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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 calcium (CAC) for risk stratification in obesity, in which imaging is often limited due to reduced signal-to-noise ratio, has not been well studied.

Methods: We used data from 9,334 participants(mean age:53.3±9.7years;67.9%-men) with BMI≥30kg/m^2 from the CAC Consortium, a retrospectively-assembled cohort of individuals with no prior CVD. We evaluated the predictive value of CAC for all-cause and cause-specific mortality using multivariable-adjusted Cox proportional hazards and competing risks regression.

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Results: Mean BMI was 34.5±4.4kg/m^2 (22.7%-Class-II;10.8%-Class-III obesity), and 5,461(58.5%) had CAC. Compared to CAC=0, those with CAC=1-99, 100-299, and ≥300 had higher rates(per 1,000-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 CHD mortality(0.2 vs 0.6 vs 0.6 vs 2.5), after mean follow-up of 10.8±3.0years. After adjusting for traditional cardiovascular risk factors, CAC≥300 was associated with significantly higher risk of all-cause(HR:2.05;95%CI:1.49–2.82), CVD(SHR:3.48;95%CI:1.81–6.70), and CHD mortality(SHR:5.44;95%CI:2.02–14.66), compared to CAC=0. When restricting our sample to individuals with BMI≥35kg/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.

Keywords

Obesity; Risk Stratification; Coronary Artery Calcium; Pharmacotherapy; Cardiovascular

Introduction:

The prevalence of obesity has significantly increased over several decades, with an estimated prevalence of 42.4% in 2017-2018 among adults in the United States (US).[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 healthcare costs associated with obesity have more than doubled over the past two decades and accounted for over $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] While bariatric surgery has proven efficacy in the treatment of obesity,[9,10] newer incretin-based anti-obesity medications (AOMs) such as the glucagon-like peptide (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 co-morbidities, and significant reduction in CVD when used in patients with diabetes.[11-13] Due to the significant cost 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 heterogeneity 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 2018 AHA/ACC/Multi-society Cholesterol Guideline, although it was regarded as a “risk modifier” in the 2019 ESC Dyslipidemia Guideline.[17,18]

Simple, clinically relevant, and easily accessible risk stratification tools among individuals with obesity are necessary. Coronary artery calcification (CAC) is measured non-invasively 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 re-stratify 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 due to a reduced signal-to-noise ratio, and it remains unclear 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 who were 18 years and older without prior history of CVD 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, CA; PrevaHealth Wellness Diagnostic Center, Columbus, OH; Harbor-UCLA Medical Center, Torrance, CA; and Minneapolis Heart Institute, Minneapolis, MN. 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 have been previously described;[23] 36,892 individuals in the CAC Consortium had well-documented and EMR-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 9,334 individuals (Figure 1).

Measurement of CAC:

Non-contrast 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 (EBT), while the remaining participants (7%) were scanned using multi-detector CT (MDCT). Prior studies have shown no clinically

meaningful differences between CAC scores derived from EBT versus MDCT scanners.[24] We stratified CAC as absent versus present and by traditional clinical CAC categories: 0, 1-99, 100-299, and ≥300 Agatston units.[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 everyone in the death index data. Death certificates were obtained from the National Death Index, and deaths were categorized using ICD (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 anti-hypertensive 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 LDL-C, or low 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 non-current. 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 non-missing 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-square test, whereas the differences in means were tested using the analysis of variance 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 sub-distribution hazard ratios (SHR) of the association of CAC with cardiovascular and CHD mortality. To further assess if the association of CAC with the three outcomes of interest was maintained among patients with moderate-severe

obesity, we restricted our analysis to individuals with ≥ Class II obesity (≥35 kg/m^2; N=3,124). 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 due to missingness (8.7%) which would have led to 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 receiver operating curves for fully adjusted models with and without CAC.

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

Results:

Of the 9,334 study participants with a mean age of 53.3 (±9.7) years and mean BMI of 34.5±4.4 kg/m^2, the majority were males (67.9%) and White (92.5%), and 58.5% (5,461) had any CAC; 22.7% had Class II obesity (BMI 35 – 39.9 kg/m^2) while 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%), while diabetes was the least prevalent risk factor (10.5%). There was a graded increase in age, proportion of males, and the 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 follow-up of 10.8 ± 3.0 years, there were 414 all-cause deaths, 129 cardiovascular deaths, and 69 CHD deaths. When compared to persons with a CAC score of 0 who had very low event rates, those with CAC >0 had a higher mortality rate from all-cause (5.65 vs. 1.97 per 1,000 person-years), CVD (1.89 vs. 0.43 per 1,000 person-years), and CHD (1.04 vs. 0.19 per 1,000 person-years). The all-cause mortality rate increased in a graded fashion with increasing CAC burden categories (Figure 2). A similar trend was observed for cardiovascular and CHD mortality rates (Figure 2).

