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Advanced Subclinical Atherosclerosis in Young Individuals and Risk of Mortality Over 30 Years

The Coronary Artery Calcium Consortium

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IMPORTANCE Coronary artery calcium (CAC) scoring is a well-established tool for predicting cardiovascular risk, but its long-term prognostic value in young adults remains unclear. As early preventive intervention may yield substantial lifetime benefit, understanding long-term implications of elevated CAC in young adults is important for informing prevention strategies.

OBJECTIVE To investigate the long-term risk of all-cause, cardiovascular disease (CVD), and coronary heart disease (CHD) mortality associated with premature advanced subclinical atherosclerosis.

DESIGN, SETTING, AND PARTICIPANTS This cohort study used the CAC Consortium dataset, a retrospectively assembled cohort of referred individuals with clinically indicated CAC scans. Using multivariable regression models for time-to-event analysis, the association of CAC with all-cause, CVD, and CHD mortality was assessed, adjusting for age, sex, and traditional atherosclerotic CVD risk factors. Cumulative incidence was derived for these outcomes in 5-year increments up to 30 years using a mixed approach involving the Kaplan-Meier method and Weibull modeling. The proportion of deaths attributable to CVD and CHD across CAC groups was evaluated. Four institutions across the US provided patient-level data to assemble the CAC Consortium. Included in the analysis were adults aged 30 to 45 years from the CAC Consortium. They were followed up for a median of 22.6 years. Study data were analyzed from October 2025 to September 2026.

EXPOSURE Elevated CAC in adults aged 30 to 45 years, specifically CAC score greater than 90%.

MAIN OUTCOMES AND MEASURES Participants were followed up for underlying cause of mortality.

RESULTS Among 12 847 participants, the mean (SD) age was 40.5 (3.6) years, and 9922 (77.2%) were male; 9262 (72.1%) had CAC score of 0, 1626 (12.7%) had a CAC score between 75% to 90%, and 1703 (13.3%) had a CAC score greater than 90%. In total, there were 624 deaths (149 CVD and 81 CHD). Multivariable adjusted hazard ratios for CAC score greater than 90% vs CAC score of 0 were 1.87 (95% CI, 1.54-2.27), 2.60 (95% CI, 1.77-3.82), and 3.71 (95% CI, 2.24-6.16), for all-cause, CVD, and CHD mortality, respectively. Over 30 years, the group with a CAC score greater than 90% had significantly higher modeled risk of all-cause (12.9% vs 7.5%), CVD (4.5% vs 1.5%), and CHD (3.0% vs 0.6%) mortality, compared with the group with a CAC score of 0.

CONCLUSIONS AND RELEVANCE Results of this cohort study suggest that young adults with a CAC score greater than 90% face significantly higher long-term risk of all-cause, CVD, and CHD mortality, suggesting potential implications for guiding the intensification of preventive intervention in this high-risk phenotype.

Supplemental content

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Coronary artery calcium (CAC) scanning is an imaging modality that uses noncontrast gated cardiac computed tomography (CT) to detect and quantify the burden of calcified atherosclerosis. Higher CAC scores are strongly associated with an increased risk for cardiovascular events over the 10-year time horizon, independent of traditional risk factors.[1]

The recently updated 2026 American Heart Association (AHA)/American College of Cardiology (ACC) "Guideline on the Management of Dyslipidemia" emphasized the value of early prevention, as it translates to larger lifetime benefits than later-life intervention.[2-4] Importantly, it designated a class I recommendation for using CAC to guide decisions for initiation and intensification of lipid-lowering therapy in intermediate-risk and select borderline-risk adults, a major update from the class IIa recommendations in both the previous 2018 AHA/ACC cholesterol guidelines and the 2019 ACC/AHA prevention guidelines.[5,6]

Increasing data support the value of CAC in young adults.[7-9] Over an extended period, CAC percentiles offer additional value to CAC scores in young adults, in whom high absolute scores are typically not expected.[10-12] The discordance in perceived risk between absolute and relative CAC scores in young adults highlights the need to assess the long-term risk implications of elevated CAC in this population.[13-15]

The 20- to 30-year time horizons provide a promising framework for extended risk estimation because, over this period, young adults would reach the age range generally associated with higher disease burden in clinical practice. However, no prior studies have had sufficient data to be able to study the long-term risk implications of CAC to this extent, particularly in the 30- to 45-year age group. Therefore, we aimed to investigate long-term mortality risks among a well-defined age group of young adults aged 30 to 45 years, focusing on those in the highest percentiles of CAC, specifically the 90th percentile.

Key Points

Question What are the long-term implications of having elevated coronary artery calcium (CAC) scores in young adults compared with their peers?

Findings In this cohort study including 12 847 participants, those aged 30 to 45 years with CAC above the 90th percentile had statistically significantly higher modeled 30-year mortality risks than those without CAC.

Meaning Results suggest that young adults with CAC above the 90th percentile face markedly increased long-term risk of all-cause, cardiovascular disease, and coronary heart disease mortality compared with the majority of their peers with absent CAC; there may be potential benefits of intensive preventive intervention in this high-risk phenotype.

