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Cardiovascular risk stratification among individuals with obesity: The Coronary Artery Calcium Consortium

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Abstract

Objective: The effectiveness of coronary artery calcification (CAC) for risk stratification in obesity, in which imaging is often limited because of a reduced signal to noise ratio, has not been well studied.

Methods: Data from 9334 participants (mean age: 53.3 ± 9.7 years; 67.9% men) with BMI ≥ 30 kg/m^2 from the CAC Consortium, a retrospectively assembled cohort of individuals with no prior cardiovascular diseases (CVD), were used. The predictive value of CAC for all-cause and cause-specific mortality was evaluated using multivariable-adjusted Cox proportional hazards and competing-risks regression.

Results: Mean BMI was 34.5 (SD 4.4) kg/m^2 (22.7% Class II and 10.8% Class III obesity), and 5461 (58.5%) had CAC. Compared with CAC = 0, those with CAC = 1–99, 100–299, and ≥300 Agatston units had higher rates (per 1000 person-years) of all-cause (1.97 vs. 3.5 vs. 5.2 vs. 11.3), CVD (0.4 vs. 1.1 vs. 1.5 vs. 4.2), and coronary heart disease (CHD) mortality (0.2 vs. 0.6 vs. 0.6 vs. 2.5), respectively, after mean follow-up of 10.8 ± 3.0 years. After adjusting for traditional cardiovascular risk factors,

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CAC ≥ 300 was associated with significantly higher risk of all-cause (hazard ratio [HR]: 2.05; 95% CI: 1.49–2.82), CVD (subdistribution HR: 3.48; 95% CI: 1.81–6.70), and CHD mortality (subdistribution HR: 5.44; 95% CI: 2.02–14.66), compared with CAC = 0. When restricting the sample to individuals with BMI ≥ 35 kg/m^2, CAC ≥ 300 remained significantly associated with the highest risk.

Conclusions: Among individuals with obesity, including moderate–severe obesity, CAC strongly predicts all-cause, CVD, and CHD mortality and may serve as an effective cardiovascular risk stratification tool to prioritize the allocation of therapies for weight management.

INTRODUCTION

The prevalence of obesity has significantly increased over several decades, with an estimated prevalence of 42.4% among adults in the United States (US) in the 2017–2018 National Health and Nutrition Examination Survey (NHANES) [1–3]. Obesity not only increases the likelihood of developing cardiovascular risk factors, including diabetes and hypertension, but it is also an independent risk factor for cardiovascular diseases (CVD), including coronary heart disease (CHD), atrial fibrillation, heart failure, and stroke [4–6]. Additionally, the health care costs associated with obesity have more than doubled over the past two decades and they accounted for more than $260 billion in medical expenditures among US adults in 2016 [7].

Comprehensive and multimodal approaches such as evidence-based behavioral interventions, including healthy diet and physical activity as well as pharmacotherapy and bariatric surgery, are crucial in managing obesity and its associated complications [8]. Although bariatric surgery has proven efficacy in the treatment of obesity [9, 10], newer incretin-based antiobesity medications (AOMs) such as the glucagon-like peptide-1 (GLP-1) analogs and the combined glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 analogs have emerged as promising new therapies, demonstrating impressive weight loss outcomes, improvements in obesity-associated comorbidities, and significant reduction in CVD when used in patients with diabetes [11–13]. Because of the significant costs associated with these newer AOMs, it is important to risk-stratify individuals with obesity to identify those who would likely benefit the most from these medications. Risk stratification may be particularly important in this population because there are known heterogeneities in the cardiovascular and metabolic risks associated with different obesity phenotypes [14]. However, most current risk algorithms, including the Pooled Cohort Equation and the Framingham Risk Score [15, 16], do not consider obesity an independent risk factor for CVD. Additionally, obesity was not considered a "risk-enhancing" factor for CVD in the 2019 American College of Cardiology (ACC)/American Heart Association (AHA) prevention guidelines, although it was regarded as a "risk modifier" in the 2019 European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) dyslipidemia guidelines [17, 18].

