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The Association of Coronary Artery Calcium With Noncardiovascular Disease

The Multi-Ethnic Study of Atherosclerosis

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ABSTRACT

OBJECTIVES This study sought to determine if coronary artery calcium (CAC) is associated with incident noncardiovascular disease.

BACKGROUND CAC is considered a measure of vascular aging, associated with increased risk of cardiovascular and all-cause mortality. The relationship with noncardiovascular disease is not well defined.

METHODS A total of 6,814 participants from 6 MESA (Multi-Ethnic Study of Atherosclerosis) field centers were followed for a median of 10.2 years. Modified Cox proportional hazards ratios accounting for the competing risk of fatal coronary heart disease were calculated for new diagnoses of cancer, pneumonia, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), deep vein thrombosis/pulmonary embolism, hip fracture, and dementia. Analyses were adjusted for age; sex; race; socioeconomic status; health insurance status; body mass index; physical activity; diet; tobacco use; number of medications used; systolic and diastolic blood pressure; total and high-density lipoprotein cholesterol; antihypertensive, aspirin, and cholesterol medication; and diabetes. The outcome was first incident noncardiovascular disease diagnosis.

RESULTS Compared with those with CAC = 0, those with CAC >400 had an increased hazard of cancer (hazard ratio [HR]: 1.53; 95% confidence interval [CI]: 1.18 to 1.99), CKD (HR: 1.70; 95% CI: 1.21 to 2.39), pneumonia (HR: 1.97; 95% CI: 1.37 to 2.82), COPD (HR: 2.71; 95% CI: 1.60 to 4.57), and hip fracture (HR: 4.29; 95% CI: 1.47 to 12.50). CAC >400 was not associated with dementia or deep vein thrombosis/pulmonary embolism. Those with CAC = 0 had decreased risk of cancer (HR: 0.76; 95% CI: 0.63 to 0.92), CKD (HR: 0.77; 95% CI: 0.60 to 0.98), COPD (HR: 0.61; 95% CI: 0.40 to 0.91), and hip fracture (HR: 0.31; 95% CI: 0.14 to 0.70) compared to those with CAC >0. CAC = 0 was not associated with less pneumonia, dementia, or deep vein thrombosis/pulmonary embolism. The results were attenuated, but remained significant, after removing participants developing interim nonfatal coronary heart disease.

CONCLUSIONS Participants with elevated CAC were at increased risk of cancer, CKD, COPD, and hip fractures. Those with CAC = 0 are less likely to develop common age-related comorbid conditions, and represent a unique population of "healthy agers." (J Am Coll Cardiol Img 2016;■:■–■) © 2016 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CAC = coronary artery calcium
CHD = coronary heart disease
CI = confidence interval
CKD = chronic kidney disease
COPD = chronic obstructive pulmonary disease
CVD = cardiovascular disease
DVT = deep vein thrombosis
HR = hazard ratio
MESA = Multi-Ethnic Study of Atherosclerosis
PE = pulmonary embolism
SES = socioeconomic status

Over the last 4 decades, there has been a substantial decline in cardiovascular disease (CVD) mortality, partly from improved identification and modification of risk factors (1). The rate of non-CVD deaths has not declined as rapidly (2), resulting in CVD decreasing to the second leading cause of death in certain populations (3).

Coronary artery calcium (CAC) scoring is a noninvasive, direct measure of coronary atherosclerosis and powerful predictor of incident CVD and all-cause mortality (4). CAC scores increase with chronologic age (5). However, there is considerable heterogeneity within age groups (6) translating into an "equivalent" chronologic age varying up to 30 years (7). This potentially permits CAC scores to reclassify risk independent of age (8). Indeed, CAC retains a strong predictive value for all-cause mortality beyond age (9), raising the idea that CAC scores may provide a superior estimate of "arterial age" (10).

CAC scores have been associated with the presence of traditional risk factors and likely partially represent the cumulative burden of risk factor exposure. However, even those with no traditional CV risk factors can have elevated CAC scores and increased risk of CVD (11). Higher levels of CAC are also associated with an increased risk of death from non-CVD causes (12). This may be from higher incidences of other age-related diseases, such as cancer, which has been associated with very high CAC scores (13). There have been mixed results when examining the relationship between CAC and other non-CVDs, such as kidney disease (14,15) and decreased bone density (16,17).

To our knowledge, there have been no studies examining the relationship between CAC and other age-related diseases associated with significant morbidity and mortality, such as osteoporotic fractures, pneumonia, dementia, deep vein thrombosis (DVT), or pulmonary embolism (PE). We sought to evaluate whether CAC, as a marker of arterial age, is an independent predictor of non-CVD diagnoses. We hypothesized that having CAC = 0 would be associated with a low risk of disease and having elevated CAC would be associated with a higher burden of non-CVD.

METHODS

STUDY POPULATION. Participants were from MESA (Multi-Ethnic Study of Atherosclerosis) (18). MESA is a prospective, observational cohort of 6,814 people from 6 U.S. cities, between 45 and 84 years old and of diverse backgrounds, who were free of CVD and not under active cancer treatment. Baseline lifestyle characteristics and anthropometric measurements were measured at the initial examination. All participants with CAC scanning at baseline and follow-up data were eligible for inclusion. Institutional Review Board approval was obtained at each site. Each participant gave written informed consent (http://www.mesa-nhlbi.org).