Methods

Original Study Design

The CAC Consortium is a retrospectively assembled cohort that consists of 66 636 participants who underwent clinically indicated CAC scans referred by a physician. All participants included were 18 years of age or older, asymptomatic, free of known coronary heart disease (CHD), and had a dedicated CAC scan quantified with an Agatston score (reported as Agatston units [AU]). Four select institutions across the US contributed patient-level data from as early as 1991. In this analysis, all individuals aged 30 to 45 years were included.[16] Self-identified information on race (Asian, Black, Hispanic, White, and other race, which included American Indian or Alaska Native, Hawaiian, or unspecified) was collected from contributing institutions as part of individual clinical data. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Measurement of CAC

CAC scans were performed using noncontrast cardiac-gated CT scans adhering to standard protocols for each scanner. CAC was scanned predominantly with electron beam tomography, with a minority using multidetector CT, and was quantified using the Agatston method; both modalities are known to yield comparable CAC scores.[17] We stratified our study participants aged 30 to 45 years into CAC percentile groups as follows: (1) CAC of 0, (2) CAC less than or equal to 75%, (3) CAC between 75% and 90%, and (4) CAC greater than 90% based on age-, sex-, and race-specific CAC percentiles obtained from an online CAC percentile calculator, developed based on the study of Javaid et al.[10]

Covariate Assessment and Definition of Atherosclerotic Cardiovascular Disease Risk Factors

Four sites were selected across the US to assemble the CAC Consortium as follows: Cedars-Sinai Medical Center (Los Angeles, California), PrevaHealth Wellness Diagnostic Center (Columbus, Ohio), Harbor-UCLA Medical Center (Torrance, California), and Minneapolis Heart Institute (Minneapolis, Minnesota). Each participating institution provided patient-level data on demographics and atherosclerotic cardiovascular disease (ASCVD) risk factors, which were evaluated from an interview at the time of the CAC scan and/or from electronic medical records. Hypertension was defined as a previous diagnosis of hypertension or treatment with antihypertensive therapy. Diabetes was considered present if there was a prior diagnosis of diabetes or treatment with oral hypoglycemic drugs or insulin. Similarly, dyslipidemia was considered present if there was a prior diagnosis of primary hyperlipidemia, prior diagnosis of dyslipidemia (elevated triglycerides, and/or low high-density lipoprotein cholesterol [HDL-C]), treatment with any lipid-lowering drug, or abnormal lipid levels on testing (low-density lipoprotein cholesterol [LDL-C] >160 mg/dL, to convert to millimoles per liter, multiply by 0.0259; HDL-C <40 mg/dL in men and <50 mg/dL in women, to convert to millimoles per liter, multiply by 0.0259; or fasting triglycerides >150 mg/dL, to convert to millimoles per liter, multiply by 0.0113). Smoking status was categorized as current and noncurrent. Lastly, family history of CHD was defined as the presence of a first-degree relative with a history of CHD, except at

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the Columbus, Ohio, site, which defined it as premature family history (<55 years old in a male relative and <65 years old in a female relative). Imputations were conducted for missing risk factors, using a multivariable model adjusting for age, sex, race, CAC score, and the remaining nonmissing traditional risk factors.[16]

Follow-Up and Death Ascertainment

Methods for follow-up and ascertaining mortality have been described in the original study.[16] Follow-up and ascertainment of the underlying cause of death were previously performed through June 1, 2014. The top 2 supporting causes of death per death certificate were used in addition to the underlying cause of death when conducting survival analysis based on extended definitions of CVD and CHD mortality. Similar protocols, prioritizing the National Death Index and underlying cause of death, were applied in the most recent update of the dataset to include mortality events through calendar year 2024.

Statistical Analysis

We summarized the baseline characteristics of our study participants by CAC percentile group (CAC = 0, CAC ≤75%, CAC 75%-90%, CAC >90%). For the remainder of the analysis, the percentile group with CAC less than or equal to 75% was excluded due to its lack of power and lack of relevance to our objectives.

To examine associations between CAC percentile groups and mortality, we used Cox proportional hazards regression for all-cause mortality and Fine and Gray competing risks regression for cause-specific mortality (CVD and CHD deaths), adjusting for age, sex, and traditional ASCVD risk factors such as hypertension, hyperlipidemia, smoking, diabetes, and family history of CHD.[18,19]

For Cox models, proportional hazards assumptions were assessed using Schoenfeld residuals tests. Hypertension violated the assumption ($P < .001$) and was stratified in final models, which satisfied all assumptions ($P > .05$). For Fine and Gray models, competing events were non-CVD deaths for CVD mortality models and non-CHD deaths for CHD mortality models. Given the extended follow-up and evidence of time-varying effects, subdistribution hazard ratios (HRs) represent time-averaged associations. Separate analyses using CAC equal to 0 and CAC between 75% and 90% as reference categories were conducted for both models. Results using CAC equal to 0 as the reference were visualized with forest plots.

Cumulative incidence per 5-year follow-up increments was analyzed using a mixed approach. Over the initial 20-year time horizon, all-cause mortality, CVD mortality, and CHD mortality were assessed using the Kaplan-Meier method.[20] To accurately compare the risk of different causes of death across CAC percentile groups beyond the median follow-up of 22.6 years (follow-up time ranged from 0.1-31.9 years; 3.5% with follow-up beyond 30 years), we fitted the Weibull parametric survival model to our data, and estimated 30-year risk of all-cause, CVD, and CHD mortality by CAC percentile group, adjusting for age and sex.[21,22] The process of model selection is further explained in eMethods in Supplement 1.

To mitigate the influence of potentially uninformative early events and sparse data at later time points, Weibull model fitting was restricted to the central portion of the follow-up distribution, as reflected in the Kaplan-Meier curves, specifically the central 97.5% to 99% of the distribution for cardiovascular mortality (CVD and CHD deaths), and all-cause mortality, respectively. This trimming approach was motivated by the method of trimmed moments, which has demonstrated resistance to bias arising from outliers in survival datasettings.[23,24] This approach had excellent visual and statistical model fit and provided more robust survival estimates than a simple Kaplan-Meier approach at the extremes of follow-up. Cumulative incidence was calculated as 100 – survival probability (percentage units). The methods for survival analysis using an extended definition of CVD and CHD mortality are described in the eMethods in Supplement 1.