In multivariable-adjusted analysis, individuals with CAC >0 had higher hazards of all-cause (HR: 1.43; 95% CI: 1.10 - 1.85), cardiovascular (Sub-distribution Hazards Ratio [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 ≥300AU 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 CAC score of 0 (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). Also, when the models were additionally adjusted for race, CAC remained strongly associated with all-cause, cardiovascular, and CHD mortality (Supplementary Table 1). The addition of CAC

to the model with age, sex, study site, and risk factors significantly increased the area under the curve for all three outcomes explored (Supplementary Table 2).

When restricting our sample to the 3,124 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] While 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 one year of therapy) among individuals with obesity when combined with lifestyle interventions.[11,12] Due to 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 2.4mg 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, to prioritize 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 that would benefit the most from these medications.

We demonstrate that CAC, which is more prevalent in persons with obesity compared to 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, i.e., the power of zero, appears 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 re-classify 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 that 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 underway.[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 comprised 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 healthcare system. Secondly, the CAC Consortium has few patients with BMI ≥50 kg/m^2, a group that is growing clinically. Also, due to 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 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 supports a strong predictive value for CAC, similar to what has been seen in persons without obesity, is notable and argues 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 race/ethnicity.

Conclusions:

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, due to the current significant cost and side

effects associated with the newer treatments for obesity, such as the incretin analogs, it is essential to identify patient in whom these risk-reducing medications would provide the most value. We have demonstrated in this study that CAC, which is measured non-invasively using a cardiac-gated CT scan, can serve as an effective risk stratification tool among individuals with obesity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data used in this study are from the CAC consortium and can be made available upon reasonable request.

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References:

1. Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of Obesity Among Adults and Youth: United States, 2015-2016 Key findings Data from the National Health and Nutrition Examination Survey. Published online 2015. Accessed January 14, 2023. https://www.cdc.gov/nchs/data/databriefs/db288_table.pdf#1.
2. Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of Obesity and Severe Obesity Among Adults: United States, 2017-2018 Key findings Data from the National Health and Nutrition Examination Survey. Published online 2017. Accessed January 14, 2023. https://www.cdc.gov/nchs/products/index.htm.
3. Tsao CW, Aday AW, Almarzooq ZI, et al. Heart Disease and Stroke Statistics-2022 Update: A Report from the American Heart Association. Circulation. 2022;145(8):E153–E639. doi:10.1161/CIR.0000000000001052/FORMAT/EPUB [PubMed: 35078371]
4. Khan SS, Ning H, Wilkins JT, et al. Association of Body Mass Index With Lifetime Risk of Cardiovascular Disease and Compression of Morbidity. JAMA Cardiol. 2018;3(4):280–287. doi:10.1001/JAMACARDIO.2018.0022 [PubMed: 29490333]
5. Lavie CJ, Pandey A, Lau DH, Alpert MA, Sanders P. Obesity and Atrial Fibrillation Prevalence, Pathogenesis, and Prognosis: Effects of Weight Loss and Exercise. J Am Coll Cardiol. 2017;70(16):2022–2035. doi:10.1016/J.JACC.2017.09.002 [PubMed: 29025560]
6. Wang TJ, Parise H, Levy D, et al. Obesity and the Risk of New-Onset Atrial Fibrillation. JAMA. 2004;292(20):2471–2477. doi:10.1001/JAMA.292.20.2471 [PubMed: 15562125]
7. Cawley J, Biener A, Meyerhoefer C, et al. Direct medical costs of obesity in the United States and the most populous states. https://doi.org/1018553/jmcp202120410. 2021;27(3):354–366. doi:10.18553/JMCP.2021.20410
8. Lavie CJ, Laddu D, Arena R, Ortega FB, Alpert MA, Kushner RF. Healthy Weight and Obesity Prevention: JACC Health Promotion Series. J Am Coll Cardiol. 2018;72(13):1506–1531. doi:10.1016/J.JACC.2018.08.1037/SUPPL_FILE/MMC1.DOCX [PubMed: 30236314]
9. Gloy VL, Briel M, Bhatt DL, et al. Bariatric surgery versus non-surgical treatment for obesity: a systematic review and meta-analysis of randomised controlled trials. BMJ. 2013;347. doi:10.1136/BMJ.F5934
10. Wolfe BM, Kvach E, Eckel RH. Treatment of Obesity: Weight Loss and Bariatric Surgery. Circ Res. 2016;118(11):1844. doi:10.1161/CIRCRESAHA.116.307591 [PubMed: 27230645]
11. Wilding JPH, Batterham RL, Calanna S, et al. Once-Weekly Semaglutide in Adults with Overweight or Obesity. New England Journal of Medicine. 2021;384(11):989–