Simple, clinically relevant, and easily accessible risk stratification tools among individuals with obesity are necessary. Coronary artery calcification (CAC) is measured noninvasively using cardiac-gated computed tomography (CT) scans and quantified using the Agatston score. The association between body mass index (BMI) and CAC has previously been studied, showing that individuals with obesity were more likely to have prevalent CAC compared with those with normal BMI [19]. CAC is an effective and reliable risk stratification tool across different population subgroups [20]. For example, among individuals with borderline (5%–7.5%) or intermediate (7.5%–20%) 10-year atherosclerotic cardiovascular disease (ASCVD) risk, CAC has the potential to restratify these persons to guide in the allocation of preventive therapies such as statin therapy and possibly aspirin [21]. Cainzos-Achirica et al. demonstrated that CAC could be used to identify subgroups of patients in whom the number needed to treat with aspirin is significantly lower than the number needed to harm across ASCVD risk strata [21]. However, among individuals with obesity, imaging can be challenging because of a reduced signal to noise ratio, and it remains unclear

Study Importance

What is already known?

- There is considerable heterogeneity in cardiometabolic risk among individuals with obesity. However, little attention has been paid to risk stratification in this population.

What does this study add?

- Coronary artery calcification (CAC), measured noninvasively with cardiac-gated computed tomography, can serve as an effective cardiovascular risk stratification tool among individuals with obesity.

How might these results change the direction of research or the focus of clinical practice?

- CAC can risk-stratify individuals with obesity and may help identify optimal candidates for novel but costly antiobesity medications.

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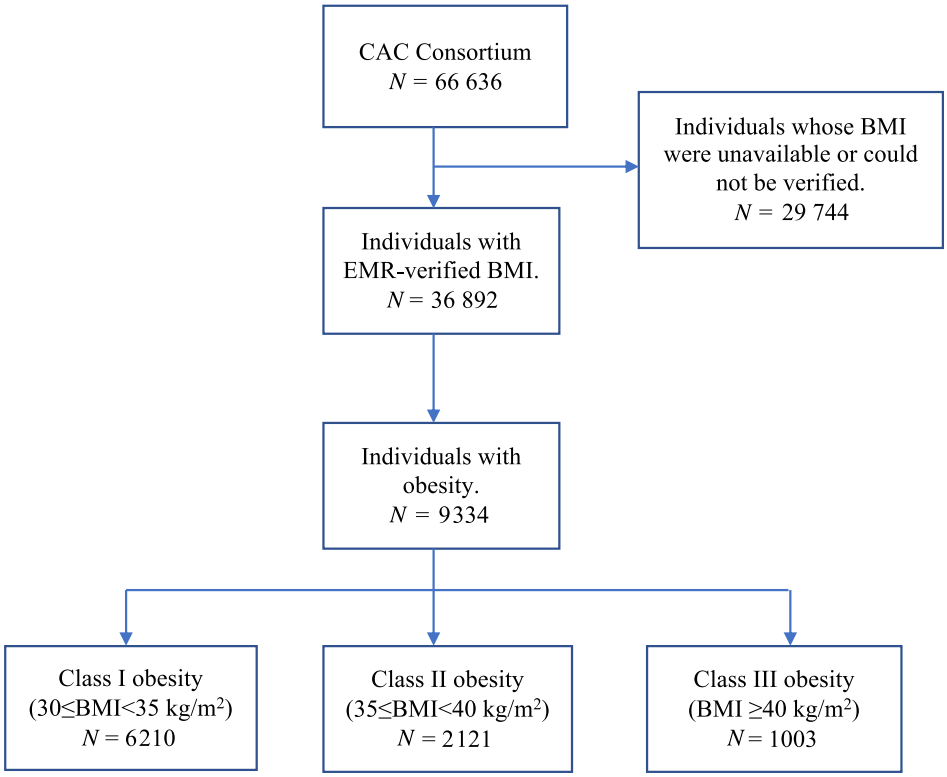

FIGURE 1 Flowchart of the analytic sample. CAC, coronary artery calcification, EMR, electronic medical records [Color figure can be viewed at wileyonlinelibrary.com]

whether CT-obtained CAC scores are an effective risk stratification tool in this population [22].

We hypothesized that despite the imaging challenges, CAC would be an effective cardiovascular risk stratification tool among individuals with obesity, including those with severe obesity. We, therefore, examined the utility of CAC for risk stratification among individuals with obesity by evaluating the predictive value of CAC for all-cause, cardiovascular, and CHD mortality in this population.