To study the contribution of CAC to cardiovascular causes of death across CAC percentile groups, we derived the proportions of deaths attributable to CVD or CHD over the 30-year time horizon. To quantify the impact of CAC on the fraction of CVD attributable specifically to CHD, we calculated the proportion of CHD mortality among total CVD mortality.

Finally, to study event rates across the full spectrum of follow-up, we first stratified our participants into CAC score strata of CAC equal to 0, CAC 1 to 10, CAC 11 to 100, CAC 101 to 300, and CAC greater than 300 and calculated the respective event rates per 1000 person-years. We then calculated and visualized the contribution of CAC percentile groups within each CAC score strata. Cox models and Fine and Gray models were used to demonstrate long-term cumulative incidence of all-cause, CVD, and CHD mortality with CAC score as a continuous variable, further described in the eMethods in Supplement 1. All analyses were performed from October 2025 to September 2026 using R statistical software, version 4.4.3 (R Core Team 2025). A 2-sided α of $P < .05$ was considered statistically significant.

Results

Baseline Characteristics

Baseline characteristics of our study population are shown in **Table 1**. Among the 12 847 participants in our study, the mean (SD) age was 40.5 (3.6) years, 2925 (22.8%) were female, and 9922 (77.2%) were male. Information on race was available in 10 715 of 13 972 participants from Cedars-Sinai Medical Center, 12 878 of 25 563 participants from Harbor-UCLA Medical Center, and 19 379 of 20 059 participants from Minneapolis Heart Institute; such information was not available for the Columbus, Ohio site. In total, information on race was collected from 42 964 of 66 636 participants.

CAC scores ranged from 0 to 3650, with a total of 9262 participants (72.1%) having a CAC score of 0. Among those with positive CAC scores, the median (IQR) CAC score was 12.4 (3.0-52.1), and the mean (SD) CAC score was 69.3 (194.3). A total of 256 participants (2.0%) had CAC scores above 0 but at or below the 75th percentile for age, sex, and race; 1626 participants (12.7%) had a CAC score between 75% and 90%, and 1703

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Table 1. Baseline Characteristics of Young Adults Aged 30 to 45 Years Stratified by Coronary Artery Calcium (CAC) Percentile Groups

Characteristics	Total (N = 12 847)	CAC = 0 (9262 [72.1%])	CAC ≤75% (256 [1.9%])	CAC 75%-90% (1626 [12.7%])	CAC >90% (1703 [13.3%])	*P* value
Age, mean (SD), y	40.5 (3.6)	40.2 (3.7)	44.2 (0.7)	41.6 (2.5)	40.4 (3.7)	<.001
Sex (%)						
Female	2925 (22.8)	2552 (27.6)	NA	NA	373 (21.9)	<.001
Male	9922 (77.2)	6710 (72.4)	256 (100)	1626 (100)	1330 (78.1)	
CAC score, median (IQR)	0 (0-1.0)	0	1.5 (1.0-2.0)	6.0 (2.0-13.0)	56.4 (19.0-127.8)	<.001
Female	0	0	NA	NA	11.0 (2.0-49.0)	<.001
Male	0 (0-3.0)	0	1.5 (1.0-2.0)	6.0 (2.0-13.0)	70.0 (33.0-151.6)	
Hypertension, No. (%)	2281 (17.8)	1434 (15.5)	52 (20.3)	346 (21.3)	449 (26.4)	<.001
Dyslipidemia, No. (%)	6260 (48.7)	4228 (45.6)	155 (60.5)	908 (55.8)	969 (56.9)	<.001
Current smoking, No. (%)	1442 (11.2)	992 (10.7)	33 (12.9)	168 (10.3)	249 (14.6)	<.001
Diabetes, No. (%)	427 (3.3)	253 (2.7)	10 (3.9)	71 (4.4)	93 (5.5)	<.001
Family history of CHD, No. (%)	6521 (50.8)	4544 (49.1)	125 (48.8)	841 (51.7)	1011 (59.4)	<.001

Abbreviations: CHD, coronary heart disease; NA, not applicable.

(13.3%) had a CAC score greater than 90%. The absence of female participants in the group with CAC scores less than or equal to 75% and the group with CAC scores between 75% and 90% can be explained by Javaid et al,[10] who reported that any CAC detected in female individuals of this age places them in the group with CAC score greater than 90%. In the group with CAC scores less than or equal to 75% and the group with CAC scores between 75% and 90%, all of whom were male individuals, the median (IQR) CAC scores were 1.5 (1.0-2.0) and 6 (2.0-13.4), respectively. Among the group with CAC scores greater than 90%, the median (IQR) CAC score was 56.4 (19.0-127.8) overall, and 70.0 (33.0-151.6) and 11.0 (2.0-49.0) for males and females, respectively. The distribution of CAC scores across different CAC percentile groups is described in eTable 1 in Supplement 1. The distribution of ASCVD risk factors within our study population is described in Table 1 and the eResults in Supplement 1.

