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### Authors

Blaha, Michael J  
Whelton, Seamus P  
Rifai, Mahmoud Al  
et al.

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## Research paper

## Rationale and design of the coronary artery calcium consortium: A multicenter cohort study

Michael J. Blaha<sup>a,\*</sup>, Seamus P. Whelton<sup>a</sup>, Mahmoud Al Rifai<sup>a</sup>, Zeina A. Dardari<sup>a</sup>,  
 Leslee J. Shaw<sup>b</sup>, Mouaz H. Al-Mallah<sup>c</sup>, Kuni Matsushita<sup>d</sup>, John A. Rumberger<sup>e</sup>,  
 Daniel S. Berman<sup>f</sup>, Matthew J. Budoff<sup>g</sup>, Michael D. Miedema<sup>h</sup>, Khurram Nasir<sup>a,i</sup>

<sup>a</sup> Johns Hopkins Ciccarone Center for Prevention of Heart Disease, Baltimore, MD, United States<sup>b</sup> Department of Medicine, Emory University School of Medicine, Atlanta, GA, United States<sup>c</sup> King Abdul-Aziz Cardiac Center, Riyadh, Saudi Arabia<sup>d</sup> Department of Epidemiology, Welch Center for Prevention, Epidemiology, and Clinical Research, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, United States<sup>e</sup> Princeton Longevity Center, Princeton, NJ, United States<sup>f</sup> Department of Imaging, Cedars-Sinai Medical Center, Los Angeles, CA, United States<sup>g</sup> Department of Medicine, Harbor UCLA Medical Center, Los Angeles, CA, United States<sup>h</sup> Minneapolis Heart Institute, Abbott Northwestern Hospital, Minneapolis, MN, United States<sup>i</sup> Center for Prevention and Wellness, Baptist Health South Florida, Miami, FL, United States

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## ABSTRACT

**Background:** Although coronary artery calcium (CAC) has been investigated for over two decades, there is very limited data on the association of CAC with cause of death. The CAC Consortium is a large ongoing multi-center observational cohort of individuals who underwent non-contrast cardiac-gated CAC testing and systematic, prospective, long-term follow-up for mortality with ascertainment of cause of death.

**Methods:** Four participating institutions from three states within the US (California, Minnesota, and Ohio) have contributed individual-level patient data to the CAC Consortium (spanning years 1991–2010). All CAC scans were clinically indicated and physician-referred in patients without a known history of coronary heart disease. Using strict inclusion and exclusion criteria to minimize missing data and to eliminate non-dedicated CAC scans (i.e. concomitant CT angiography), a sharply defined and well-characterized cohort of 66,636 patients was assembled. Mortality status was ascertained using the Social Security Administration Death Master File and a validated algorithm. In addition, death certificates were obtained from the National Death Index and categorized using ICD (International Classification of Diseases) codes into common causes of death.

**Results:** Mean patient age was  $54 \pm 11$  years and the majority were male (67%). Prevalence of CVD risk factors was similar across sites and 55% had a <5% estimated 10-year atherosclerotic cardiovascular disease (ASCVD) risk. Approximately 45% had a Calcium score of 0 and 11% had an Agatston Score  $\geq 400$ . Over a mean follow-up of  $12 \pm 4$  years, there were 3158 deaths (4.15 per 1000 person-years). The majority of deaths were due to cancer (37%) and CVD (32%). Most CVD deaths were due to CHD (54%) followed by stroke (17%). In general, CAC score distributions were similar across sites, and there were similar cause of death patterns.

**Conclusions:** The CAC Consortium is large and highly generalizable data set that is uniquely positioned to expand the understanding of CAC as a predictor of mortality risk across the spectrum of disease states, allowing innovative modeling of the competing risks of cardiovascular and non-cardiovascular death.

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## 1. Introduction

Coronary artery calcium (CAC) scanning is a non-invasive test using non-contrast cardiac-gated computed tomography to assess

\* Corresponding author.

E-mail address: [mblaha1@jhmi.edu](mailto:mblaha1@jhmi.edu) (M.J. Blaha).

the presence and burden of subclinical coronary atherosclerosis. It is well-established that increasing levels of CAC are strongly associated with risk of coronary heart disease (CHD).<sup>1,2</sup> This is thought to be due to the fact that CAC integrates the cumulative lifetime effects of both measured and non-measurable risk factors, accounting for individual vulnerability to these risk determinants, via the direct representation of accumulated damage within the coronary vascular bed.<sup>3</sup> Accordingly, CAC can be considered a measure of arterial aging.<sup>4</sup>

Of interest, CAC may predict risk beyond the coronary arteries. New data suggests that CAC is also an independent predictor of stroke,<sup>5</sup> dementia,<sup>6</sup> as well as non-cardiovascular outcomes like cancer, chronic kidney disease, chronic obstructive pulmonary disease, and potentially hip fracture.<sup>7</sup> Recent research has also suggested existence of a “healthy aging” phenotype characterized by individuals with persistently absent CAC. These individuals may be protected against a variety of chronic age-related diseases.<sup>8</sup> Therefore, the interpretation of CAC has been extended to an estimate of overall “biologic age”.