1002. doi:10.1056/NEJMOA2032183/SUPPL_FILE/NEJMOA2032183_DATA-SHARING.PDF [PubMed: 33567185]

12. Jastreboff AM, Aronne LJ, Ahmad NN, et al. Tirzepatide Once Weekly for the Treatment of Obesity. New England Journal of Medicine. 2022;387(3):205–216. doi:10.1056/NEJMOA2206038/SUPPL_FILE/NEJMOA2206038_DATA-SHARING.PDF [PubMed: 35658024]
13. Marso SP, Bain SC, Consoli A, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. New England Journal of Medicine. 2016;375(19):1834–1844. doi:10.1056/NEJMOA1607141/SUPPL_FILE/NEJMOA1607141_DISCLOSURES.PDF [PubMed: 27633186]
14. Neeland IJ, Poirier P, Després JP. The Cardiovascular and Metabolic Heterogeneity of Obesity: Clinical Challenges and Implications for Management. Circulation. 2018;137(13):1391. doi:10.1161/CIRCULATIONAHA.117.029617 [PubMed: 29581366]
15. ASCVD Risk Calculator: 10-Year Risk of First Cardiovascular Event Using Pooled Cohort Equations - ClinCalc.com. Accessed April 16, 2023. https://clincalc.com/Cardiology/ASCVD/PooledCohort.aspx
16. Cardiovascular Disease (10-year risk) | Framingham Heart Study. Accessed April 16, 2023. https://www.framinghamheartstudy.org/fhs-risk-functions/cardiovascular-disease-10-year-risk/
17. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2019;74(10):e177–e232. doi:10.1016/J.JACC.2019.03.010 [PubMed: 30894318]
18. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular riskThe Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). Eur Heart J. 2020;41(1):111–188. doi:10.1093/EURHEARTJ/EHZ455 [PubMed: 31504418]
19. Jensen JC, Dardari ZA, Blaha MJ, et al. Association of Body Mass Index with Coronary Artery Calcium and Subsequent Cardiovascular Mortality: The Coronary Artery Calcium Consortium. Circ Cardiovasc Imaging. 2020;13(7):9495. doi:10.1161/CIRCIMAGING.119.009495
20. Adelhoefer S, Uddin SMI, Osei AD, Obisesan OH, Blaha MJ, Dzaye O. Coronary Artery Calcium Scoring: New Insights into Clinical Interpretation—Lessons from the CAC Consortium. Radiol Cardiothorac Imaging. 2020;2(6). doi:10.1148/RYCT.2020200281
21. Cainzos-Achirica M, Miedema MD, McEvoy JW, et al. Coronary Artery Calcium for Personalized Allocation of Aspirin in Primary Prevention of Cardiovascular Disease in 2019. Circulation. 2020;141(19):1541–1553. doi:10.1161/CIRCULATIONAHA.119.045010 [PubMed: 32233663]
22. Uppot RN. Technical challenges of imaging & image-guided interventions in obese patients. Br J Radiol. 2018;91(1089). doi:10.1259/BJR.20170931
23. Blaha MJ, Whelton SP, Al Rifai M, et al. Rationale and Design of the Coronary Artery Calcium Consortium: A Multicenter Cohort Study. J Cardiovasc Comput Tomogr. 2017;11(1):54. doi:10.1016/J.JCCT.2016.11.004 [PubMed: 27884729]
24. Mao SS, Pal RS, McKay CR, et al. Comparison of coronary artery calcium scores between electron beam computed tomography and 64-multidetector computed tomographic scanner. J Comput Assist Tomogr. 2009;33(2):175–178. doi:10.1097/RCT.0B013E31817579EE [PubMed: 19346841]
25. Fresno CU, Tijmes FS, Thavendiranathan P, et al. Visual Ordinal Scoring of Coronary Artery Calcium on Contrast-Enhanced and Noncontrast Chest CT: A Retrospective Study of Diagnostic Performance and Prognostic Utility. AJR Am J Roentgenol. 2022;219(4):569–578. doi:10.2214/AJR.22.27664 [PubMed: 35475394]
26. Wadden TA, Tronieri JS, Butryn ML. Lifestyle Modification Approaches for the Treatment of Obesity in Adults. Am Psychol. 2020;75(2):235. doi:10.1037/AMP0000517 [PubMed: 32052997]
27. Wadden TA, Butryn ML, Byrne KJ. Efficacy of Lifestyle Modification for Long-Term Weight Control. Obes Res. 2004;12(S12):151S–162S. doi:10.1038/OBY.2004.282 [PubMed: 15687411]
28. Tahrani AA, Morton J. Benefits of weight loss of 10% or more in patients with overweight or obesity: A review. Obesity. 2022;30(4):802–840. doi:10.1002/OBY.23371 [PubMed: 35333446]