Follow-Up Time and Outcomes

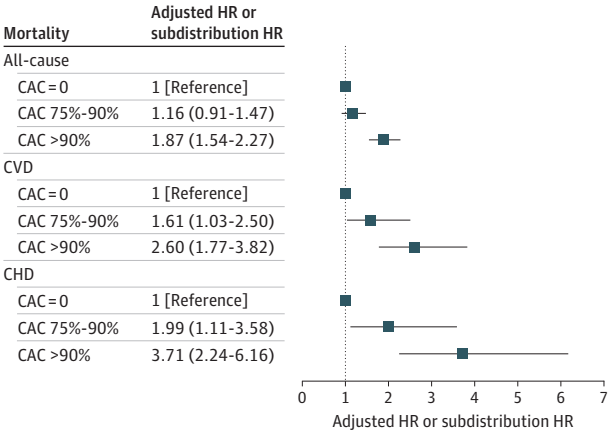
The follow-up time was a median (IQR) of 22.6 (20.6-24.0) years, with a maximum of 31.9 years; 452 participants (3.5%) had follow-up beyond 30 years. There were 624 deaths in total; 149 were due to CVD, 81 of which were due to CHD. A total of 470 deaths were due to non-CVD causes; 5 deaths had missing information on the cause. In the group with CAC score greater than 90%, there were 148 deaths in total, of which 45 were due to CVD and 29 due to CHD.

Multivariable Risk

In multivariable-adjusted models, participants in the group with CAC score greater than 90% had nearly double the risk of all-cause mortality compared with those with CAC score of 0 (HR, 1.87; 95% CI, 1.54-2.27) (eTable 2 in Supplement 1). When compared with individuals in the group with CAC score between 75% and 90%, those in the group with CAC score greater than 90% had significantly higher hazards for all-cause mortality (HR, 1.64; 95% CI, 1.23-2.18) (eTable 3 in Supplement 1).

Higher HRs for CVD and CHD mortality were observed for the overall follow-up period. The group with CAC score between 75% and 90% was associated with 1.61 (95% CI, 1.03-2.50) and 1.99 (95% CI, 1.11-3.58) times the hazard compared with the group with CAC score of 0, whereas the group with CAC score greater than 90% had 2.60 (95% CI, 1.77-3.82) and 3.71 (95% CI, 2.24-6.16) times the hazard, respectively (**Figure 1** and eTable 2 in Supplement 1).

Figure 1. Forest Plot Showing Hazard Ratios (HRs) of Mortality Across Percentile Categories



CAC indicates coronary artery calcium; CHD, coronary heart disease; CVD, cardiovascular disease.

Cumulative Incidence by CAC Percentile Group

Cumulative incidence of mortality over the 10-year horizon is presented in the eResults in Supplement 1.

Over the initial 20 years, those with CAC score of 0 had a 3% (95% CI, 2.7%-3.4%) risk of all-cause mortality, whereas those in the group with CAC score between 75% and 90% and the group with CAC score greater than 90% had 3.5% (95% CI, 2.6%-4.4%) and 6.9% (95% CI, 5.7%-8.1%) risk, respectively. For CVD mortality, groups with CAC score of 0, CAC score between 75% and 90%, and CAC score greater than 90% showed 0.7% (95% CI, 0.5%-0.9%), 1.2% (95% CI, 0.7%-1.1%), and 2.1%

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Table 2. Cumulative Incidence of All-Cause, Cardiovascular Disease (CVD), and Coronary Heart Disease (CHD) Mortality per 5-Year Follow-Up Increments

Variable	All-cause mortality risk, % (95% CI)						CVD mortality risk, % (95% CI)						CHD mortality risk, % (95% CI)					
	5 y	10 y	15 y	20 y	25 y[a]	30 y[a]	5 y	10 y	15 y	20 y	25 y[a]	30 y[a]	5 y	10 y	15 y	20 y	25 y[a]	30 y[a]
CAC = 0	0.4 (0.3-0.5)	0.9 (0.7-1.1)	1.9 (1.6-2.2)	3.0 (2.7-3.4)	4.9 (4.5-5.5)	7.5 (6.8-8.5)	0.1 (0.0-0.2)	0.2 (0.1-0.3)	0.4 (0.3-0.6)	0.7 (0.5-0.9)	1.0 (0.8-1.3)	1.5 (1.2-2.1)	0.02 (0.0-0.1)	0.04 (0.0-0.1)	0.2 (0.1-0.2)	0.3 (0.2-0.4)	0.4 (0.3-0.7)	0.6 (0.5-1.3)
CAC 75%-90%	0.5 (0.2-0.8)	1.0 (0.5-1.5)	2.1 (1.4-2.8)	3.5 (2.6-4.4)	6.6 (5.4-8.4)	10.3 (8.4-14.0)	0.1 (0.0-0.3)	0.3 (0.0-0.6)	0.7 (0.3-1.1)	1.2 (0.7-1.1)	2.0 (1.4-3.6)	3.0 (2.1-6.0)	0.1 (0.0-0.2)	0.2 (0.0-0.3)	0.4 (0.1-0.7)	0.8 (0.3-1.2)	1.2 (1.0-3.0)	1.8 (1.4-4.9)
CAC >90%	1.4 (0.8-1.9)	2.8 (2.0-3.6)	4.6 (3.6-5.6)	6.9 (5.7-8.1)	9.9 (8.6-11.6)	12.9 (11.1-15.6)	0.6 (0.2-1.0)	0.9 (0.4-1.3)	1.4 (0.9-2.0)	2.1 (1.4-2.8)	3.1 (2.4-4.6)	4.5 (3.3-7.4)	0.3 (0.0-0.6)	0.5 (0.2-0.9)	0.8 (0.4-1.3)	1.4 (0.8-2.0)	2.1 (1.6-3.9)	3.0 (2.3-5.9)
Absolute risk difference (CAC 75%-90% – CAC = 0)	0.1	0.1	0.2	0.5	1.7	2.8	0	0.1	0.3	0.5	1.0	1.5	0.04	0.1	0.2	0.5	0.8	1.2
Absolute risk difference (CAC >90% – CAC = 0)	1.0	1.9	2.7	3.9	5.0	5.4	0.5	0.7	1.0	1.4	2.1	3.0	0.3	0.5	0.7	1.2	1.7	2.4

[a] Results for 25 and 30 years reflect the mixed approach used to analyze cumulative incidence, calculated as 100 – survival probability (%). For the initial 20 years, the raw data were assessed using the Kaplan-Meier method. For 25 and 30 years, the fitted data was assessed using Weibull modeling.