While the association of CAC with non-fatal cardiovascular disease (CVD) and all-cause mortality is well-described, the association of CAC with specific causes of death remains unknown. In older adult populations, it becomes increasingly important to model competing causes of death, such as cancer and CVD, as they share some common risk factors.<sup>9</sup> These relationships have public health importance, as decisions regarding healthcare resource allocation are driven by a common goal of improving longevity, prioritizing focused healthcare spending on an individual’s most likely causes of future morbidity and mortality.

The CAC Consortium project was initiated to address several gaps in the CAC literature. First, there is limited data on the association of CAC with specific causes of mortality. Second, there exists a need to describe the association of CAC with cardiovascular vs. non-cardiovascular mortality throughout the spectrum of subclinical disease burden. Third, there is a need to describe the risk association of CAC in important subgroups that have been underrepresented in previous studies, particularly the very young and the elderly and those with very high CAC scores. Finally, there is an ongoing need to describe the long-term implications of CAC, as most prior studies had follow-up of less than 10 years.

This article describes the design and methods used to develop the CAC Consortium, as well as general results from the cohort.

## 2. Methods

### 2.1. Overall study design

The CAC Consortium is an investigator-initiated initiative that is comprised of four participating institutions in the United States, all of which have long-standing expertise in CAC scanning and interpretation. The overall design is a retrospectively assembled observational real-world cohort study of participants 18 years and older who underwent a clinically indicated CAC scan after physician referral. Emphasis was placed on long follow-up, and therefore only CAC scans prior to the year 2010 were considered for this initial iteration of the cohort. A strong emphasis was placed on inclusion of only asymptomatic individuals free of known CHD.

Each institution contributed individual patient-level data on demographics, cardiovascular risk factors, medications, and symptoms which were collected at the clinical visit associated with the referral for CAC testing, from a semi-structured in-person interview at the time of the CAC scan, and/or from established diagnosis recorded in the electronic medical record (EMR). Consent for participation in research was collected at the individual centers at the time of CAC scanning, and IRB approval for coordinating

center activities including death ascertainment was obtained at the Johns Hopkins Hospital.

### 2.2. Study objectives

The overarching goal of the CAC Consortium was to provide a framework for harmonizing clinical data into the largest, most generalizable cohort yet assembled. The primary objective of phase 1 of the CAC Consortium was to describe the association between CAC and long-term cause-specific mortality, including modeling the competing risks of cardiovascular vs. non-cardiovascular mortality and the specific relative association between CVD and cancer mortality. Secondary objectives of this first phase include the following: (1) to examine the association between CAC and CVD mortality in understudied subgroups including women, individuals with diabetes, and those at the extremes of age; (2) to study the incremental value of the regional distribution of CAC; (3) to describe the association of extracoronary calcification with cause-specific mortality, including stroke mortality; (4) to examine the association of CAC lesion count and density with CVD risk; and (5) to describe potential temporal changes and cohort effects in the impact of CAC on risk over time.

### 2.3. Target population

The target population for the CAC Consortium was adult patients who were asymptomatic and without known CHD at the time of scanning. Possibly or partially symptomatic patients were excluded from the final data set. A prior history of CHD was defined as history of myocardial infarction, obstructive coronary artery disease, percutaneous coronary intervention, or coronary artery bypass surgery. All CAC scans were physician referred and clinically indicated for cardiovascular risk stratification; only dedicated CAC scans (i.e. not performed in the context of coronary CT angiography or other testing) were targeted for inclusion in the CAC Consortium.

### 2.4. Study outcomes

The primary outcome of the CAC Consortium is cause-specific mortality, with first-order categorization into CVD mortality (inclusive of CHD, stroke, heart failure, and other cardiovascular mortality) and non-CVD mortality (cancer, pulmonary disease, gastrointestinal disease, nervous system disorders, endocrine/metabolic disease, injury and poisoning, or other). Death certificates have been catalogued for all patients, allowing further analysis of specific underlying causes of death as well as supporting causes of death.

### 2.5. Eligibility criteria

#### 2.5.1. Site eligibility criteria

To be eligible to contribute patients to the CAC Consortium, participating sites were required to: 1) Have a CAC scanning program for at least 10 years (to emphasize long-term patient follow-up); 2) Provide individual patient-level data; 3) Contribute at least 5000 patients; 4) Have complete patient identifiers and complete or near-complete collection (>90% of all required fields) of patient demographics and cardiovascular risk factors.

#### 2.5.2. Patient eligibility criteria

Patients were included if: 1) they were  $\geq 18$  years of age, 2) were asymptomatic, 3) had no known CHD at the time of the CAC scan, and 4) had a CAC scan with an Agatston score. Patients were excluded if they: 1) had a non-dedicated CAC scan ( $n = 4669$ ), 2) had another concomitant non-CAC CT scan (for example lung CT,

( $n = 4833$ ), 3) were missing complete CAC scan identifiers ( $n = 2650$ ), 4) had an improbable date of birth ( $n = 150$ ), or 5) had an improbable scan date ( $n = 11$ ). Of the resulting 76,986 patients, an additional 10,320 were excluded due to insufficient data for algorithmic death ascertainment. The final complete study population consisted of 66,636 patients (Fig. 1). In addition, we identified a subcohort of 56,208 patients in whom we cross-validated our death ascertainment using a stricter algorithmic death ascertainment. This subcohort is available for sensitivity analysis requiring the most precise mortality rates.