METHODS

Study population and study design

The CAC Consortium is a retrospectively assembled cohort of 66,636 individuals 18 years and older and without prior history of CVD who were referred for CAC scoring between 1991 and 2010 by their clinicians to evaluate for subclinical atherosclerosis. Baseline data on participants were obtained from four study institutions: 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. Consent for participation was collected at each study center, and institutional review board approval for coordinating center activities was obtained at the Johns Hopkins Hospital. A detailed description of the study design and methods has been previously published [23]; 36,892 individuals in the CAC Consortium had well-documented and electronic medical record-verified BMI data recorded at the time of CAC scoring. In this study, we restricted our sample to individuals with obesity defined as BMI ≥ 30 kg/m^2, giving an analytic sample size of 9334 individuals (Figure 1).

Measurement of CAC

Noncontrast cardiac-gated CT scans for CAC scoring were performed at each site according to a common standard protocol, which involves altering the tube current based on a patient's weight/BMI. CAC was quantified using the Agatston method. Most patients (93%) were scanned using electron beam tomography, whereas the remaining participants (7%) were scanned using multidetector CT. Prior studies have shown no clinically meaningful differences between CAC scores derived from electron beam tomography versus multidetector CT scanners [24]. We stratified CAC as absent versus present and by traditional clinical CAC categories: 0, 1–99, 100–299, and ≥300 Agatston units (AU) [25].

Outcome ascertainment

Mortality status was ascertained by linking patients' records with the Social Security Administration Death Master File via a validated algorithm. Unique patient identifiers including first/last name, date of birth, and Social Security number were used to search almost

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everyone in the death index data. Death certificates were obtained from the National Death Index, and deaths were categorized using International Classification of Diseases codes into common causes of death [23]. Outcomes of interest in this study were all-cause, cardiovascular, and CHD mortality.

Covariate assessment and evaluation of ASCVD risk factors

Patient demographics (age, sex, and race [Asian, Black, Hispanic, White, and other]) and data on ASCVD risk factors were collected at the time of CAC scanning. Hypertension was present if there was a prior diagnosis of hypertension or treatment with antihypertensive therapy. Similarly, diabetes was defined as a previous diagnosis of diabetes or treatment with oral hypoglycemic drugs or insulin. Dyslipidemia was defined as a prior diagnosis of dyslipidemia (elevated triglycerides, elevated low-density lipoprotein cholesterol [LDL-C], or low high-density lipoprotein cholesterol [HDL-C]), treatment with any lipid-lowering drug, or abnormal lipid parameters on testing (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 determined by the presence of smoking at the time of CAC scanning and categorized as current and noncurrent. Finally, a family history of CHD was determined by the presence of a first-degree relative with a history of CHD or a family history of premature CHD (< 55 years old in a male relative and < 65 years old in a female relative) [23]. Missing risk factors were imputed using a multivariable model adjusting for age, sex, race, CAC score, and the remaining nonmissing traditional risk factors, as per the design of the CAC Consortium [23].

Statistical analysis

We summarized the baseline characteristics of the study participants using means, medians, and proportions for normally distributed continuous variables, non-normally distributed continuous variables, and categorical variables, respectively. The baseline characteristics were summarized first for the entire sample and then by CAC burden categories (0, 1–99, 100–299, and ≥ 300 AU). Differences in proportions were tested using the $\chi 2$ test, whereas the differences in means were tested using the ANOVA test.

We estimated the crude rates for all-cause, cardiovascular, and CHD mortality at the end of the follow-up period (mean follow-up of 10.8 ± 3.0 years) for each CAC burden category. Then, using Cox proportional hazard models to obtain hazard ratios (HR), we examined the association of CAC with all-cause mortality. Additionally, we used Fine and Gray competing-risk regression models to obtain subdistribution hazard ratios (SHR) of the association of CAC with cardiovascular and CHD mortality. To further assess whether the association of CAC with the three outcomes of interest was maintained among patients with moderate to severe obesity, we restricted our analysis to individuals with ≥ Class II obesity (≥ 35 kg/m^2; $N = 3124$). Model 1 was unadjusted; Model 2 was adjusted for age and sex; and Model 3 was adjusted for age, sex, study site, hypertension, dyslipidemia, smoking, diabetes, and family history of CHD. Race was not adjusted for in our primary analysis because of missingness (8.7%), which would have led to a smaller analytic sample and imprecise estimates, particularly for our restricted analysis. However, in supplementary analysis using the overall study sample, we additionally adjusted for race. Finally, to further evaluate the discriminatory value of CAC independent of traditional ASCVD risk factors for the prediction of mortality, we assessed the area under the receiver operating curves for fully adjusted models with and without CAC.