(95% CI, 1.4%-2.8%) risk, respectively. For CHD mortality, these groups showed 0.3% (95% CI, 0.2%-0.4%), 0.8% (95% CI, 0.3%-1.2%), and 1.4% (95% CI, 0.8%-2.0%) risk, respectively (**Table 2**).

Figure 2 presents Kaplan-Meier survival curves for all-cause mortality, superimposed with corresponding fitted Weibull curves and 95% CIs, stratified by CAC percentile groups. Results for CVD and CHD mortality are presented in eFigure1 in Supplement 1. For all-cause mortality, groups with CAC score of 0, CAC score between 75% and 90%, and CAC score greater than 90% showed 92.5%, 89.7%, and 87.2% estimated 30-year survival, respectively. For CVD mortality, each group showed 98.5%, 97.0%, and 95.6% estimated 30-year survival, respectively. For CHD mortality, each group showed 99.4%, 98.2%, and 97.1% estimated 30-year survival, respectively.

Participants in the highest CAC percentile group had markedly higher long-term risks of total, CVD, and CHD mortality compared with the large majority reference group with CAC score of 0. Over the 25-year time horizon, individuals in the group with CAC score greater than 90% had a 9.9% (95% CI, 8.6%-11.6%) risk of all-cause mortality, more than double the risk observed in the group with CAC score of 0 (4.9%; 95% CI, 4.5%-5.5%) (Table 2). Similar trends were observed for CVD and CHD mortality. CVD mortality risk was more than 3 times higher in the group with CAC score greater than 90% than in those with CAC score of 0 (3.1% vs 1.0%, respectively), whereas CHD mortality risk was more than 5 times higher (2.1% vs 0.4%, respectively).

Over the 30-year time horizon, individuals in the group with CAC score greater than 90% were estimated to have a 12.9% (95% CI, 11.1%-15.6%) risk of all-cause mortality, compared with 7.5% (95% CI, 6.8%-8.5%) risk in the group with CAC score of 0. CVD mortality risk was estimated to be 3-fold higher in the group with CAC score greater than 90% than in those with CAC score of 0 (4.5%; 95% CI, 3.3%-7.4%) vs 1.5% (95% CI, 1.2%-2.1%), whereas CHD mortality risk was estimated to be 5-fold higher (3.0%; 95% CI, 2.3%-5.9%) vs 0.6% (95% CI, 0.5%-1.3%).

Survival probability and cumulative incidence of CVD and CHD mortality using extended definitions of CVD and CHD mortality are described in the eResults in Supplement 1 and are shown in eFigures 2 and 3 in Supplement 1.

Mortality Due to Cardiovascular Causes

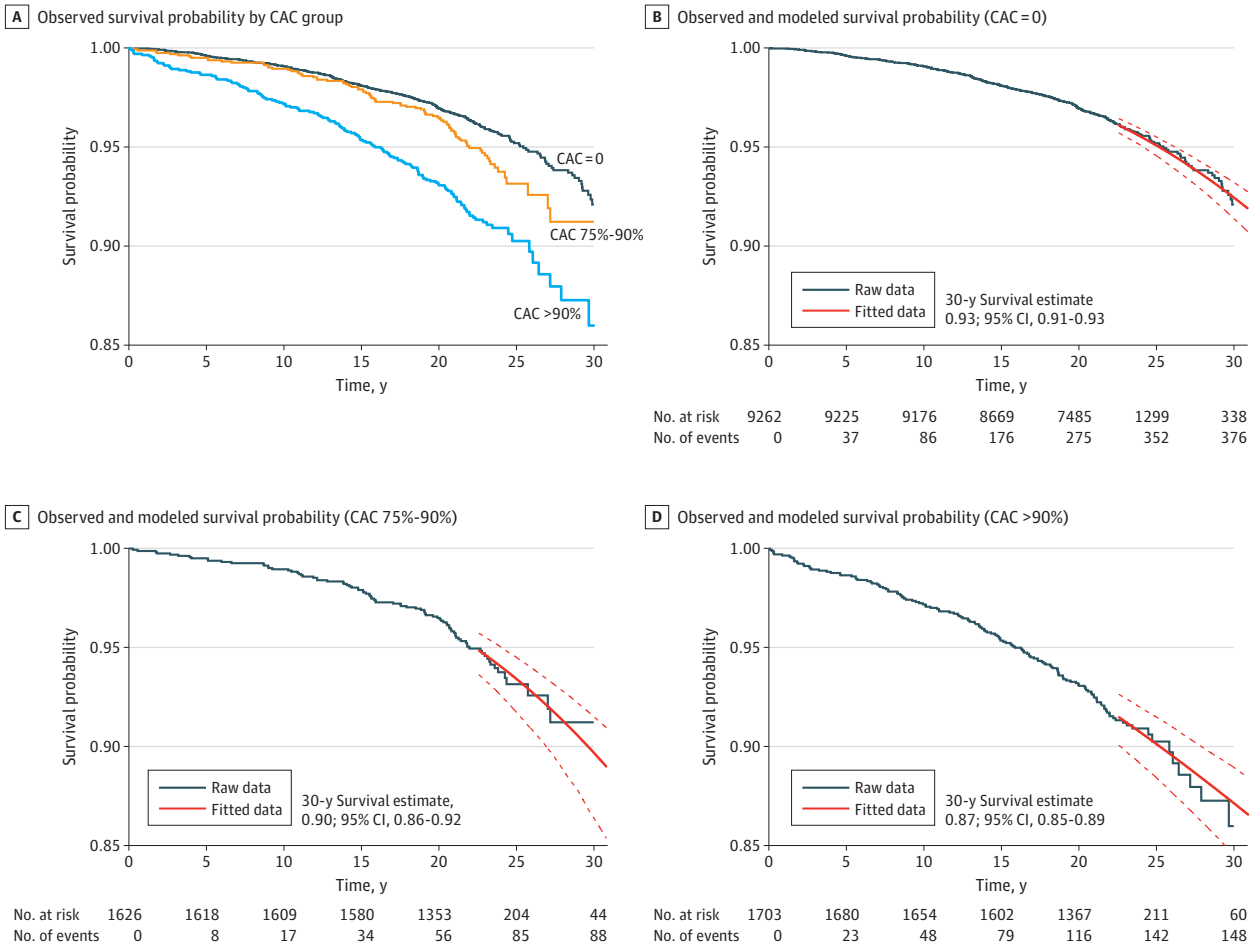
Over the 30-year time horizon, the proportion of mortality attributable to CVD was estimated to be 20% in individuals with CAC score of 0, 29% in the group with CAC score between 75% and 90%, and 35% in the group with CAC score greater than 90%. The proportion of mortality attributable to CHD was estimated to be 8% in individuals with CAC score of 0, 18% in the group with CAC score between 75% and 90%, and 23% in the group with CAC score greater than 90% (**Table 3** and eFigure 4 in Supplement 1).