29. Ochner CN, Tsai AG, Kushner RF, Wadden TA. Treating obesity seriously: when recommendations for lifestyle change confront biological adaptations. Lancet Diabetes Endocrinol. 2015;3(4):232–234. doi:10.1016/S2213-8587(15)00009-1 [PubMed: 25682354]
30. Clark JM, Garvey WT, Niswender KD, et al. Obesity and Overweight: Probing Causes, Consequences, and Novel Therapeutic Approaches Through the American Heart Association's Strategically Focused Research Network. J Am Heart Assoc. 2023;12:e8192. doi:10.1161/JAHA.122.027693
31. Kim N, Wang J, Burudpakdee C, et al. Cost-effectiveness analysis of semaglutide 2.4 mg for the treatment of adult patients with overweight and obesity in the United States. https://doi.org/1018553/jmcp2022287740. 2022;28(7):740–752. doi:10.18553/JMCP.2022.28.7.740
32. Wadden TA, Bailey TS, Billings LK, et al. Effect of Subcutaneous Semaglutide vs Placebo as an Adjunct to Intensive Behavioral Therapy on Body Weight in Adults With Overweight or Obesity: The STEP 3 Randomized Clinical Trial. JAMA. 2021;325(14):1403–1413. doi:10.1001/JAMA.2021.1831 [PubMed: 33625476]
33. Javaid A, Mitchell JD, Villines TC. Predictors of coronary artery calcium and long-term risks of death, myocardial infarction, and stroke in young adults. J Am Heart Assoc. 2021;10(22):22513. doi:10.1161/JAHA.121.022513
34. Malik S, Zhao Y, Budoff M, et al. Coronary Artery Calcium Score for Long-term Risk Classification in Individuals With Type 2 Diabetes and Metabolic Syndrome From the Multi-Ethnic Study of Atherosclerosis. JAMA Cardiol. 2017;2(12):1332–1340. doi:10.1001/JAMACARDIO.2017.4191 [PubMed: 29117273]
35. Budoff MJ, Raggi P, Beller GA, et al. Noninvasive Cardiovascular Risk Assessment of the Asymptomatic Diabetic Patient: The Imaging Council of the American College of Cardiology. JACC Cardiovasc Imaging. 2016;9(2):176. doi:10.1016/J.JCMG.2015.11.011 [PubMed: 26846937]
36. Blaha MJ, Cainzos-Achirica M, Greenland P, et al. Role of Coronary Artery Calcium Score of Zero and Other Negative Risk Markers for Cardiovascular Disease: The Multi-Ethnic Study Of Atherosclerosis (MESA). Circulation. 2016;133(9):849. doi:10.1161/CIRCULATIONAHA.115.018524 [PubMed: 26801055]
37. Blaha MJ, Cainzos-Achirica M, Dardari Z, et al. All-cause and cause-specific mortality in individuals with zero and minimal coronary artery calcium: A long-term, competing risk analysis in the Coronary Artery Calcium Consortium. Atherosclerosis. 2020;294:72–79. doi:10.1016/j.atherosclerosis.2019.11.008 [PubMed: 31784032]
38. Miguel Cainzos-Achirica MMP, Kershaw V. Patel M, Renato Quispe MM, et al. Coronary Artery Calcium for the Allocation of GLP-1RA for Primary Prevention of Atherosclerotic Cardiovascular Disease. Cardiovascular Imaging. 2021;14(7):1470–1472. doi:10.1016/J.JCMG.2020.12.024 [PubMed: 33582063]
39. Ryan DH, Lingvay I, Colhoun HM, et al. Semaglutide Effects on Cardiovascular Outcomes in People With Overweight or Obesity (SELECT) rationale and design. Am Heart J. 2020;229:61–69. doi:10.1016/J.AHJ.2020.07.008 [PubMed: 32916609]
40. A Study of Tirzepatide (LY3298176) on the Reduction on Morbidity and Mortality in Adults With Obesity - Full Text View - ClinicalTrials.gov. Accessed January 23, 2023. https://clinicaltrials.gov/ct2/show/NCT05556512