All analyses were conducted using Stata 16 software (StataCorp LLC, College Station, Texas). A two-sided α of $p < 0.05$ was considered statistically significant.

RESULTS

Of the 9334 study participants with a mean (SD) age of 53.3 (9.7) years and mean (SD) BMI of 34.5 (4.4) kg/m^2, the majority were males (67.9%) and White (92.5%), and 58.5% (5461) had any CAC; 22.7% had Class II obesity (BMI 35–39.9 kg/m^2), whereas 10.8% had Class III obesity (BMI ≥ 40 kg/m^2). Dyslipidemia was the most prevalent ASCVD risk factor (62.1%), followed by family history of CHD (50.9%), whereas diabetes was the least prevalent risk factor (10.5%). There was a graded increase in age, proportion of males, and prevalence of hypertension, dyslipidemia, and diabetes across increasing CAC categories. There was no significant difference in BMI distribution across CAC categories (Table 1). The distribution of CAC across the classes of obesity is presented in Table 2.

After a mean (SD) follow-up of 10.8 (3.0) years, there were 414 all-cause deaths, 129 cardiovascular deaths, and 69 CHD deaths. When compared with persons with a CAC score of 0 who had very low event rates, those with CAC > 0 AU had a higher mortality rate from all-cause (5.65 vs. 1.97 per 1000 person-years), CVD (1.89 vs. 0.43 per 1000 person-years), and CHD (1.04 vs. 0.19 per 1000 person-years). The all-cause mortality rate increased in a graded fashion with increasing CAC burden category (Figure 2). A similar trend was observed for cardiovascular and CHD mortality rates (Figure 2).

In multivariable-adjusted analysis, individuals with CAC > 0 AU had higher hazards of all-cause (HR: 1.43; 95% CI: 1.10–1.85), cardiovascular (SHR: 2.14; 95% CI: 1.25–3.68), and CHD mortality (SHR: 2.79; 95% CI: 1.23–6.31) compared with those without CAC (Table 3). When further stratified by CAC burden categories, individuals with CAC ≥300 AU consistently had significantly higher hazards of all-cause (HR: 2.05; 95% CI: 1.49–2.82), cardiovascular (SHR: 3.48; 95% CI: 1.81–6.70), and CHD mortality (SHR: 5.44; 95% CI: 2.02–14.66) compared with those with a CAC score of 0 AU (Table 3). There was no significant sex interaction with the association of CAC with all-cause, cardiovascular, and CHD mortality. Modeling CAC as a log-transformed continuous variable did not alter the inference of our findings (Table 3). In addition, when the models were additionally adjusted for race, CAC remained strongly associated with all-cause, cardiovascular, and CHD mortality (Supporting Information Table S1). The addition of CAC to the model with age, sex, study site, and ASCVD risk factors significantly increased the area under

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TABLE 1 Baseline characteristics of study population stratified by categories of CAC score