## 2.6. Study sites

Four sites were included in the CAC Consortium: Cedars-Sinai Medical Center, Los Angeles, CA ( $n = 13,972$ , years 1998–2010); PrevaHealth Wellness Diagnostic Center, Columbus, OH ( $n = 7,042$ , 1999–2003); Harbor-UCLA Medical Center, Torrance, CA ( $n = 25,563$ , 1991–2008); and Minneapolis Heart Institute, Minneapolis, MN ( $n = 20,059$ , 1999–2005). Scans at each site were performed consecutively and interpreted locally by experienced readers.

## 2.7. Definition of risk factors

Patient information including risk factor and laboratory data

were collected as part of the routine clinical visit and/or at the time of the CAC scan. Hypertension was considered present if there was a prior diagnosis of hypertension or treatment with anti-hypertensive therapy. Blood pressure taken at the time of CT scanning was not used to override a diagnosis of hypertension. Dyslipidemia was defined as a prior diagnosis of primary hyperlipidemia, prior diagnosis of dyslipidemia (elevated triglycerides and/or low HDL-C), or treatment with any lipid-lowering drug. In patients with concomitant laboratory data, dyslipidemia was additionally considered present if LDL-C  $>160$  mg/dL, HDL-C  $<40$  mg/dL in men and  $<50$  mg/dL in women, or fasting triglycerides  $>150$  mg/dL. Smoking status was categorized as never, former, or current smoking. Diabetes was defined as a prior diagnosis of diabetes or treatment with oral hypoglycemic drugs or insulin. Family history of CHD was predominantly determined by the presence of a first degree relative with a history of CHD, however the Columbus, OH site used a definition of premature family history ( $<55$  years in old in a male relative and  $<65$  years old in a female relative).

Multiple imputation was conducted in the case of partially missing risk factor data (28% of cohort). Missing risk factors were imputed using a multivariable model adjusting for age, sex, race, CAC score, and the remaining non-missing traditional risk factors.

The 10-year ASCVD risk score, which requires lipid levels and blood pressure measurements, was calculated in all patients using

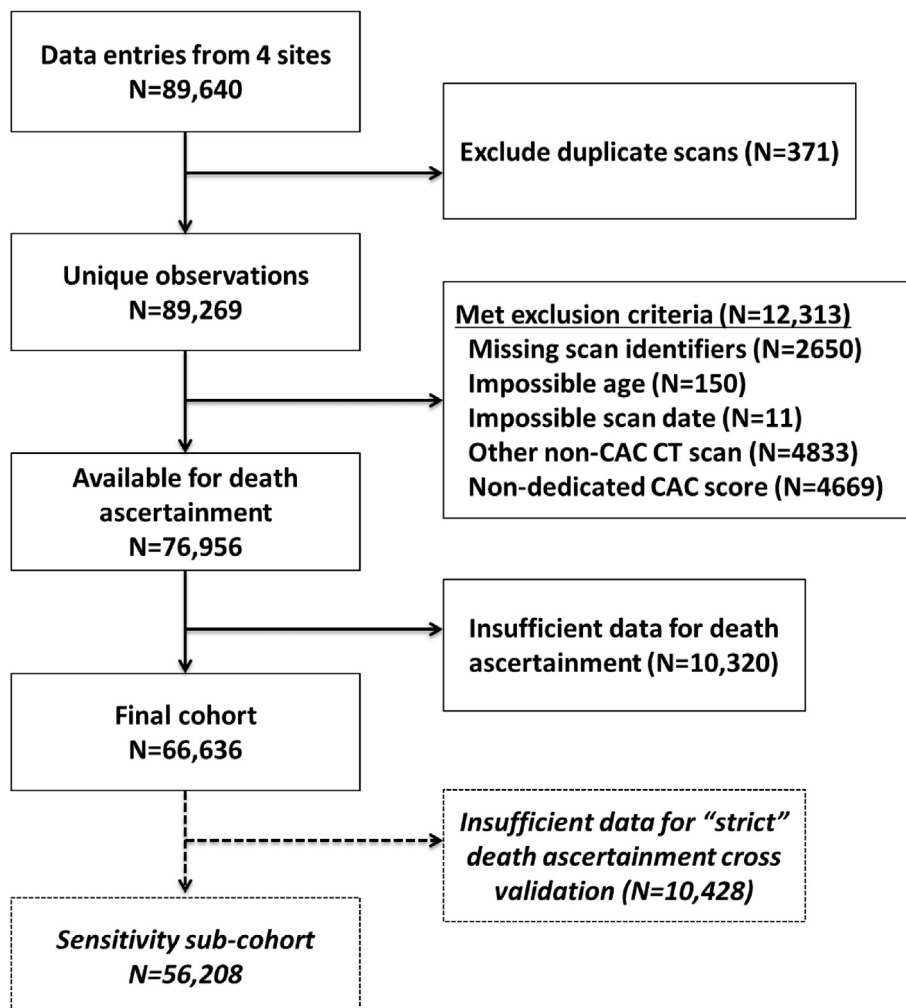


Fig. 1. Study design.