CAC SCORE MEASUREMENTS. Detailed methods for computed tomography scan technique and interpretation were previously described (19). Chicago, Los Angeles, and New York used cardiac-gated electron-beam computed tomography scanning. The other sites used multidetector computed tomography scanning. At the baseline examination, each participant was scanned 2 consecutive times with mean Agatston score used for the analysis. All images were interpreted at a single center, with good intrareader and inter-reader agreement (kappa = 0.92).

FOLLOW-UP. Follow-up occurred every 9 to 12 months for a median of 10.2 years (mean 9.5 years; interquartile range: 9.7 to 10.7 years). New diagnoses were verified by review of hospital records and death certificates. Coronary heart disease (CHD)-related endpoints were adjudicated and classified by 2 physicians from the MESA mortality and morbidity review committee. Non-CVD diagnoses were abstracted from inpatient records by International Classification of Diseases-9 codes. Codes related to the following broader groups were included: chronic kidney disease (CKD) and indicators of end-stage renal failure, any malignant neoplasm, dementia, hip fracture, DVT or PE, pneumonia, and chronic obstructive pulmonary disease (COPD). A full list of codes used is in Online Table 1.

STATISTICAL ANALYSIS. We modeled CAC as a continuous and binary variable (present/absent and zero or >400). In accordance with prior reports, CAC was analyzed as a continuous variable using base-2 logarithm of coronary calcium score plus 1 (log2 [CAC+1]) to determine how the doubling of calcium score affects risk and to include those with CAC = 0 (20). There were no deviations from the linear assumption when modeling continuous CAC.

Baseline characteristics are presented by CAC stratum. Continuous variables are presented as mean ± SD, whereas categorical variables as the number with the attribute (percentage of total). Analysis of variance was used to test means across groups for normally distributed variables and Kruskal-Wallis for not normally distributed variables. Chi-square analysis was used to test differences in distributions for categorical variables.

The risk of each non-CVD diagnosis was analyzed individually and with a composite measure of the first occurrence of any one of the diagnoses. Raw proportions experiencing each diagnosis were calculated by CAC stratum and compared using chi-square analysis. Kaplan-Meier curves for non-CVD-free survival were constructed. Hazard ratios (HRs) and 95% confidence intervals (CIs) for non-CVD and CVD-free survival were then calculated for each CAC definition with sequentially adjusted modified Cox proportional hazards regression models. To account for the competing risk of a fatal CHD event, regression models were modified, which creates informative censoring because of the strong relationship between CAC and CHD. Other non-CVD diagnoses were not considered as competing risks.

Model 1 was unadjusted. In Model 2, analyses were adjusted for age, sex, race, health insurance status, and socioeconomic status (SES) using education and income level. Because age varied between CAC groups, additional strategies were used to limit residual confounding. For each outcome, sequential fractional polynomial terms for age were fit (using the flexible "fp" command in Stata [StataCorp, College Station, Texas]), and retained throughout all outcome-specific models if their inclusion resulted in significant improvement in model variance. An age^2 term was also empirically tested for each outcome; however, this did not further improve model fit beyond the best fit fractional polynomial age term. Additionally, age × CAC interaction terms were tested and retained for outcomes in which they were statistically significant.

Model 3 added adjustments for body mass index; physical activity; diet; and smoking status, including never, former, and current use and pack-years of smoking. Descriptions of physical activity and diet are included in the online supplement. Model 4 added the total number of medications used as a surrogate for burden of comorbid illness and access to care. Model 5 added adjustments for traditional cardiovascular risk factors including systolic and diastolic blood pressure, use of antihypertensive and lipid-lowering medications, total and high-density lipoprotein cholesterol, use of aspirin, and presence of diabetes.

Model 6 added a sensitivity analysis where participants with any nonfatal CHD event at or before the time of the non-CVD diagnosis were removed from the sample (Online Table 2). This accounted for the potential identification bias of a comorbid illness during an admission for CHD. Additional sensitivity analyses were performed stratifying by age category (< and ≥ 65). Statistical analysis was done using Stata 13 (StataCorp). A p value <0.05 was considered statistically significant.

RESULTS

BASELINE CHARACTERISTICS. Baseline characteristics are presented in Table 1. Among the 6,814 participants, 50.1% (n = 3,416) had CAC = 0, 39.9% (n = 2,721) had CAC scores 1 to 400, and 9.9% (n = 677) had CAC >400. The mean age was 62 years with 52.9% female, 38.5% Caucasian, 27.8% African American, 22% Hispanic, and 11.8% Chinese. Those with CAC = 0 were more likely to be younger, female, and more physically active.