The proportion of CHD mortality among CVD mortality was higher with increasing CAC percentile group. Over 30 years, 40% of CVD deaths were estimated to be CHD deaths in individuals with CAC score of 0. This proportion was greater in higher CAC percentile groups, amounting to 60% in the group

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Figure 2. Observed and Modeled Survival Probability of All-Cause Mortality by Coronary Artery Calcium (CAC) Percentile Group



with CAC score between 75% and 90% and 67% in the group with CAC score greater than 90% (Table 3 and eFigure 4 in Supplement 1).

Event Rates and Cumulative Incidence of All-Cause Mortality With CAC as a Continuous Variable

Figure 3 presents event rates of overall and sex-specific all-cause mortality per CAC score strata and proportional contributions of CAC percentile groups within each strata, along with long-term (20-, 25-, and 30-year) cumulative incidence of all-cause mortality, using CAC score as a continuous variable. eFigure 5 in Supplement 1 presents additional panels showing cumulative incidence in a rescaled y-axis to better illustrate differences in outcomes with increasing CAC.

Overall event rates of all-cause mortality for CAC of 0, CAC 1 to 10, CAC 101 to 300, and CAC greater than 300 were 1.8, 2.1, 3.3, 3.6, and 9.6 deaths per 1000 person-years, respectively. In male participants, all-cause mortality event rates were 1.8, 2.0, 3.2, 3.3, and 9.4 deaths per 1000 person-years, respectively. In female participants, all-cause mortality event rates were 1.8, 3.0, 4.1, 7.4, and 12.2, respectively. Cumulative incidences of all-cause mortality for the group with CAC of 0, median CAC score of the group with CAC between 75% and 95% (6.0 AU), and median CAC score of the group with CAC greater than 90% (56.4 AU) were 2.6% (95% CI, 2.5-2.7), 3.6% (95% CI, 3.0-4.4), and 4.7% (95% CI, 3.8-5.8), respectively, at 20 years, 4.2% (95% CI, 4.0-4.4), 5.7% (95% CI, 4.6-7.0), and 7.4% (95% CI, 6.0-9.1), respectively, at 25 years, and 6.5% (95% CI, 6.2-6.8), 8.8% (95% CI, 7.2-10.7), and 11.4% (95% CI, 9.3-13.9), respectively, at 30 years.