the Pooled Cohort Equations.<sup>10</sup> In the event of missing continuous data for lipid and blood pressure measurements, we used simple rule-based imputation leveraging the relevant non-missing lipid, blood pressure, and binary risk factor data from remainder of the dataset as well average blood pressure and lipid data from analogous subgroups in MESA (see [Supplemental Methods](#)). The following protocol was used for the purposes of estimating 10-year ASCVD risk: For an untreated dyslipidemic patient, total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C) were imputed as 220 mg/dL and 40 mg/dL respectively, and for non-dyslipidemic patients as 190 mg/dL and 60 mg/dL. Treated dyslipidemic patients were imputed as a TC of 180 mg/dL and HDL-C of 50 mg/dL. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were imputed as 150 mmHg and 90 mmHg respectively if the patient had untreated hypertension, 135 mmHg and 85 mmHg for treated hypertension, and 120 mmHg and 80 mmHg for normotensive patients. A complete validation of this approach within the non-missing CAC Consortium data, including mean and median ASCVD risk scores and relevant ASCVD risk reclassification statistics, is shown in the [Supplemental Methods](#). Within the CAC Consortium, these methods produce nearly identical mean and median ASCVD risk score values (9.3% vs. 9.4% and 5.0% vs. 4.9%, respectively) and an overall correlation coefficient of 0.952 between the imputed and directly calculated scores. Using conventional ASCVD risk group cutpoints, the imputed risk score leads to reclassification of 13.1% of patients, with equivalent movement upwards and downwards within the risk spectrum. The C-statistic for predicting all-cause mortality was similar between the imputed risk score and directly calculated risk score (0.790 vs. 0.781, see [Supplemental Methods](#)).

## 2.8. Computed tomography data

Non-contrast cardiac-gated CT scans for CAC scoring were performed at each individual site according to a common standard protocol for each scanner technology. CAC was quantified using the Agatston method in all patients. Most patients were scanned using electron beam tomography (EBT, approximately 93% of scans), while more recent CAC data at two sites was obtained using multi-detector CT (MDCT, approximately 7% of scans). Prior studies have demonstrated no clinically meaningful differences between CAC score derived from EBT versus MDCT scanners.<sup>11</sup> In total, approximately 13% of patients were scanned with the Imatron C-100 scanner, 38% with the C-150, 38% with the C-300, and 3.5% with the e-Speed scanner (GE-Imatron). The remaining scans (7%) were performed on a 4-slice MDCT scanner (Somatom Volume Zoom, Siemens Medical Solutions) and the General Electric LightSpeed VCT 64-slice platform (GE Healthcare).

Vessel-specific Agatston scores were available in 54,678 patients (82%), total number of calcified lesions in 45,615 patients (68%), volume scores in 34,024 patients (51%), density (CT attenuation) of calcified lesions in 20,052 patients (30%), thoracic aortic calcium presence (41,066 [62%]) and scoring in 34,024 patients (51%), aortic valve calcification in 10,007 patients (15%), and mitral valve calcium and volume scores in 10,008 patients (15%).

## 2.9. Follow-up and death ascertainment

Participants were followed with ascertainment of death through linkage to the Social Security Death Index (SSDI) Death Master File (DMF) using an algorithm previously validated in The FIT Project.<sup>12</sup> In brief, the algorithm uses unique patient identifiers (for example name, date of birth, and social security number [SSN]) in a semi-flexible hierarchical matching process prioritizing social security number matching, then date of birth, and then patient name similar

to the algorithm used by the National Death Index (NDI) service. Death was considered to be present if there was a match on SSN and one additional patient identifier. In instances where SSN was not available, a death match required a complete match on all other patient identifiers. These rules prioritize specificity over sensitivity. Internal validation studies against known deaths identified via the electronic medical record revealed >90% specificity for identifying known deaths. Death linkage to the SSDI DMF was performed through June 1st, 2014. Mean follow-up for the cohort was  $12 \pm 4$  years with maximum follow-up across sites ranging from 13.6 to 22.5 years.

Cause of death was obtained via coded death certificates obtained from the NDI. Of the 3158 patients identified through SSDI DMF linkage, the NDI returned cause of death information on 3033 patients (96%). Cause of death and axis conditions (supporting causes of death) were reported as ICD-9 and ICD-10 codes. These codes were then subsequently categorized as CVD, cancer, pulmonary disease, gastrointestinal disease, nervous system disorders, endocrine and metabolic disease, injury and poisoning, or other.

## 2.10. Data analysis

An internal Steering Committee will review proposals, abstracts, and manuscripts before analysis and dissemination of results. Approved statistical analysis plans (SAPs) will be archived in a searchable database.

For this manuscript, baseline characteristics of patients at each study site were calculated using means  $\pm$  standard deviation for continuous variables and numbers (percentages) for categorical variables. Comparisons were made to published data from NHANES 2001–2002, baseline data from the Multi-Ethnic Study of Atherosclerosis (MESA) (2000–20002), and the CT imaging subset of the Framingham Offspring and 3rd Generation cohorts (2002–2005) as these were collected at a similar time to the majority of patients from the CAC Consortium.