TABLE 1 Baseline Characteristics of Participants by CAC Stratum

	All Participants (n = 6,814)	CAC = 0 (n = 3,416)	CAC 1-400 (n = 2,721)	CAC >400 (n = 677)	p Value
Age, yrs	62.15 ± 10.2	57.97 ± 9.1	65.32 ± 9.6	70.50 ± 7.8	<0.001
Female	3,601 (52.9)	2,167 (63.4)	1,232 (45.3)	202 (29.8)	<0.001
Race/ethnicity					<0.001
Caucasian	2,622 (38.5)	1,127 (33.0)	1,144 (42.0)	351 (51.9)	
Chinese	803 (11.8)	399 (11.7)	352 (12.9)	52 (7.7)	
African American	1,893 (27.8)	1,072 (31.4)	669 (24.6)	152 (22.5)	
Hispanic	1,496 (22.0)	818 (24.0)	556 (20.4)	122 (18.0)	
Socioeconomic status					
Completed high school	5,566 (82.0)	2,808 (82.6)	2,206 (81.3)	552 (81.7)	0.42
Income level	3,232 (49.4)	1,723 (52.3)	1,215 (46.6)	294 (45.9)	<0.001
% with no health insurance	609 (8.97)	379 (11.14)	204 (7.51)	26 (3.85)	<0.001
BMI, kg/m^2	28 ± 5.5	28 ± 5.7	28 ± 5.4	29 ± 5.0	0.49
Moderate and vigorous physical activity, MET-min/wk	5,749 ± 5,896	6,013 ± 5,822	5,596 ± 6,136	5,036 ± 5,166	<0.001
Healthy diet	2,824 (45.3)	1,340 (43.2)	1,176 (47.1)	308 (48.5)	0.004
Smoking status					<0.001
Never	3,418 (50.3)	1,905 (56.0)	1,248 (46.0)	265 (39.2)	
Former	2,487 (36.6)	1,045 (30.7)	1,113 (41.0)	329 (48.7)	
Current	887 (13.1)	451 (13.3)	354 (13.0)	82 (12.1)	
Pack-years of smoking	11.3 (20.9)	7.94 (16.5)	13.42 (22.58)	19.84 (28.64)	<0.001
Systolic blood pressure, mm Hg	127 ± 21	122 ± 21	130 ± 22	135 ± 22	<0.001
Diastolic blood pressure, mm Hg	72 ± 10	71 ± 10	72 ± 10	73 ± 10	<0.001
Total cholesterol, mg/dl	194 ± 35.7	194 ± 35.0	195 ± 36.2	192 ± 37.3	0.051
HDL-C, mg/dl	51 ± 14.8	53 ± 15.0	50 ± 14.4	49 ± 14.6	<0.001
Antihypertensive therapy	2,536 (37)	984 (29)	1,161 (43)	391 (58)	<0.001
Lipid-lowering therapy	1,100 (16)	360 (11)	543 (20)	197 (29)	<0.001
Average total number of medications	3.25 ± 2.9	2.90 ± 2.7	3.43 ± 2.9	4.26 ± 3.2	<0.001
Presence of diabetes	859 (12.7)	318 (9.4)	387 (14.3)	154 (22.9)	<0.001
Aspirin use	1,298 (19.9)	462 (14.2)	607 (23.1)	229 (35.5)	<0.001

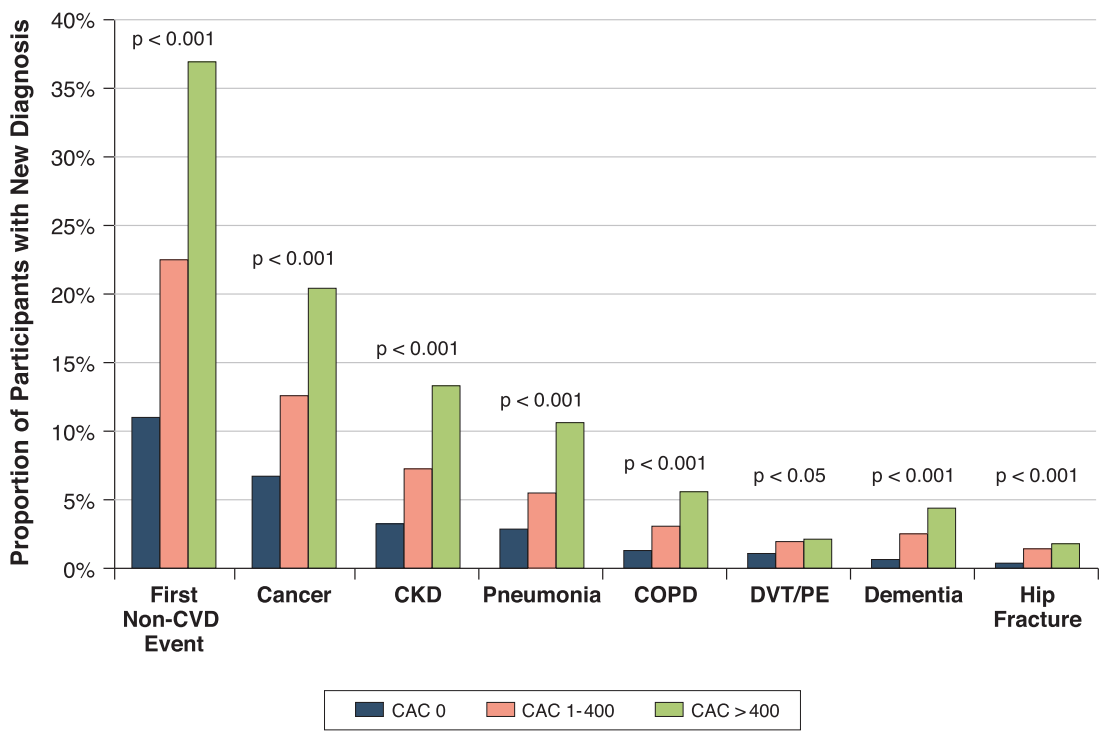
Values are mean ± SD or n (%).
BMI = body mass index; CAC = coronary artery calcium; HDL-C = high-density lipoprotein cholesterol.