What is already known about this subject?

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

What are the new findings in your manuscript?

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

How might your 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 anti-obesity medications.

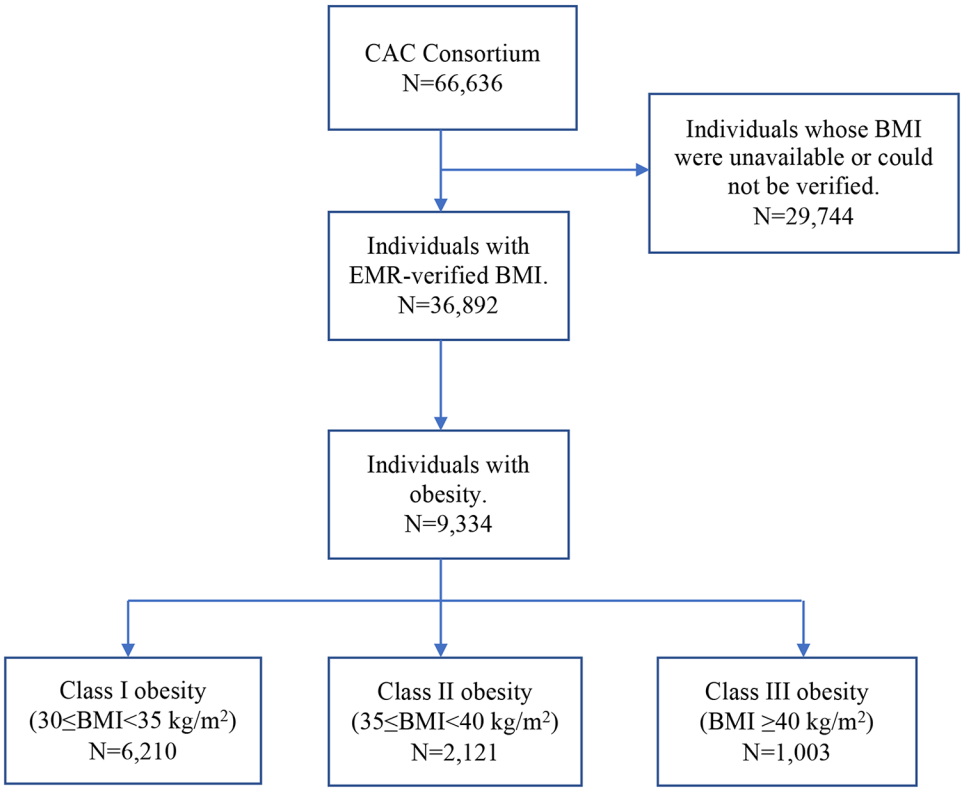

Figure 1:
Flowchart of the Analytic Sample

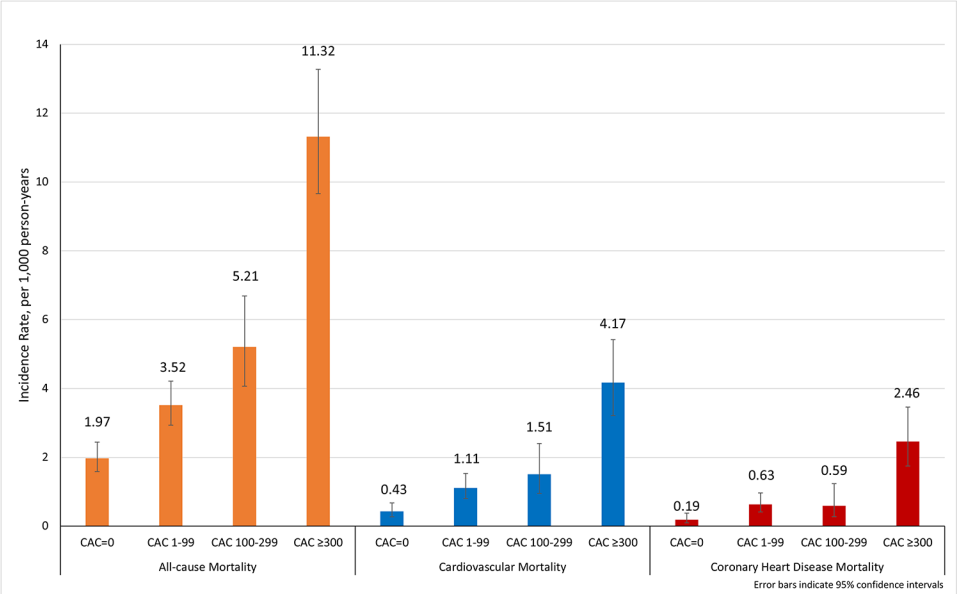

Figure 2:

Rates of All-cause, Cardiovascular, and Coronary Heart Disease Mortality by CAC Burden Categories

Table 1:

Baseline Characteristics of Study Population Stratified by Categories of Coronary Artery Calcium Score

Characteristic	Total N=9,334	CAC=0 N=3,873	CAC=1-99AU N=3,032	CAC=100-299AU N=1,101	CAC ≥300 AU N=1,328	p-values
Age, years	53.3 (±9.7)	49.1 (±8.7)	53.4 (±8.7)	57.6 (±8.3)	61.3 (±9.0)	<0.001
Male sex	6,340 (67.9)	2,168 (56.0)	2,193 (72.3)	855 (77.7)	1,124 (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	7,877 (92.5)	3,248 (92.4)	2,575 (91.8)	927 (92.5)	1,127 (93.9)	
Other	145 (1.7)	53 (1.5)	50 (1.8)	21 (2.1)	21 (1.8)	
Hypertension	3,604 (38.6)	1,200 (31.0)	1,165 (38.4)	512 (46.5)	727 (54.7)	<0.001
Dyslipidemia	5,799 (62.1)	2,196 (56.7)	1,913 (63.1)	741 (67.3)	949 (71.5)	<0.001
Current smoker	1,003 (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	4,750 (50.9)	1,962 (50.7)	1,549 (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	6,210 (66.5)	2,608 (67.3)	1,991 (65.7)	712 (64.7)	899 (67.7)	