CAC was categorized as 0, 1–100, 100–400, and  $\geq 400$  Agatston Units. The distribution of CAC categories was calculated for each site. Death rates were calculated by dividing the number of deaths by the total follow-up time, and expressed as a rate per 1000 patient-years. Age-stratified death rates were compared with published data from MESA and for the general U.S Population (2014 death rates published by the National Center for Health Statistics National Vital Statistics System [NVSS], adjusted to the 2010 U.S Census Population). Since the CAC Consortium is predominantly of employed White individuals, death rates were compared to Whites in MESA and to the general White population from the U.S. Census Bureau. In sensitivity analysis, death rates were compared to Whites in MESA with >\$40,000 annual income and to all non-Black races.

An innovative feature of the CAC Consortium will be the ability to model competing causes of death, for example CVD vs. non-CVD deaths, which will result in more accurate estimates of cause-specific risk. For future competing risk analysis we plan to use the methods proposed by Lunn and McNeil, and Fine and Gray, to estimate and compare cause-specific hazards as well as sub-distribution hazard ratios (SHRs).<sup>13</sup>

## 3. Results

Baseline characteristics of the CAC Consortium are shown in [Table 1](#), and a histogram of the age distribution is shown in [Supplementary Fig. 1](#). The mean age of the patients was  $54 \pm 11$  years and 67% were males. The cohort is predominantly White (89%). A total of 31% of participants had hypertension, 7% had diabetes, 54% had hyperlipidemia, 10% were current cigarette smokers,



**Table 1**  
Baseline characteristics.

	CAC Consortium (N = 66,636)	Cedars-Sinai (N = 13,972)	Columbus, OH (N = 7042)	Harbor-UCLA (N = 25,563)	MHI (N = 20,059)
Age, years	54 ± 11	55 ± 11	53 ± 10	55 ± 11	53 ± 10
Gender					
Women	22,003 (33)	4789 (34)	2227 (32)	7885 (31)	7102 (35)
Men	44,633 (67)	9183 (66)	4815 (68)	17,678 (69)	12,957 (65)
Race <sup>a</sup>					
White	38,277 (89)	9659 (90)	–	9965 (77)	18,653 (96)
Black	977 (2)	371 (4)	–	484 (4)	122 (0.6)
Hispanic	1349 (3)	309 (3)	–	961 (7)	79 (0.4)
BMI, kg/m <sup>2b</sup>	27.5 ± 5.3	26.3 ± 4.8	–	27.1 ± 4.9	28.4 ± 5.5
Obesity <sup>b</sup>	9334 (25)	18%	–	22%	31%
Hypertension	20,624 (31)	5826 (42)	2048 (29)	8264 (32)	4486 (22)
Diabetes	4503 (7)	1200 (9)	456 (6)	1999 (8)	848 (4)
Hyperlipidemia	36,227 (54)	7729 (55)	1824 (26)	15,081 (59)	11,593 (58)
Current Smoking	6400 (10)	1258 (9)	646 (9)	2372 (9)	2124 (11)
Family History of CHD	30,720 (46)	5162 (37)	1945 (28)	13,278 (52)	10,335 (52)
Statin use <sup>b</sup>	6815 (22)	28%	–	–	18%
Aspirin use <sup>b</sup>	13,573 (43)	40%	–	–	45%
10-year Framingham risk, %	11.1 ± 8.9	10.0 ± 8.8	8.5 ± 7.5	12.9 ± 10.4	10.6 ± 8.0
10-year ASCVD risk, %	7.4 ± 9.2	8.7 ± 11.4	5.9 ± 7.2	8.4 ± 9.3	5.8 ± 6.5
10-year ASCVD risk category					
<5%	36,793 (55)	7487 (54)	4412 (63)	12,568 (49)	12,326 (61)
5–7.5%	8939 (13)	1704 (12)	936 (13)	3561 (14)	2738 (14)
≥7.5%	20,904 (31)	4781 (34)	1694 (24)	9434 (37)	4995 (25)
Follow-up time, years	12 ± 4	9 ± 4	13 ± 2	15 ± 4	11 ± 2
Max follow-up time, years	22.5	13.6	15.2	22.5	14.3

Continuous variables, mean ± SD. Categorical variables, number (%).

<sup>a</sup> Information on race available in N = 10,715 in Cedars-Sinai, N = 12,878 in Harbor-UCLA, and N = 19,379 in MHI.

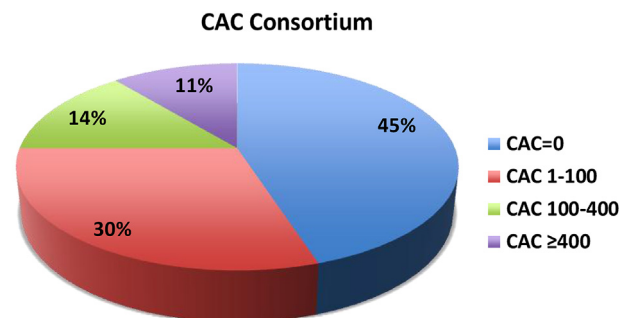
<sup>b</sup> Information on BMI/obesity available in N = 36,892, statin use in N = 31,194, and aspirin use in N = 32,092.

and 46% reported a family history of CHD. The mean 10-year ASCVD risk score was 7.4 ± 8.9% with 55% of the cohort having a low ASCVD risk score (<5%) and nearly a third (31%) having a high ASCVD risk score ≥7.5%. Median 10-year ASCVD risk was 4.4%.