CANCER. There were 710 new cancer diagnoses. The proportions of participants with cancer by CAC stratum were 6.67%, 12.6%, and 20.4% for CAC = 0, CAC 1 to 400, and CAC >400, respectively ($p < 0.001$) (Figure 1). Those with CAC >0 accounted for 67.9% of cancer cases. Unadjusted and adjusted HRs are in Tables 2 and 3. In multivariable-adjusted models (Model 5), a doubling of CAC score was associated with a 4% increased risk of cancer (HR: 1.04; 95% CI: 1.02 to 1.07) (Table 2). Those with CAC >400 had a 53% greater hazard of cancer compared with those with CAC = 0 (HR: 1.53; 95% CI: 1.18 to 1.99) (Table 3). Those with CAC = 0 had a lower hazard of being diagnosed when compared with those with CAC >0 (HR: 0.76; 95% CI: 0.63 to 0.92) (Table 4). Prostate cancer was the most common cancer diagnosed (21% of cancer cases), followed by lung cancer (14% of cancer cases), gastrointestinal/colon cancer (13% of cancer cases), breast cancer (10% of cancer cases), skin cancer (9% of cancer cases), hematologic malignancies (6% of cancer cases), and uterine/ovarian cancer (5% of cancer cases). After accounting for sex differences, there was no strong association between CAC score stratum and overall cancer type.

CHRONIC KIDNEY DISEASE. CKD was diagnosed in 395 participants. The proportion increased with increasing CAC stratum from 3.2% in participants with CAC = 0.0 to 13.3% in participants with CAC >400 ($p < 0.001$) (Figure 1). With adjustment for CVD risk factors, a doubling of CAC score remained significantly associated with an increased hazard of being diagnosed (HR: 1.07; 95% CI: 1.03 to 1.10) (Table 2). Those with CAC >400 were 70% more likely to develop CKD compared with those with CAC = 0 (HR: 1.70; 95% CI: 1.21 to 2.39) (Table 3) and those with CAC = 0 had a lower hazard of being diagnosed with CKD (HR: 0.77; 95% CI: 0.60 to 0.98) (Table 4).

PNEUMONIA. There were 315 cases of pneumonia. Proportions ranged from 2.8% when CAC = 0 to 10.6% in those with CAC >400 ($p < 0.001$) (Figure 1). In multivariable-adjusted models (Model 5), there

FIGURE 1 Proportion With Non-CVD by CAC Stratum



Proportion of participants within each CAC score stratum with any new non-CVD diagnosis and by each specific diagnosis. The **blue bars** represent CAC scores = 0, **pink bars** represent CAC scores of 1 to 400, and **green bars** represent CAC scores >400. CAC = coronary artery calcium; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; DVT = deep vein thrombosis; PE = pulmonary embolism.

TABLE 2 Hazard of New Non-CVD and CVD Diagnosis With Doubling of CAC Score

	$Log_2[CAC + 1]$				
	Model 1	**Model 2**	**Model 3**	**Model 4**	**Model 5**
Cancer	1.13 (1.11–1.15)	1.05 (1.02–1.07)	1.04 (1.01–1.06)	1.03 (1.01–1.06)	**1.04 (1.02–1.07)**
CKD	1.18 (1.15–1.20)	1.08 (1.05–1.12)	1.08 (1.04–1.11)	1.07 (1.04–1.10)	**1.07 (1.03–1.10)**
Pneumonia	1.17 (1.13–1.20)	1.08 (1.04–1.12)	1.07 (1.03–1.10)	1.06 (1.02–1.09)	**1.07 (1.03–1.11)**
DVT/PE	1.10 (1.06–1.13)	*1.04 (0.99–1.08)*	*1.01 (0.97–1.06)*	*1.01 (0.96–1.05)*	*1.03 (0.98–1.08)*
COPD	1.19 (1.14–1.24)	1.11 (1.05–1.16)	1.09 (1.04–1.15)	1.08 (1.03–1.14)	**1.10 (1.05–1.16)**
Dementia	1.23 (1.18–1.28)	1.05 (1.00–1.10)	1.06 (1.003–1.11)	1.06 (1.002–1.11)	**1.06 (1.01–1.12)**
Hip fracture	1.22 (1.14–1.29)	1.09 (1.003–1.18)	1.11 (1.02–1.20)	1.10 (1.01–1.20)	**1.10 (1.01–1.21)**
Any non-CVD	1.15 (1.14–1.17)	1.06 (1.04–1.08)	1.06 (1.04–1.08)	1.05 (1.03–1.07)	**1.06 (1.04–1.08)**
CVD	1.26 (1.23–1.28)	1.20 (1.17–1.23)	1.19 (1.16–1.22)	1.19 (1.16–1.22)	**1.17 (1.14–1.20)**

Statistically significant values are in **bold** for Model 5. Nonsignificant values are in **italics**. Cox proportional hazards ratios and 95% confidence intervals for non-CVD diagnoses comparing doubling of CAC score. Model 1: unadjusted. Model 2: age (best fit model, see Methods section), sex, race, health insurance status, and socioeconomic status (completed high school and income level). Model 3: Model 2 + body mass index, physical activity, diet, smoking status, and pack-years. Model 4: Model 3 + total medications used. Model 5: Model 4 + systolic blood pressure, diastolic blood pressure, antihypertensive medications, total cholesterol, high-density lipoprotein cholesterol, lipid-lowering medications, diabetes, and aspirin use.

CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; DVT = deep vein thrombosis; PE = pulmonary embolism; other abbreviations as in Table 1.

was a 7% increased hazard of being diagnosed with pneumonia with doubling of the CAC score (HR: 1.07; 95% CI: 1.03 to 1.11) (Table 2). Those with CAC >400 had 2 times the hazard of developing pneumonia compared with those with CAC = 0 (HR: 1.97; 95% CI: 1.37 to 2.82) (Table 3). Those with CAC = 0 did not have a significantly decreased risk of pneumonia (HR: 0.77; 95% CI: 0.58 to 1.01) when compared with those with CAC >0 (Table 4). This was associated in unadjusted models but lost after controlling for demographic and lifestyle factors (Model 3, Table 4).

DVT OR PE. DVT or PE was documented in 205 participants. Among those with CAC = 0, 1.1% were diagnosed, 1.9% in those with CAC = 1 to 400 and 2.1% in those with CAC >400 ($p < 0.05$) (Figure 1). In unadjusted models, doubling of CAC score and CAC >400 were associated with increased hazard of DVT or PE (1.10, 1.06 to 1.13; and 2.24, 1.50 to 3.35, respectively) (Tables 2 and 3, respectively). Having CAC = 0 was protective in unadjusted models (0.57, 0.44 to 0.75) (Table 4). These relationships were lost after controlling for age, sex, race, SES, and health insurance status (Tables 2 to 4). In multivariable adjusted models (Model 5), there was no association with a new diagnosis of DVT/PE and doubling of the CAC score (HR: 1.03; 95% CI: 0.98 to 1.08) (Table 2), having CAC >400 (HR: 1.07; 95% CI: 0.64 to 1.78)

TABLE 3 Hazard of New Non-CVD and CVD Diagnosis With CAC >400 Compared With Those With CAC = 0

	CAC >400 Versus CAC = 0				
	Model 1	**Model 2**	**Model 3**	**Model 4**	**Model 5**
Cancer	3.60 (2.95–4.41)	1.64 (1.29–2.07)	1.49 (1.16–1.92)	1.45 (1.13–1.86)	**1.53 (1.18–1.99)**
CKD	4.57 (3.55–5.89)	2.00 (1.47–2.74)	1.93 (1.39–2.70)	1.75 (1.27–2.43)	**1.70 (1.21–2.39)**
Pneumonia	4.72 (3.53–6.30)	2.16 (1.54–3.02)	1.88 (1.33–2.68)	1.71 (1.21–2.41)	**1.97 (1.37–2.82)**
DVT/PE	2.24 (1.50–3.35)	*1.26 (0.80–2.00)*	*0.89 (0.54–1.47)*	*0.86 (0.52–1.41)*	*1.07 (0.64–1.78)*
COPD	5.50 (3.64–8.32)	2.69 (1.61–4.50)	2.45 (1.44–4.18)	2.17 (1.30–3.64)	**2.71 (1.60–4.57)**
Dementia	6.45 (4.14–10.05)	*1.33 (0.81–2.19)*	*1.47 (0.88–2.47)*	*1.48 (0.87–2.50)*	*1.61 (0.93–2.79)*
Hip fracture	8.74 (3.93–19.45)	3.18 (1.19–8.50)	4.16 (1.48–11.73)	3.91 (1.39–10.97)	**4.29 (1.47–12.50)**
Any non-CVD	4.16 (3.58–4.84)	1.88 (1.57–2.24)	1.78 (1.47–2.15)	1.69 (1.40–2.04)	**1.80 (1.48–2.18)**
CVD	9.52 (7.65–11.86)	6.01 (4.65–7.77)	5.44 (4.16–7.10)	5.11 (3.91–6.67)	**4.45 (3.36–5.88)**

Statistically significant values are in **bold** for Model 5. Nonsignificant values are in **italics**. Cox proportional hazards ratios and 95% confidence intervals for non-CVD diagnoses comparing those with CAC >400 with those with CAC = 0. Model 1: unadjusted. Model 2: age (best fit model, see Methods section), sex, race, health insurance status, and socioeconomic status (completed high school and income level). Model 3: Model 2 + body mass index, physical activity, diet, smoking status, and pack-years. Model 4: Model 3 + total medications used. Model 5: Model 4 + systolic blood pressure, diastolic blood pressure, antihypertensive medications, total cholesterol, high-density lipoprotein cholesterol, lipid-lowering medications, diabetes, and aspirin use.

Abbreviations as in Tables 1 and 2.