	Total, $N = 9334$	CAC = 0 AU, $N = 3873$	CAC = 1–99 AU, $N = 3032$	CAC = 100–299 AU, $N = 1101$	CAC ≥300 AU, $N = 1328$	*p* value
Age (y)	53.3 (±9.7)	49.1 (±8.7)	53.4 (±8.7)	57.6 (±8.3)	61.3 (±9.0)	<0.001
Male sex	6340 (67.9)	2168 (56.0)	2193 (72.3)	855 (77.7)	1124 (84.6)	<0.001
Race						0.048
Asian	79 (0.9)	32 (0.9)	27 (1.0)	9 (0.9)	11 (0.9)	
Black	214 (2.5)	109 (3.1)	69 (2.4)	18 (1.8)	18 (1.5)	
Hispanic	207 (2.4)	73 (2.1)	84 (3.0)	27 (2.7)	23 (1.9)	
White	7877 (92.5)	3248 (92.4)	2575 (91.8)	927 (92.5)	1127 (93.9)	
Other	145 (1.7)	53 (1.5)	50 (1.8)	21 (2.1)	21 (1.8)	
Hypertension	3604 (38.6)	1200 (31.0)	1165 (38.4)	512 (46.5)	727 (54.7)	<0.001
Dyslipidemia	5799 (62.1)	2196 (56.7)	1913 (63.1)	741 (67.3)	949 (71.5)	<0.001
Current smoker	1003 (10.8)	392 (10.1)	297 (9.8)	141 (12.8)	173 (13.0)	0.001
Diabetes	981 (10.5)	231 (6.0)	296 (9.8)	164 (14.9)	290 (21.8)	<0.001
Family history of CHD	4750 (50.9)	1962 (50.7)	1549 (51.1)	573 (52.0)	666 (50.2)	0.799
BMI, kg/m^2	34.5 (±4.4)	34.5 (±4.4)	34.6 (±4.7)	34.6 (±4.2)	34.3 (±4.2)	0.132
Class of obesity						0.310
I	6210 (66.5)	2608 (67.3)	1991 (65.7)	712 (64.7)	899 (67.7)	
II	2121 (22.7)	852 (22.0)	696 (23.0)	272 (24.7)	301 (22.7)	
III	1003 (10.8)	413 (10.7)	345 (11.4)	117 (10.6)	128 (9.6)	
Median CAC score, AU	6 (0.0, 109.4)	0 (0.0, 0.0)	19 (5.7, 44.0)	170 (129.5, 218.3)	686.6 (434.4, 1242.7)	

Abbreviations: AU, Agatston units; CAC, coronary artery calcification; CHD, coronary heart disease.

TABLE 2 Distribution of CAC by classes of obesity

	Class I obesity, $N = 6210$ (%)	Class II obesity, $N = 2121$ (%)	Class III obesity, $N = 1003$ (%)
CAC = 0	2608 (42.0)	852 (40.2)	413 (41.2)
CAC 1–99	1991 (32.1)	696 (32.8)	345 (34.4)
CAC 100–299	712 (11.5)	272 (12.8)	117 (11.7)
CAC ≥ 300	899 (14.5)	301 (14.2)	128 (12.8)
Median CAC (interquartile interval)	5.9 (0, 109)	7.2 (0, 117)	6.0 (0, 92.9)

Abbreviation: CAC, coronary artery calcification.

the curve for all three outcomes explored (Supporting Information Table S2).

When restricting our sample to the 3124 participants with ≥ Class II obesity, CAC ≥ 300 AU remained significantly associated with all-cause (HR: 2.23; 95% CI: 1.32–3.78), cardiovascular (SHR: 4.99; 95% CI: 1.84–13.56), and CHD mortality (SHR: 29.87; 95% CI: 3.44–259.04) after adjustment for age, sex, study site, and ASCVD risk factors (Table 4).

DISCUSSION

In this cohort of individuals with obesity but without CVD at baseline, we found that CAC was common, being prevalent in 58.5% of the study population. In addition, CAC strongly and independently predicted all-cause, cardiovascular, and CHD mortality, with a similarly strong predictive relationship particularly among patients with Class II or Class III obesity.

The prevalence of obesity among adults in the US has been increasing over the past several decades [3]. Although behavioral and lifestyle modifications are the foundation of obesity management, they have not demonstrated reliable or sustained large weight loss (≥ 10% of total body weight) in the majority of people with obesity [8, 26–28]. Moreover, the pathophysiology of obesity involves complex interactions between biological, behavioral, and environmental factors, and hence, effective treatment for obesity often requires the addition of biological-based measures, such as bariatric surgery or pharmacotherapy to lifestyle modifications [29, 30].

