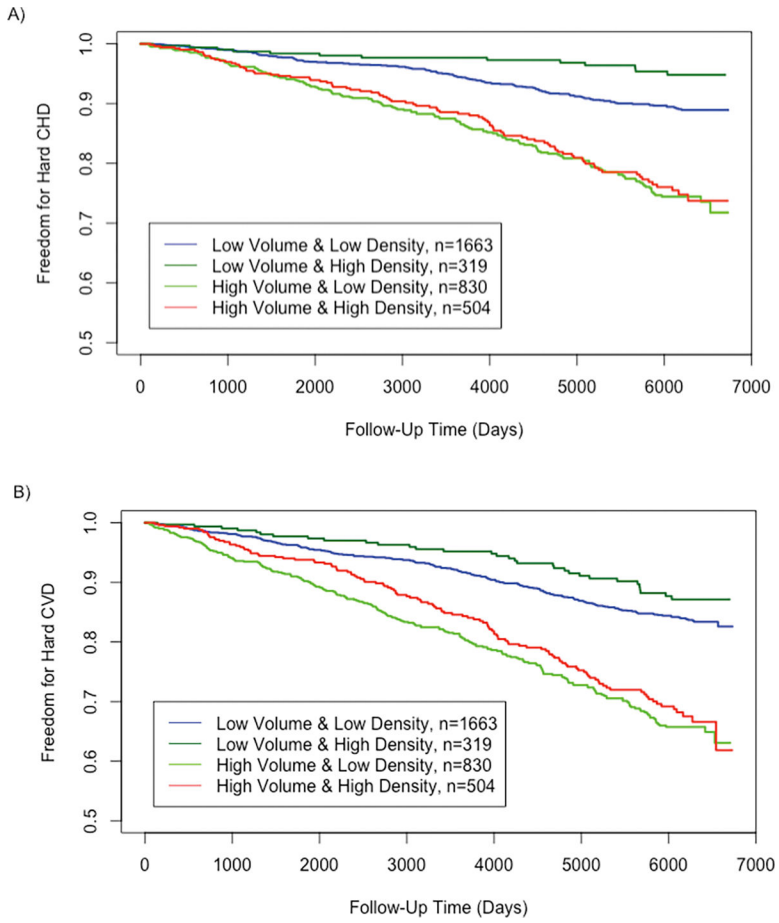

Figure 3.

Freedom from CHD and CVD by Volume and Density Categories

A) Freedom from CHD. Risk is lowest in Low Volume & High Density. Both High Volume categories appear similar regardless of density. $p<0.001$ for trend.

B) Freedom from CVD. Risk is lowest in Low Volume & High Density. Both High Volume categories appear similar regardless of density. $p<0.001$ for trend.

Risk categories defined by volume level (above or below 130 mm^3) and density level (fourth quartile versus all others).

Table 1.

Baseline Characteristics of Study Participants by Volume and Density Quartile

	Volume (mm^3)				
	Quartile 1 **2.3 – 24.5** (n=836)	**Quartile 2** **24.5–85.0** (n=825)	**Quartile 3** **85.0–273.4** (n=828)	**Quartile 4** **>273.4** (n=827)	**p**
Age, years	62.4 (9.8)	65.3 (9.3)	67.6 (9.1)	70.2 (8.2)	<0.001
Female	428 (51.2)	381 (46.2)	332 (40.1)	261 (31.6)	<0.001
Race / ethnicity					<0.001
Black	218 (26.1)	213 (25.8)	179 (21.6)	187 (22.6)	
Chinese	104 (12.4)	122 (14.8)	107 (12.9)	66 (8.0)	
Hispanic	181 (21.7)	178 (21.6)	161 (19.4)	142 (17.2)	
White	333 (39.8)	312 (37.8)	381 (46.0)	432 (52.2)	
Hypertension	383 (45.8)	424 (51.4)	472 (57.0)	538 (65.1)	<0.001
Diabetes	98 (11.7)	112 (13.6)	135 (16.3)	181 (21.9)	<0.001
Smoking, pack years	12.2 (23.0)	12.3 (20.5)	14.8 (23.4)	19.7 (28.1)	<0.001
Treatment for Hypertension	301 (36.0)	355 (43.0)	401 (48.4)	462 (55.9)	<0.001
Statin therapy	137 (16.4)	158 (19.2)	174 (21.0)	201 (24.3)	0.001
SBP, mmHg	126.5 (20.7)	130.6 (21.8)	131.7 (21.6)	134.6 (22.1)	<0.001
Total cholesterol, mg/dL	196.9 (35.2)	193.4 (37.1)	195.2 (35.6)	192.7 (37.5)	0.08
HDL-C, mg/dL	49.9 (13.9)	49.6 (14.7)	49.3 (14.8)	48.9 (14.6)	0.55
LDL-C, mg/dL	121.2 (32.9)	116.8 (31.5)	119.4 (32.3)	116.1 (31.4)	0.004
Density score, unitless	2.2 (0.8)	2.9 (0.6)	3.2 (0.4)	3.4 (0.3)	<0.001
Density score range, unitless	1.0–4.0	1.2–4.0	1.7–4.0	2.3–4.0	
CHD events	53 (6.3)	73 (8.8)	126 (15.2)	166 (20.1)	<0.001
CVD events	82 (9.8)	120 (14.5)	182 (22.0)	224 (27.1)	<0.001
Follow-up time, years	16.7 [12.5, 17.6]	16.6 [11.4, 17.4]	16.3 [9.7, 17.1]	13.6 [7.9, 16.8]	<0.001
	Density (unitless)				
	Quartile 1 **1.0–2.5** (n=834)	**Quartile 2** **2.5–3.1** (n=831)	**Quartile 3** **3.1–3.5** (n=828)	**Quartile 4** **3.5–4.0** (n=823)	**p**