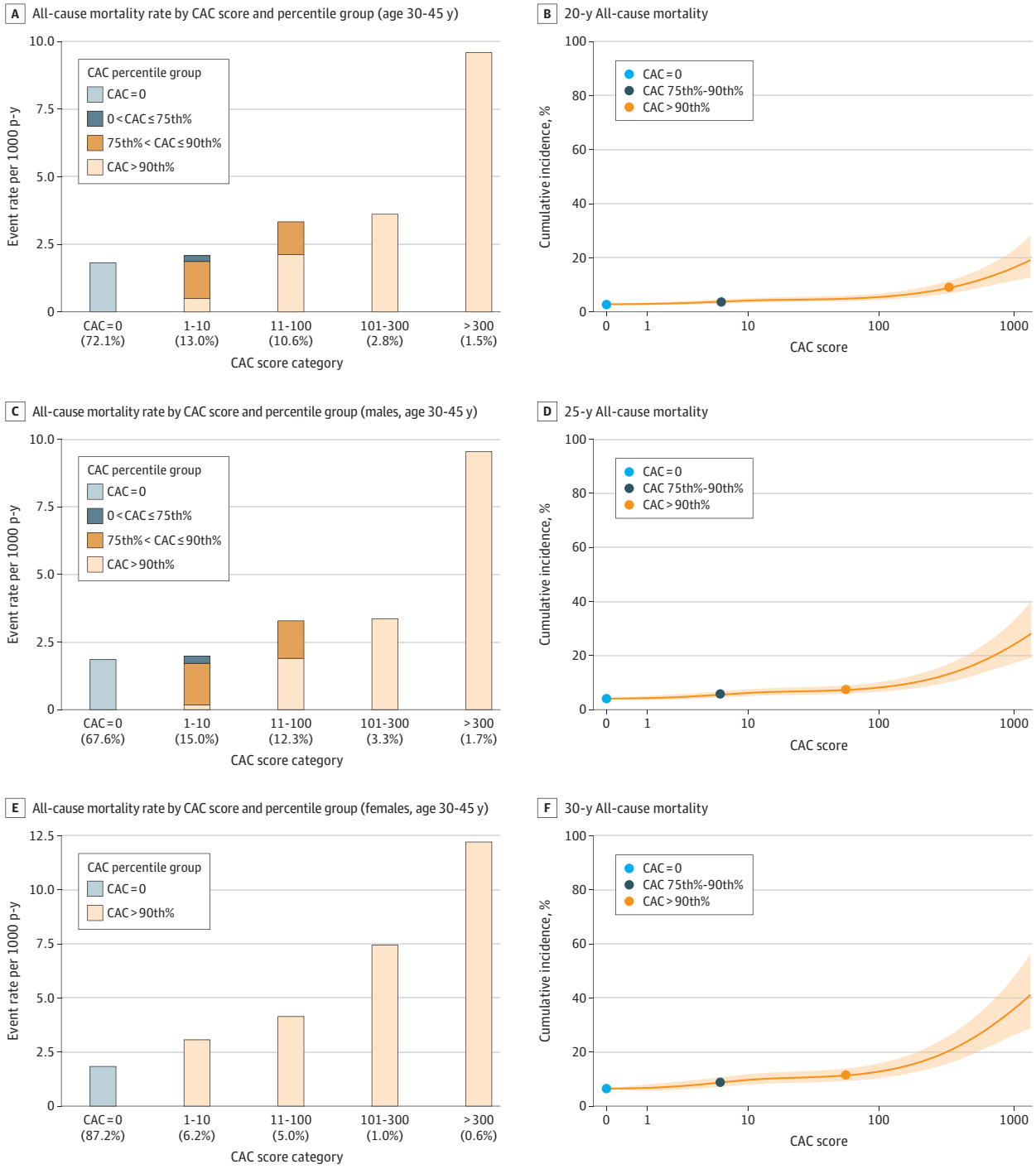
Event rates and long-term (20-, 25-, and 30-year) cumulative incidence of CVD and CHD mortality, using the continuous CAC variable, are reported in the eResults in Supplement 1 and are shown in eFigures 6 and 7 in Supplement 1.

Discussion

In this study, we used the most up-to-date long-term mortality follow-up data from the CAC Consortium to assess and quantify the implications of premature subclinical atherosclerosis over the 20- to 30-year time horizon in young adults aged 30 to 45 years. Within this population, in whom the presence of CAC is typically unexpected and considered premature, we focused on individuals in the top decile of CAC scores for their demographics. The significance of CAC greater than 90% largely lies in the

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Figure 3. Bar and Line Graphs Showing Event Rates and Cumulative Incidence of All-Cause Mortality



A, C, and E, Bar height equals the total event rate, and segments show proportional contribution of each percentile group; total participant number is 12 847, 9922, and 2925, respectively. The percentage below each score category indicates its contribution to the demographic represented by the respective panel. B, Of 12 847 participants, 10 421 (81.1%) had follow-up beyond 20 years. D, Of 12 847 participants, 1759 (13.7%) had follow-up beyond 25 years. F, Of 12 847 participants, 452 (3.5%) had follow-up beyond 30 years. CAC indicates coronary artery calcium.

markedly elevated ASCVD risk it confers over an extended period. It is noteworthy that, although the group with CAC greater than 90% comprised only 13% of our study population, they accounted for 30.2% of CVD deaths and 35.8% of CHD deaths over 30 years. With growing recognition of the benefits of early detection and preventive intervention, our study addresses a critical gap in the literature and offers utility in guiding the intensification of preventive management.[6,25,26]

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Table 3. Long-Term (25- and 30-Year) Cardiovascular Mortality Risk and Proportion of Mortality by Coronary Artery Calcium (CAC) Percentile Group

Group	25-y Follow-up, cumulative incidence, No. (%)		25-y Follow-up, proportion of total deaths[a]		25-y Follow-up, CHD death proportion of CVD deaths[b]	30-y Follow-up, cumulative incidence, No. (%)		30-y Follow-up, proportion of total deaths[a]		30-y Follow-up, CHD death proportion of CVD deaths, No. (%)[b]
	CVD death	CHD death	CVD death	CHD death		CVD death	CHD death	CVD death	CHD death	
CAC = 0	73 (1.0)	33 (0.4)	20.4	8.2	40.2	76 (1.5)	34 (0.6)	20.0	8.0	40.0
CAC 75%-90%	27 (2.0)	17 (1.2)	30.3	18.2	60.1	27 (3.0)	17 (1.8)	29.1	17.5	60.1
CAC >90%	45 (3.1)	29 (2.1)	31.3	21.2	67.7	45 (4.5)	29 (3.0)	34.9	23.3	66.8

Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease.

[a] Proportion of deaths attributable to the specific cause, presented as a percentage.

[b] Proportion of CVD deaths attributable to CHD, presented as a percentage.

Despite the risk associated with CAC greater than 90%, current prevention and cholesterol guidelines do not specifically address this phenotype and provide limited guidance on CAC scoring in young adults.[2,4] The 2026 AHA/ACC cholesterol guidelines endorse a uniform LDL goal of 70 mg/dL for CAC score greater than or equal to 100 AU or greater than or equal to 75th percentile in accordance with the 2022 ACC expert consensus decision pathway (ECDP) on nonstatin use.[27] However, this broad threshold may overlook individuals at distinctly high long-term risk of events, such as the group with CAC greater than 90%. Our findings are consistent with the proposed updates of Burka et al[28] to the 2022 ACC ECDP document to highlight the group with CAC greater than 90% alongside those with CAC greater than 300 AU. Despite relatively low absolute CAC scores compared with thresholds in current guidelines, our analyses demonstrate that young adults with CAC greater than 90% (median CAC score of 56) have a 64% higher hazard of total mortality and a 73% higher hazard of CVD mortality over the duration of follow-up compared with those in the group with CAC between 75% and 90% (median CAC score of 6), arguing for recognition of young adults above the 90th percentile of CAC as a distinct clinical phenotype that potentially benefits from dedicated prevention and management strategies (eTable 3 in Supplement 1).