Newer AOMs, including the GLP-1 analogs and the combined GIP/GLP-1 analogs, effectively cause significant and sustained weight loss (16%–22% weight loss over approximately 1 year of therapy) among individuals with obesity when combined with lifestyle interventions [11, 12]. Because of the rising costs associated with the expanding population of patients with obesity along with worldwide shortages in supply, access to these newer AOMs is limited. For example, the cost of 2.4 mg weekly of semaglutide is approximately $17,600 per year for a patient on maintenance treatment, which places a significant financial burden on patients and society to cover ongoing costs of expensive treatment [31]. Additionally, these medications are not without side effects [32]. Therefore, as we enter into an era of expanded obesity pharmacotherapy and to prioritize

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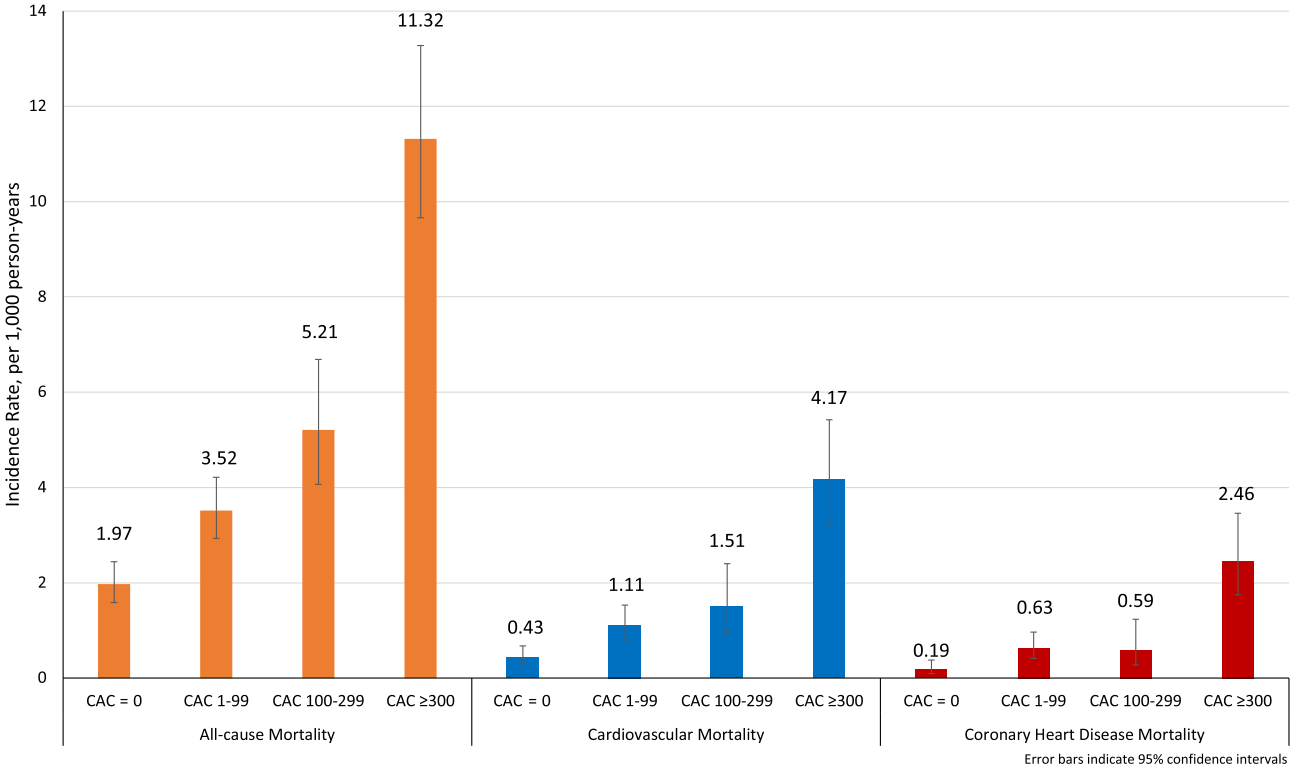

FIGURE 2 Rates of all-cause, cardiovascular, and coronary heart disease mortality by coronary artery calcification (CAC) burden categories. [Color figure can be viewed at wileyonlinelibrary.com]

treatment to those most likely to benefit—which is a key tenet of prevention—it will be necessary to risk-stratify people with obesity, identifying patients who would benefit the most from these medications.