The majority of participants at all sites were men. The prevalence of hypertension and diabetes was lowest in MHI (22% and 4% respectively) while the prevalence of hypertension and diabetes was highest in Cedars-Sinai (42% and 9%, respectively). Participants in Columbus, OH were most likely to have a low <5% 10-year ASCVD risk (63%) while those in Harbor-UCLA were most likely to have a high ≥7.5% ASCVD risk (37%) compared to the other sites (p-value <0.01).

The baseline mean age of participants in the CAC Consortium was similar to those in the contemporary NHANES 2001–2002 cohort and the Framingham CT imaging cohort, but lower compared to participants in MESA (Table 2). The CAC Consortium has a higher percentage of males (67%) compared to these other cohorts (44–48%), but the prevalence of traditional CVD risk factors is otherwise similar to MESA except for a mildly higher prevalence of hypertension (45% vs. 31%), diabetes (13% vs. 7%), and smoking (13% vs. 10%) in MESA compared to the CAC Consortium.

The distribution of CAC score categories was as follows: 45% had an Agatston score of 0, 31% had Agatston scores between 1 and 100, 14% had an Agatston score between 100 and 400, and 11% had an Agatston score >400 (Fig. 2). This was similar in all sites with the



\* The mean CAC percentile is 45<sup>th</sup> based on age/sex/race-based references scores from MESA

**Fig. 2.** Distribution of CAC scores. \*The mean CAC percentile is 45<sup>th</sup> based on age/sex/race-based references scores from MESA.

**Table 2**  
Comparison of the CAC consortium with other contemporary cohorts.

	CAC Consortium	NHANES (2001–2002)	Framingham Offspring & 3rd generation (2002–2005)	MESA (2000–2002)
N	66,636	3849	2435	6814
Age, years	54 ± 11	54 ± 22	51 ± 9	62 ± 10
Gender, %				
Female	33%	52%	56%	53%
Male	67%	48%	44%	47%
Hypertension, %	31%	33%	25%	45%
Diabetes, %	7%	9%	4%	13%
Hyperlipidemia, %	54%	39%	26%	59%
Active Smoking, %	10%	22%	13%	13%
Family History of CHD, %				
Any	46%	–	–	43%
Premature	–	14%	22%	20%

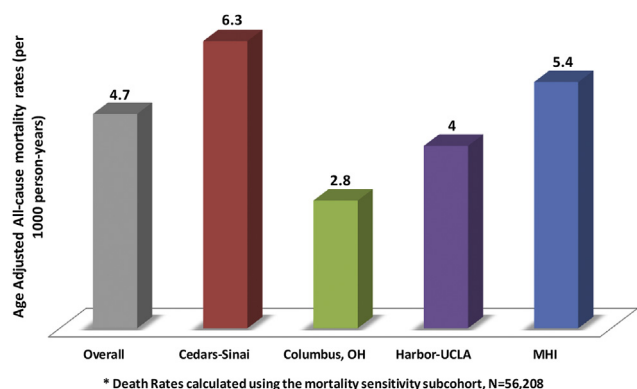


Fig. 3. Age-Adjusted Mortality Rates By Study Site. \*Death Rates calculated using the mortality sensitivity subcohort, N = 56,208.

notable exception of Harbor-UCLA which had a lower prevalence of Agatston scores of 0 (40%,  $p < 0.01$ ) (Supplementary Fig. 2A–D). The mean age/sex/race-based CAC percentile was at the 45th percentile based on reference values published from MESA, and at the 74th percentile considering only those patients with Agatston scores  $>0$ .

Over a mean follow-up of  $12 \pm 4$  years, there were 3158 deaths (4.7%). The death rate was 4.15 per 1000 person-years of follow-up, with an age-adjusted rate standardized to the entire study population of 4.7 per 1000 person-years (Fig. 3). The age-adjusted death rate was highest in Cedars-Sinai at 6.3 per 1000 person-years and lowest in Columbus, OH at 2.8 per 1000 person-years (Supplemental Fig. 3A–D).

The death rate in the CAC Consortium dataset was mildly but systematically lower compared to the White population from the MESA study (age-adjusted difference of  $-26.7\%$ ). These differences appeared to be most pronounced in the 60–64 year-old age group (Table 3). Age-adjusted differences were diminished to  $-11.7\%$  when limiting to the MESA populations earning  $>\$40,000$ , which may be more representative of the CAC Consortium (Supplemental Table 1). As expected, the death rate in the CAC Consortium was more similar to MESA than to the general U.S. White Population (Table 3).