Age, years	62.9 (10.1)	66.5 (9.4)	67.8 (8.6)	68.4 (9.0)	<0.001
Female	398 (47.7)	355 (42.7)	304 (36.7)	345 (41.9)	<0.001
Race / ethnicity					<0.001
Black	188 (22.5)	218 (26.2)	202 (24.4)	189 (23.0)	
Chinese	103 (12.4)	90 (10.8)	109 (13.2)	97 (11.8)	
Hispanic	200 (24.0)	187 (22.5)	143 (17.3)	132 (16.0)	
White	343 (41.1)	336 (40.4)	374 (45.2)	405 (49.2)	
Hypertension	399 (47.8)	479 (57.6)	477 (57.6)	462 (56.1)	<0.001
Diabetes	119 (14.3)	134 (16.1)	155 (18.7)	118 (14.3)	0.043
Smoking, pack years	12.7 (23.0)	13.9 (23.4)	15.6 (24.0)	16.6 (25.9)	0.005
Treatment for Hypertension	334 (40.0)	389 (46.8)	411 (49.6)	385 (46.8)	0.001
Statin therapy	160 (19.2)	149 (17.9)	181 (21.9)	180 (21.9)	0.11
SBP, mmHg	128.1 (21.4)	132.0 (21.0)	131.1 (21.8)	132.1 (22.5)	<0.001
Total cholesterol, mg/dL	198.0 (38.1)	195.3 (36.0)	192.8 (35.1)	192.2 (35.9)	0.004
HDL-C, mg/dL	49.2 (14.1)	49.1 (14.2)	48.4 (14.4)	51.1 (15.1)	0.001
LDL-C, mg/dL	121.3 (32.9)	119.4 (32.2)	117.9 (32.4)	114.8 (30.6)	<0.001
Volume score, mm^3	28.3 (38.5)	143.0 (195.0)	354.3 (431.6)	501.0 (684.3)	<0.001
Volume score range, mm^3	2.3–290.9	2.9–2238.9	5.8–4309.1	7.0–4991.9	
CHD events	78 (9.4)	102 (12.3)	132 (15.9)	106 (12.9)	0.001
CVD events	117 (14.0)	143 (17.2)	193 (23.3)	155 (18.8)	<0.001
ollow-up time, years	16.7 [12.0, 17.5]	16.5 [10.4, 17.4]	15.4 [9.0, 17.1]	15.4 [9.1, 17.1]	<0.001

Values are presented as mean (standard deviation), median (interquartile range), or n (%). CHD = coronary heart disease. CVD = cardiovascular disease. HDL-C = high-density lipoprotein cholesterol. LDL-C = low-density lipoprotein cholesterol. SBP = systolic blood pressure.

Table 2.

CAC Density and Risk for CHD by Volume Quartile

	Volume Quartile							
	Q1		Q2		Q3		Q4	
Range, mm^3	2.3 – 24.5		24.5 – 85.0		85.0 – 273.4		>273.4	
Events / ppts	53 / 836		73 / 825		126 / 828		166 / 827	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Continuous Density	0.45 (0.28, 0.73)	**0.001**	0.59 (0.39, 0.88)	**0.010**	0.76 (0.49, 1.16)	0.20	0.86 (0.48, 1.55)	0.62

Adjusted for age, sex, race/ethnicity, total cholesterol, HDL-C, SBP, diabetes, smoking pack years, hypertension treatment, statin use, and ln-volume score. Ppts = Participants.

Table 3.

CAC Density and Risk for CHD by Volume Cut-Point

	Volume ≤ 130 mm^3				Volume > 130 mm^3			
	Events / ppts	**HR**	**95% CI**	**P**	**Events / ppts**	**HR**	**95% CI**	**P**
Density, unitless	163/1982	0.57	0.43, 0.75	<0.001	255/1334	0.82	0.55, 1.22	0.34
Density Quartile, unitless								
Quartile 1 (1.0–2.5)	74/812	REF			4/22	--	--	--
Quartile 2 (2.5–3.1)	47/538	0.61	0.41, 0.90	0.013	55/293	REF		
Quartile 3 (3.1–3.5)	29/313	0.68	0.43, 1.10	0.12	103/515	0.96	0.68, 1.35	0.80
Quartile 4 (3.5–4.0)	13/319	0.29	0.16, 0.54	<0.001	93/504	0.86	0.60, 1.23	0.41

Adjusted for age, sex, race/ethnicity, total cholesterol, HDL-C, SBP, diabetes, smoking pack years, hypertension treatment, statin use, and ln-volume score. Ppts = participants.

Table 4.

Predictive Value of Volume and Density for CHD Risk

	HR per SD	95% CI	C-index	SE	NRI v Agatston (95% CI)	NRI events	NRI non-events
PCE	1.62	1.50, 1.75	0.666	0.013	--	--	--
PCE + ln(Agatston)	1.59 (Agatston)	1.42, 1.77	0.687	0.013	--	--	--
PCE + ln(Volume) + Density	1.95 (Volume) 0.73 (Density)	1.69, 2.25 0.63, 0.85	0.703	0.012	0.2082 (0.1020, 0.3064)	0.1427 (0.0614, 0.2142)	0.0654 (0.0217, 0.1119)

PCE = Pooled Cohort Equations