TABLE 4 Hazard of New Non-CVD Diagnosis for Those With CAC = 0 Compared With Those With CAC >0

	CAC = 0 Versus CAC >0				
	Model 1	Model 2	Model 3	Model 4	Model 5
Cancer	0.44 (0.38–0.51)	0.75 (0.64–0.89)	0.77 (0.64–0.92)	0.79 (0.66–0.94)	**0.76 (0.63–0.92)**
CKD	0.38 (0.31–0.46)	0.69 (0.55–0.86)	0.71 (0.56–0.90)	0.74 (0.58–0.94)	**0.77 (0.60–0.98)**
Pneumonia	0.40 (0.32–0.50)	0.71 (0.55–0.92)	*0.78 (0.60–1.02)*	*0.82 (0.62–1.06)*	*0.77 (0.58–1.01)*
DVT/PE	0.57 (0.44–0.75)	*0.85 (0.62–1.17)*	*1.01 (0.73–1.41)*	*1.04 (0.75–1.45)*	*0.94 (0.66–1.33)*
COPD	0.32 (0.23–0.45)	0.56 (0.38–0.81)	0.64 (0.43–0.96)	*0.69 (0.46–1.03)*	**0.61 (0.40–0.91)**
Dementia	0.26 (0.18–0.38)	*0.87 (0.59 to1.30)*	*0.81 (0.54–1.21)*	*0.80 (0.53–1.21)*	*0.76 (0.49–1.17)*
Hip fracture	0.17 (0.09–0.33)	0.37 (0.17–0.78)	0.30 (0.14–0.67)	0.31 (0.14–0.69)	**0.31 (0.14–0.70)**
Any non-CVD	0.41 (0.36–0.45)	0.71 (0.63–0.81)	0.74 (0.65–0.85)	0.76 (0.66–0.87)	**0.75 (0.65–0.86)**
CVD	0.21 (0.17–0.25)	0.31 (0.26–0.39)	0.34 (0.27–0.42)	0.35 (0.28–0.43)	**0.38 (0.30–0.47)**

Statistically significant values are in **bold** for model 5. Nonsignificant values are in **italics**. Cox proportional hazards ratios and 95% confidence intervals for non-CVD diagnoses comparing those with CAC = 0 to those with CAC >0. Model 1: unadjusted. Model 2: age (best fit model, see the Methods section), sex, race, health insurance status, and socioeconomic status (completed high school and income level). Model 3: Model 2 + body mass index, physical activity, diet, smoking status, and pack-years. Model 4: Model 3 + total medications used. Model 5: Model 4 + systolic blood pressure, diastolic blood pressure, antihypertensive medications, total cholesterol, high-density lipoprotein cholesterol, lipid-lowering medications, diabetes, and aspirin use.

Abbreviations as in Tables 1 and 2.

(Table 3), or having CAC = 0 (HR: 0.94; 95% CI: 0.66 to 1.33) (Table 4).

CHRONIC OBSTRUCTIVE PULMONARY DISEASE. During follow-up, 161 participants were diagnosed with COPD. Proportions increased with increasing CAC score stratum from 1.2% in those with CAC = 0 to 5.6% in those with CAC >400 ($p < 0.001$) (Figure 1). In Model 5, doubling of CAC score was associated with a 10% increased hazard of COPD (HR: 1.10; 95% CI: 1.05 to 1.16) (Table 2). Those with CAC >400 were 2.7 times more likely than those with CAC = 0 (HR: 2.71; 95% CI: 1.60 to 4.57) to have a new diagnosis of COPD (Table 3). Those with CAC = 0 were approximately half as likely to be diagnosed compared with those with any CAC (HR: 0.61; 95% CI: 0.40 to 0.91) (Table 4).

DEMENTIA. Dementia was diagnosed in 119 participants and had increasing proportions with higher CAC stratum from 0.61% to 4.43% ($p < 0.001$) (Figure 1). After multivariable adjustment, doubling of the CAC score was associated with a 6% increased risk (HR: 1.06; 95% CI: 1.01 to 1.12) (Table 2). Comparing those with CAC >400 with those with CAC = 0, unadjusted models showed an increased HR of 6.45 (95% CI: 4.14 to 10.05) (Table 3). This relationship was lost when controlling for age, sex, race, SES, and health insurance status (Model 2, Table 3). Similarly, those with CAC = 0 compared with those with CAC >0 had a significant association in unadjusted models (HR: 0.26; 95% CI: 0.18 to 0.38) but this was lost when controlling for age, sex, race, SES, and health insurance status (Model 2, Table 4).

HIP FRACTURES. Hip fractures were the least common with 59 cases. Proportions diagnosed by CAC category ranged from 0.26% when CAC = 0 to 1.77% in those with CAC >400 ($p < 0.001$) (Figure 1). In multivariable adjusted models, doubling of CAC was associated with a 10% increased risk of events (1.01 to 1.21) (Table 2). Participants with CAC >400 had a higher risk of hip fracture in multivariable adjusted modeling (Model 5) (HR: 4.29; 95% CI: 1.47 to 12.5) (Table 3). Participants with CAC = 0 had a 69% lower risk of hip fracture in multivariable adjusted modeling (HR: 0.31; 95% CI: 0.14 to 0.70) (Table 4).