We demonstrate that CAC, which is more prevalent in persons with obesity compared with individuals with normal BMI [19], can serve as an effective risk stratification tool among individuals with obesity, similar to its ability to risk-stratify among other population subgroups, including young adults, patients with diabetes, and individuals at borderline or intermediate ASCVD risk [17, 33–35]. The presence of CAC was associated with a 1.4-fold higher hazard of all-cause mortality and a 2.1-fold and 2.7-fold higher hazard of cardiovascular and CHD mortality, respectively. Importantly, the negative predictive value of CAC = 0 AU, that is, the power of zero, appeared to be maintained [36, 37]. Furthermore, a higher CAC burden (≥ 300 AU) was associated with even higher risk of all three outcomes of interest, particularly among individuals with ≥ Class II obesity, even after adjusting for the traditional ASCVD risk factors. Therefore, a higher CAC score may reclassify an individual with obesity who would most likely benefit from these novel AOMs. A similar approach has been suggested by Cainzos-Achirica et al. in patients with diabetes, where their study showed the utility of CAC in identifying optimal candidates for novel but costly atherosclerosis risk reduction therapies [38]. For these newer and costly AOMs, efficient and high-value care would require identifying subgroups of patients who would obtain the most benefit from these medications.

These newer incretin-based AOMs, also used in the managing type 2 diabetes, are efficacious in reducing adverse cardiovascular events among patients with diabetes while demonstrating a favorable safety profile [13]. Among individuals with obesity but without diabetes, such studies are currently under way [39, 40]. The Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity (SELECT) study and the Study of Tirzepatide on the Reduction of Morbidity and Mortality in Adults with Obesity (SURMOUNT-MMO) are two ongoing trials to evaluate the efficacy of these medications in preventing major adverse cardiovascular events in patients with overweight or obesity who do not have diabetes [39, 40]. In anticipating the results of these trials, particularly if the risk reduction is small or moderate, it is important to identify the subgroups of individuals with obesity and without ASCVD who would likely obtain the most benefit from these novel but costly medications.

Our findings should be interpreted in the setting of some limitations. First, the CAC Consortium is composed of self-referred and clinically/physician-referred patients; hence, the results of this study may be less generalizable to the general population but likely to the population actively engaged in the health care system. Secondly, the CAC Consortium has few patients with BMI ≥ 50 kg/m^2, a group that is growing clinically. In addition, because of the low event rates, particularly for CHD mortality, we were unable to present outcomes stratified according to the interplay of CAC and obesity categories. Additionally, data on other measures to assess obesity, such as waist

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TABLE 3 Mortality rates, hazard ratios (HR), and subdistribution hazard ratios (SHR) for all-cause and cause-specific mortality with increasing CAC

	Mortality rate	Model 1		Model 2		Model 3	
		HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
All-cause mortality							
Log-transformed CAC	-	1.30 (1.25–1.35)	<0.001	1.12 (1.07–1.17)	<0.001	1.11 (1.06–1.16)	<0.001
No CAC	1.97	Ref		Ref		Ref	
CAC present	5.65	2.87 (2.25–3.65)	<0.001	1.47 (1.13–1.90)	0.004	1.43 (1.10–1.85)	0.008
1–99	3.52	1.78 (1.34–2.36)	<0.001	1.27 (0.95–1.69)	0.107	1.27 (0.95–1.70)	0.107
100–300	5.21	2.64 (1.90–3.67)	<0.001	1.34 (0.95–1.90)	0.094	1.30 (0.92–1.85)	0.137
≥ 300	11.32	5.76 (4.41–7.53)	<0.001	2.20 (1.61–3.01)	<0.001	2.05 (1.49–2.82)	<0.001
Cardiovascular mortality		**SHR (95% CI)**	***p* value**	**SHR (95% CI)**	***p* value**	**SHR (95% CI)**	***p* value**
Log-transformed CAC	-	1.39 (1.29–1.50)	<0.001	1.23 (1.12–1.35)	<0.001	1.19 (1.09–1.31)	<0.001
No CAC	0.43	Ref		Ref		Ref	
CAC present	1.89	4.38 (2.66–7.21)	<0.001	2.35 (1.38–3.98)	0.002	2.14 (1.25–3.68)	0.006
1–99	1.11	2.59 (1.48–4.56)	0.001	1.95 (1.10–3.46)	0.023	1.88 (1.05–3.37)	0.033
100–300	1.51	3.50 (1.82–6.71)	<0.001	2.00 (0.99–4.03)	0.053	1.80 (0.90–3.63)	0.099
≥ 300	4.17	9.45 (5.56–16.07)	<0.001	4.19 (2.22–7.91)	<0.001	3.48 (1.81–6.70)	<0.001
CHD mortality		**SHR (95% CI)**	***p* value**	**SHR (95% CI)**	***p* value**	**SHR (95% CI)**	***p* value**
Log-transformed CAC	-	1.44 (1.29–1.59)	<0.001	1.32 (1.15–1.51)	<0.001	1.27 (1.11–1.46)	0.001
No CAC	0.19	Ref		Ref		Ref	
CAC present	1.04	5.40 (2.58–11.29)	<0.001	3.14 (1.41–7.01)	0.005	2.79 (1.23–6.31)	0.014
1–99	0.63	3.31 (1.47–7.49)	0.004	2.64 (1.14–6.13)	0.024	2.48 (1.06–5.80)	0.036
100–300	0.59	3.05 (1.11–8.39)	0.031	2.00 (0.65–6.13)	0.226	1.75 (0.56–5.40)	0.334
≥300	2.46	12.38 (5.72–26.84)	<0.001	6.74 (2.57–17.68)	<0.001	5.44 (2.02–14.66)	0.001