The majority of deaths in the CAC Consortium were from cancer (37%) and CVD (32%) (Fig. 4). Columbus, OH had the highest incidence of cancer deaths (46%) while Cedars-Sinai and Harbor-UCLA had the highest incident of CVD deaths (35%) (Supplemental

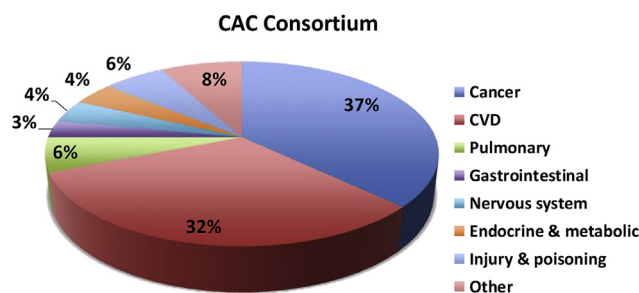


Fig. 4. Causes of death.

Fig. 4A–D). Among CVD deaths, most were due to CHD (54%) followed by stroke (17%) and these trends were similar across sites (Fig. 5 and Supplemental Fig. 5A1–4). Harbor-UCLA had the highest incidence of CHD deaths (61%) while Columbus, OH had the highest incidence of stroke deaths (21%). Among cancer deaths, the most common site was gastrointestinal (27%), followed by cancers of the respiratory tract organs (21%), and genitourinary cancers (15%). These trends were similar across all sites (Supplemental Fig. 5B1–4).

#### 4. Discussion

CAC is presently established as the strongest predictor of CHD beyond traditional risk factors and is strongly associated with all-cause mortality.<sup>14,15</sup> However, prior studies have been limited in their ability to perform analyses of cause-specific death due to smaller sample sizes that were underpowered to examine cause of death and/or a lack of cause of death ascertainment.<sup>16</sup> Using low-cost epidemiologic techniques and existing clinical data, the CAC Consortium is uniquely poised to address important knowledge gaps in the current literature as it is the largest study of individuals with a CAC scan (817,620 patient-years of follow-up), has a median follow-up of greater than 10 years, and uniquely offers cause-specific mortality.

The real-world clinical data used to assemble the CAC Consortium was obtained from four independent sites geographically dispersed throughout the United States. There is the possibility of selection and/or indication bias as all CAC scans were based on physician referral with potentially differing clinical practice patterns at each site. To account for this, all analyses will be adjusted

Table 3 Comparison of death rates across cohorts.

Death Rates <sup>a</sup> (per 10,000 person-years)	CAC Consortium			MESA (Whites) <sup>a</sup>			General U.S. Population <sup>b</sup> (2014)		
	All	Males	Females	All	Males	Females	All	Males	Females
Age Category (Years)									
25–29	7.89	5.78	12.41	–	–	–	9.81	13.57	5.86
30–34	6.03	5.48	8.08	–	–	–	11.59	15.51	7.52
35–39	8.74	8.78	8.59	–	–	–	14.41	18.19	10.53
40–44	11.95	11.84	12.28	–	–	–	19.89	24.22	15.50
45–49	13.15	14.67	9.22	15.29	22.20	9.42	30.49	37.24	23.70
50–54	17.24	18.21	15.36	29.80	34.38	25.86	48.08	59.59	36.75
55–59	30.62	35.35	22.72	45.35	54.43	36.27	70.85	89.19	53.18
60–64	52.18	55.64	46.54	93.83	130.96	63.73	99.89	126.26	75.15
65–69	76.21	87.77	59.40	125.64	154.29	97.98	142.90	175.07	113.37
70–74	152.37	162.31	138.91	200.04	246.12	156.86	223.49	269.57	183.31
75–79	275.33	308.62	239.68	340.79	393.78	290.96	357.71	425.76	302.40
80–84	460.52	450.40	471.91	562.20	876.94	372.14	603.14	710.30	525.86
>84	1006.37	1065.98	933.05	–	–	–	1374.26	1500.03	1307.91

<sup>a</sup> Death rates derived from the mortality sensitivity subcohort, N = 56,208.

<sup>b</sup> 2014 US death rates, adjusted to the 2010 U.S. Census population.

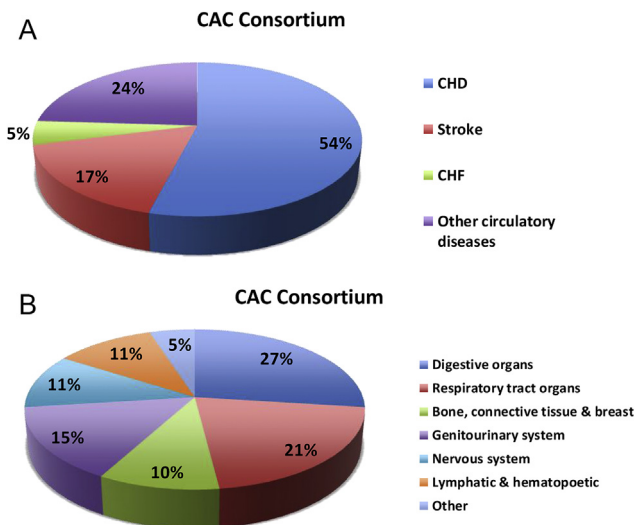


Fig. 5. A – subtypes of CVD death. B – subtypes of cancer death.