AGGREGATE OUTCOME OF FIRST ANY NON-CVD DIAGNOSIS. There were 1,238 first non-CVD diagnoses. The proportion of the first occurrence of any one of these was 11.0% for CAC = 0, 22.5% for CAC = 1 to 400, and 36.9% for CAC >400 ($p < 0.001$) (Figure 2). In multivariable adjusted models, doubling of the CAC score was associated with a 6% increased risk of any non-CVD diagnosis (HR: 1.06; 95% CI: 1.04 to 1.08) (Table 2). Those with CAC score >400 were 1.80 times more likely to be diagnosed with any non-CVD compared with those with CAC = 0 (HR: 1.80; 95% CI: 1.48 to 2.18) (Table 3). Participants with CAC = 0 had a lower rate of non-CVD compared with those with CAC >0 (HR: 0.75; 95% CI: 0.65 to 0.86) (Table 4). Kaplan-Meier curves for the composite and individual outcomes are shown in Online Figure 1.

SENSITIVITY ANALYSIS. The results of the sensitivity analysis are in Online Table 2. Results were attenuated, with similar overall conclusions after removing participants with an interim or concurrent nonfatal CHD event at the time of diagnosis of the non-CV disease. New diagnoses of cancer, CKD, COPD, and any-non CVD event remained associated with doubling of CAC score (Online Table 2).

AGE STRATIFICATION. Results of age stratified analysis are presented in Table 5. In participants ≥65, doubling of the CAC score was associated with an increased hazard of cancer (HR: 1.04; 95% CI: 1.01 to 1.07), CKD (HR: 1.07; 95% CI: 1.03 to 1.11), pneumonia (HR: 1.08; 95% CI: 1.03 to 1.13), COPD (HR: 1.09; 95% CI: 1.03 to 1.16), and the composite outcome (HR: 1.06; 95% CI: 1.04 to 1.08). Limited power prevented detailed analysis of modeling in those <65, although point estimates were similar with nonsignificant interaction with the age < or ≥65 term.

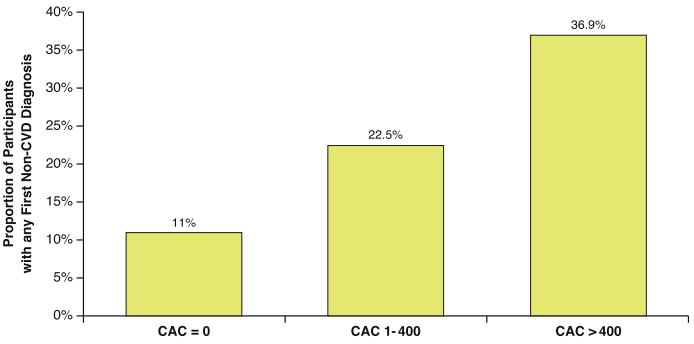
DISCUSSION

Our results demonstrate that CAC scores are associated with non-CVD diagnoses, notably cancer, CKD, COPD, and hip fractures. Participants with CAC scores >400 had a 53% adjusted increased hazard of cancer diagnosis, 70% increased hazard of CKD diagnosis, 197% increased hazard of developing pneumonia, 271% increased hazard of COPD diagnosis, and 429% increased hazard of hip fracture. Participants with CAC = 0 (50% of the population) seemed at reduced risk of non-CVD, independent of known CVD risk factors. Although these results were attenuated when excluding patients with interim nonfatal CHD events, overall conclusions remained unchanged. Taken together, higher CAC scores were highly associated with the initial development of any first non-CVD diagnosis. From a public health perspective, it is notable that 20% of the first occurrences of a non-CVD event occurred in the 10% of patients with CAC >400 and 70% of the events were in those with CAC >0.

Strengths of our analysis include the large sample, multiethnic makeup, detailed baseline risk factor assessment, and the use of a competing risk model, which is important given the known association of CAC with fatal CHD. In addition, rather than assuming a linear association, we allowed flexible modeling of age to achieve the best fit and thus limit residual confounding from age.

It is important to consider the possible mechanisms underlying these results. CAC per se is unlikely to be causally associated with non-CVD. In general, CAC is considered to be a risk integrator, and may reflect lifetime exposure to both measured and unmeasured risk factors shared in common between CVD and non-CVD outcomes (21). It may also represent a common underlying vulnerability to the development of tissue injury at sites with varying relationships to the cardiovascular system. As such, the CAC score may be one marker of an individual's risk of future disease burden.

FIGURE 2 Proportion With Any Non-CVD



	CAC = 0 vs CAC > 0	CAC > 400 vs CAC = 0
Unadjusted HR (95% CI)	0.41 (0.36, 0.45)	4.16 (3.58, 4.84)
Multivariable adjusted HR (95% CI)	0.75 (0.65, 0.86)	1.80 (1.48, 2.18)

Proportion of participants with any non-CVD diagnosis along with unadjusted (Model 1) and multivariable adjusted (Model 5) Cox proportional hazards ratios, adjusted for the competing risk of fatal coronary heart disease (95% CIs). Multivariable model was adjusted for age (best fit, see Methods section), sex, race, socioeconomic status, health insurance status, smoking status and pack-years of smoking, body mass index, physical activity, diet, total number of medications used, systolic and diastolic blood pressure, antihypertensive medication use, total and high-density lipoprotein cholesterol, lipid-lowering medication and aspirin use, and presence of diabetes. CI = confidence interval; HR = hazard ratio; other abbreviations as in Figure 1.