II	2,121 (22.7)	852 (22.0)	696 (23.0)	272 (24.7)	301 (22.7)	
III	1,003 (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)	

CHD, coronary heart disease; BMI, body mass index; CAC, coronary artery calcium; AU, Agatston units

Table 2:

The Distribution of Coronary Artery Calcium by Classes of Obesity

Coronary Artery Calcium	Class I Obesity N=6,210 (%)	Class II Obesity N=2,121 (%)	Class III Obesity N=1,003 (%)
CAC =0	2,608 (42.0)	852 (40.2)	413 (41.2)
CAC 1-99	1,991 (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)

Table 3:

Mortality Rates, Hazards ratios, and Sub-distribution Hazards ratios for All-cause and Cause-specific mortality with Increasing Coronary Artery Calcification

	Mortality rate	Model 1		Model 2		Model 3	
All-cause Mortality		**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
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

HR, Hazard Ratio; SHR, Sub-distribution Hazard Ratio; CHD, coronary heart disease

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

Table 4:

Mortality Rates, Hazards ratios, and Sub-distribution Hazards ratios for All-cause and Cause-specific mortality with Increasing Coronary Artery Calcification among the 3,124 individuals with ≥Class II Obesity (BMI ≥35 kg/m^2)

Coronary Artery Calcium	All-cause Mortality			Cardiovascular Mortality			Coronary Heart Disease Mortality		
	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

HR, Hazard Ratio; SHR, Sub-distribution Hazard Ratio

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.