for individual site. The data is less standardized than that found in the traditional prospective cohorts (for example Framingham or MESA). However, it is more reflective of what is seen in routine clinical practice, and it will provide important complementary insight into real-world patients while still enabling comparison to the traditional cohorts. Our data is also limited in that it is not a natural history cohort, that is, CAC was reported to patients and physician and may have influenced downstream procedures and revascularizations. However, this would lead to a more conservative estimate of the association between CAC and CVD mortality (would bias toward the null hypothesis), as in the CAC Consortium many patients with high CAC scores likely received preventive care such as statins that likely reduced CVD-related mortality.<sup>17</sup>

Death rates in our dataset were lower than observed in the White population from MESA. There are several potential explanations of this discrepancy. First of all, the CAC Consortium was likely to have a greater percentage of insured patients with higher socio-economic status as compared to MESA. Indeed, in sensitivity analysis, restricting the MESA population to just those with insurance or those with income >\$40,000 greatly diminished differences in death rates. In addition, participants in MESA were more likely to have hypertension, diabetes, and to be smokers. There are also potential regional differences in death rates that might explain this discrepancy. Restricting MESA analyses to the most similar geographic sites of Los Angeles, Minneapolis, and Chicago (eliminating New York City, Baltimore, and Winston-Salem) also reduced differences in death rates.

Importantly, however, the finding of a lower mortality rate compared to MESA raises the possibility of under-ascertainment of mortality using our algorithm. This is possible, likely owing to imperfections in patient identifiers (for example the use of nicknames and typographical errors at data entry) as well as deaths not captured by the DMF (for example, non-citizens or others without social security benefits). In the CAC Consortium, the age-adjusted difference in total mortality was –26.7% compared to MESA. Prior data has suggested that the DMF captures approximately 90% of all deaths, but this number may be lower after changes in privacy laws and mortality reporting at state level in 2011.<sup>18</sup> Our internal validation data suggests that sensitivity ranges from 72 to 90%.

No surprisingly, death rates in the CAC Consortium were lower

than for the total unselected U.S. Population. Such data reflects all individuals in the US, including those with pre-existing chronic diseases, those unemployed or of low socioeconomic status, and those lacking access to medical care. Indeed, the observed relationship between mortality in the CAC Consortium and in the total U.S. Population was similar to that we observed in prior studies.<sup>12</sup>

The use of death certificates has well-known limitations.<sup>19,20</sup> However, in the United States, death certificates represent the only large scale objective epidemiologic method of ascertaining cause of death. In general death certificates are expected to overestimate the proportion of CHD death, although our data is in agreement national trends showing cancer death increasingly more common than CHD death.<sup>21</sup>

With 66,636 patients, the CAC Consortium is both the largest CAC database assembled to date and has equaled the longest mean follow-up of >13 years with individual follow-up for as long as 22 years. This large sample size will allow for the investigation of important subgroups, such as very young patients and very old patients<sup>22,23</sup> or those with very high CAC scores,<sup>24</sup> with more precision. The supporting data on total CAC lesions, CAC density, regional distribution of CAC, and extracoronary calcification will help shape future approaches to CAC scoring for optimal risk prediction.<sup>25–28</sup> Most importantly, determination of cause of death will enable the study of the association of CAC with CVD and non-CVD mortality through the use of competing risks models. This information is particularly important in the setting of an aging population with uncertain estimates of the value of preventive pharmacotherapy. Accordingly, this information will help to inform policy decisions and guidelines focusing resources on the prevention of the most likely cause of death by age group and CAC score category.

Within the CAC Consortium, we plan to regularly update mortality ascertainment, and also supplement future cohort updates with additional CAC scan parameters not yet been extracted from available scans. Importantly, we also plan to expand the dataset to include other centers with CAC data that might be assimilated with the existing CAC Consortium. There are also unique opportunities to partner with oncology epidemiologists to further study the suggested association between CAC and cancer.

## 5. Conclusions

Through its large sample size, long length of follow-up, and ascertainment of cause of death the CAC Consortium is uniquely positioned to complement and expand the knowledge base from existing CAC cohorts. CAC, as a marker of biologic age, may be a predictor of multiple chronic disease states, requiring use of competing risk modeling to understand the implications of clinical CAC scanning for the estimation of longevity and allocation of resources, particularly in previously underrepresented groups such as in the young and the elderly.

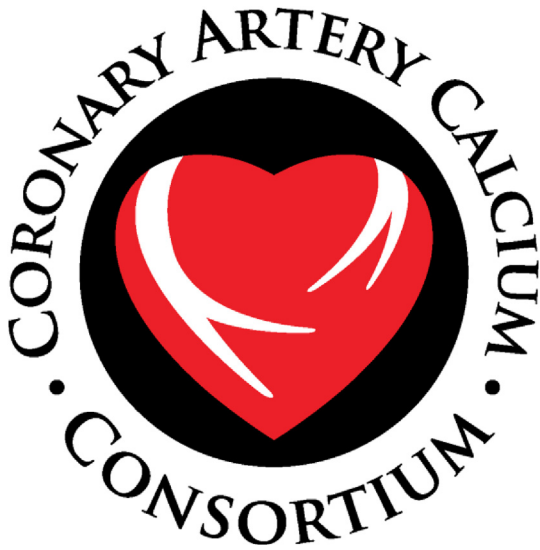
## Disclosures

We have no disclosures to report.

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#### Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.jcct.2016.11.004>.

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