Pneumonia was not associated with CAC scores in models removing individuals with an interim nonfatal CHD event, suggesting it may be a more acute event that is more likely to be an incidental codiagnosis during the inpatient care for, or related to complications of, a CHD event. Furthermore, DVT/PE were weakly associated with CAC and are well known to have a variety of more acute-onset risk factors, including trauma and surgery (22), which could be less related to CVD and arterial aging. Dementia likely had too few cases to confirm an association with CAC given the large CI.

IMPLICATIONS. We hypothesized that CAC scores could be a surrogate measure of arterial aging and identify those at increased risk of age-related, non-CV disease. CAC has been described as a measure of so-called "biologic age" (7), supported by studies showing absolute CAC scores as better predictors of CVD events than age alone (10). Our results support CAC as a marker for other age-related diseases and support limited prior findings showing an association between elevated CAC scores and non-CV diseases including cancer (13) and COPD (23). Although CAC has been shown to be associated with all-cause mortality (24–26), this association may be driven by

TABLE 5 Age-Stratified Analysis of the Doubling of CAC Score

	Log2[CAC + 1]	
	Age <65 Yrs	Age ≥65 Yrs
Cancer	*1.04 (1.00–1.09)*	**1.04 (1.01–1.07)**
CKD	*1.05 (0.98–1.12)*	**1.07 (1.03–1.11)**
Pneumonia	*1.04 (0.97–1.11)*	**1.08 (1.03–1.13)**
DVT/PE	*1.03 (0.95–1.11)*	*1.02 (0.96–1.08)*
COPD	*1.12 (1.00–1.25)*	**1.09 (1.03–1.16)**
Dementia	—	*1.06 (1.00–1.12)*
Hip fracture	*1.15 (0.94–1.41)*	*1.09 (0.99–1.20)*
Any non-CVD event	*1.04 (1.00–1.07)*	**1.06 (1.04–1.08)**
CVD	**1.19 (1.14–1.24)**	**1.16 (1.12–1.20)**

Statistically significant values are in **bold**. Nonsignificant values are in ***italics***. Cox proportional hazards ratios (and 95% confidence intervals) for those <65 and those ≥65 years of age. Model is adjusted for age (best fit, see the Methods section), sex, race, health insurance status, socioeconomic status (completed high school and income level), body mass index, physical activity, diet, smoking status and pack-years, total number of medications used, systolic blood pressure, diastolic blood pressure, antihypertensive medications, total cholesterol, high-density lipoprotein cholesterol, lipid-lowering medications, diabetes, and aspirin use. The interaction of CAC with age < or ≥ 65 years was not significant.

Abbreviations as in Tables 1 and 2.

both cardiovascular and select noncardiovascular causes. The risk ratio of cardiovascular versus non-CVD diagnoses likely varies as a function of the CAC score and future mortality studies may benefit from ascertainment of cause of death and modeling the risk of both cardiovascular and noncardiovascular causes.

An important finding is that people with CAC = 0 seem to be protected from CVD and other chronic diseases. These "healthy agers" are at very low risk of CVD and non-CVD morbidity and mortality (24,27,28). There are broad implications to identifying and studying such people in the population. These people are extremely unlikely to be high users of healthcare services because of the decreased risk of comorbidities. In contrast, those with elevated CAC are at high risk of developing multiple chronic conditions and are likely to require increased services. These findings, which mirror the observation that individuals with multiple chronic conditions use a disproportionate share of health care resources (29), have marked implications for patient-centered medical homes, accountable care organizations, insurers, public health officials, and other stakeholders in the distribution of health care resource expenditures.

STUDY LIMITATIONS. New non-CVD diagnoses in MESA were obtained via International Classification of Disease hospital coding and therefore must be interpreted as time-to-diagnosis, not necessarily time-to-disease onset. This would mostly affect the diagnoses of cancer, COPD, and CKD, which could be detected before hospitalization. Furthermore, by using inpatient codes, there may be bias toward capturing severe cases and missing milder cases that are exclusively managed in the outpatient setting. Additionally, outcome ascertainment was administrative and does not represent systematically adjudicated events as is the case for CVD-related outcomes in MESA.

The numbers of participants with hip fractures, DVT/PE, and dementia were small and our study may not be powered to firmly establish the relationship. Further studies of these outcomes are needed, perhaps leveraging electronic medical record and claims files databases that would allow examination of a larger sample of patients. In addition, follow-up time in MESA may not be sufficient for detecting risk in participants with the lowest CAC scores. At this time, our data are not powered for stratifying results based on sex or race.

CONCLUSIONS

Elevated CAC scores are associated with age-related diseases including cancer, COPD, CKD, and hip fractures. Those with CAC = 0 are less likely to develop common age-related comorbid conditions, and represent a unique population of "healthy agers."

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: CAC scoring is a noninvasive, direct measure of coronary atherosclerosis.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: CAC retains a strong predictive value for cardiovascular and noncardiovascular disease events beyond age.

TRANSLATIONAL OUTLOOK: People with CAC = 0 seem to be protected from multiple chronic noncardiovascular diseases.

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APPENDIX For supplemental tables and figures, please see the online version of this article.