The 2026 AHA/ACC cholesterol guidelines gave a class 2a recommendation to endorse that it is reasonable to initiate treatment with the presence of any CAC.[2] The markedly elevated risk in young adults associated with CAC greater than 90% has the potential to further inform discussions about refining treatment decisions specifically regarding the intensity of preventive treatment in this group. The 2026 AHA/ACC cholesterol guidelines are predicated on the philosophy that patients with the highest risk should be treated to the most aggressive LDL goals. Our data show that CAC greater than 90% represents a particularly high-risk phenotype, distinct from not only from those with CAC of 0, but also those with CAC between 75% and 90%. To treat or not to treat may be a binary decision. However, consistent with the approach of current guidelines, we believe that patients who bear the highest risk must receive treatment of the highest intensity. Our study is limited by the fact that this is not a randomized clinical trial and, therefore, cannot demonstrate treatment effects. However, with future studies that quantify the effects of such treatment intensification strategies, future guidelines may endorse lower LDL goals in these patients representing the top decile of risk.

Evidence from the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial demonstrates that statin therapy significantly reduces the incidence of first cardiovascular events and mortality, even among individuals traditionally considered low risk, thereby supporting its use for primary prevention.[29-32] Additionally, findings from the Cholesterol Treatment Trialists' Collaboration demonstrate that the benefits of statin therapy on vascular events accumulate with ongoing treatment, whereas short-term treatment yields limited benefits.[33] Therefore, future guidelines may advocate for early aggressive preventive intervention and go further as to guide the intensity of treatment in those with premature advanced subclinical atherosclerosis, the effects of which may accrue into substantial benefit over the 20- to 30-year time horizons.[34-38]

Beyond the 90th percentile of CAC, we also reaffirmed the low risk associated with a CAC score of 0, which serves as an important clinical counterpoint to CAC greater than 90%.[39-41] In our analysis, CAC of 0 was associated with only a very low 1.5% estimated risk of CVD and a 0.6% estimated risk of CHD mortality over 30 years. Our study reinforces the low risk associated with absent CAC, which, in turn, emphasizes the novelty of our findings regarding CAC greater than 90%, positioning this group as a distinct phenotype of clinical significance. Our quantification of 20- to 30-year risk provides clinicians with a practical tool for communicating long-term risk to young patients as they approach ages 60 to 75 years, when the burden of CVD typically becomes more pronounced.[42-44]

Strengths and Limitations

This study has some strengths. We used the CAC Consortium, the largest CAC database yet assembled with the longest consecutive follow-up and investigated long-term implications of CAC in young adults in the highest risk group.[16] Our study offers direct insight into mortality risk and highlights the phenotype that potentially benefits from targeted prevention efforts.

This study also has some limitations. Our study is limited by the inherent properties of the CAC Consortium. It is a clinical cohort, making it less standardized and community representative than traditional prospective cohorts such as Framingham, Atherosclerosis Risk in Communities (ARIC), and Multi-Ethnic Study of Atherosclerosis (MESA).[45-47] Also, as it is not a randomized clinical trial, there are limitations in recommending and guiding treatment initiation and intensity with the results of this study alone. Additionally, as it is not a natural history cohort, elevated CAC scores likely affected down-

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stream treatments and interventions. This may have led to an underestimation of the isolated impact of CAC, particularly in groups with higher health care use, where the effects of treatment may have attenuated the relationship between CAC and mortality. The results are, therefore, less generalizable to nonclinical populations. Nevertheless, it could be argued that data from the CAC Consortium accurately reflects scenarios encountered in everyday clinical practice.[16]

Additional limitations include those due to insufficient power and follow-up. Although the subdistribution HR for CHD mortality in the group with CAC greater than 90% was higher than that compared with the group with CAC between 75% and 90%, this difference did not reach statistical significance, likely due to the limited number of events, warranting further studies with greater statistical power (eTable 3 in Supplement 1). Although our estimations of mortality over up to 30-year time horizon are grounded in statistically robust methods and provide clinically meaningful insight, it is of note that only 3.5% of our study population had follow-up beyond 30 years and that these results cannot substitute those of future reports when CAC cohorts will have accumulated full 30-year follow-up.

Furthermore, relying solely on baseline CAC scores may have resulted in diminishing differences in risk across CAC percentile groups with extended follow-up, underlining the necessity of studies that include subsequent CAC measurements to capture residual conversions from CAC of 0 to a nonzero CAC and refine risk estimates. Lastly, limitations in mortality ascertainment using death registries and underlying cause of death from death certificates have been previously reported and discussed in the original study design of the CAC Consortium.[16,48-50]

Conclusions

This cohort study was the first, to our knowledge, to describe long-term risk of mortality up to 30 years associated with advanced subclinical atherosclerosis in young adults aged 30 to 45 years, with an emphasis on individuals with CAC above the 90th percentile. We demonstrated that this population is at elevated lifetime risk of all-cause, CVD, and CHD mortality compared with the majority of their peers. Our data may inform future guidelines to acknowledge the unique risk associated with this group, facilitating early preventive measures that mitigate the risk burden that CAC greater than 90% confers throughout the life course.

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