Note: The mortality rate is per 1000 person-years. Model 1: Unadjusted. Model 2: Adjusted for age and sex. Model 3: Adjusted for age, sex, study site, hypertension, dyslipidemia, smoking, diabetes, family history of coronary heart disease.
Abbreviations: CAC, coronary artery calcification; CHD, coronary heart disease.

TABLE 4 Mortality rates, hazard ratios (HR), and subdistribution hazard ratios (SHR) for all-cause and cause-specific mortality with increasing CAC among the 3124 individuals with ≥ Class II obesity (BMI ≥ 35 kg/m^2)

	All-cause mortality			Cardiovascular mortality			Coronary heart disease mortality		
CAC	Mortality rate	HR (95% CI)	*p* value	Mortality rate	SHR (95% CI)	*p* value	Mortality rate	SHR (95% CI)	*p* value
No CAC	2.00	Ref		0.36	Ref		0.07	Ref	
CAC present	6.27	1.44 (0.93–2.25)	0.106	2.17	2.57 (1.08–6.16)	0.034	1.04	9.44 (1.32–67.63)	0.025
1–100	3.62	1.21 (0.74–1.99)	0.441	1.12	2.15 (0.81–5.74)	0.126	0.52	6.77 (0.85–54.07)	0.071
100–300	5.89	1.38 (0.78–2.45)	0.267	1.41	1.85 (0.59–5.76)	0.288	0.71	8.68 (0.88–86.06)	0.065
≥300	13.60	2.23 (1.32–3.78)	0.003	5.67	4.99 (1.84–13.56)	0.002	2.72	29.87 (3.44–259.04)	0.002

Note: The mortality rate is per 1000 person-years. Models adjusted for age, sex, study site, hypertension, dyslipidemia, smoking, diabetes, and family history of coronary heart disease.
Abbreviation: CAC, coronary artery calcification.

circumference and waist–hip ratio, are not available in the CAC Consortium. Furthermore, among individuals with obesity, imaging can be challenging with the potential to misclassify those with low/minimal CAC as CAC = 0. However, such misclassification would have attenuated the strength of the associations explored (i.e., would have introduced a bias toward the null). Therefore, our data, which support a strong predictive value for CAC, similar to what has been seen in persons without obesity, are notable and argue against a substantial clinically relevant lack of precision of CAC in this population. Finally, this cohort consists of predominantly White participants. Future studies with more racially and ethnically diverse participants are needed to assess the utility of CAC in risk stratification among individuals with obesity across different races/ethnicities.

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CONCLUSION

There is considerable heterogeneity in cardiovascular risk among individuals with obesity. Therefore, risk stratification using simple, clinically relevant, and easily accessible tools is very important in this population. In addition, because of the current significant costs and side effects associated with the newer treatments for obesity, such as the incretin analogs, it is essential to identify patients in whom these risk-reducing medications would provide the most value. We have demonstrated in this study that CAC, which is cost-effective and measured noninvasively using a cardiac-gated CT scan, can serve as an effective risk stratification tool among individuals with obesity.O

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CONFLICT OF INTEREST STATEMENT

The authors declared no conflict of interest.

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