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Publication Date

2020-05-01

DOI

10.1016/j.atherosclerosis.2020.04.006

Peer reviewed

Published in final edited form as:

Atherosclerosis. 2020 May ; 301: 65–68. doi:10.1016/j.atherosclerosis.2020.04.006.

Predictors of coronary artery calcium among 20–30-year-olds: The Coronary Artery Calcium Consortium

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Abstract

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AUTHOR CONTRIBUTIONS

Michael Blaha, S.M Iftekhar Uddin, Omar Dzaye, Miguel Cainzos Achirica, Olufunmilayo Obisesan and Albert Osei participated in the conception and design of the study.

Albert Osei, S.M. Iftekhar Uddin, Zeina Dardari, Omar Dzaye conducted the statistical analyses, and prepared the tables and figures.

Sina Kianoush, Mohammadhassan Mirbolouk, Olusola Orimoloye, Leslee Shaw, John Rumberger, Daniel Berman, Alan Rozanki, Michael Miedema, Matthew Budoff, Ramachandran Vasan and Khurram Nasir participated in the interpretation of the data, drafting of the manuscript and revised subsequent drafts critically for important intellectual content together with Michael Blaha, S.M Iftekhar Uddin, Omar Dzaye, Miguel Cainzos Achirica, Olufunmilayo Obisesan and Albert Osei.

Michael Blaha provided mentorship and supervision of the study.

All authors approved the final version.

Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

CONFLICT OF INTEREST STATEMENT

We wish to draw the attention of the Editor that all named authors report no potential financial conflict of interest.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

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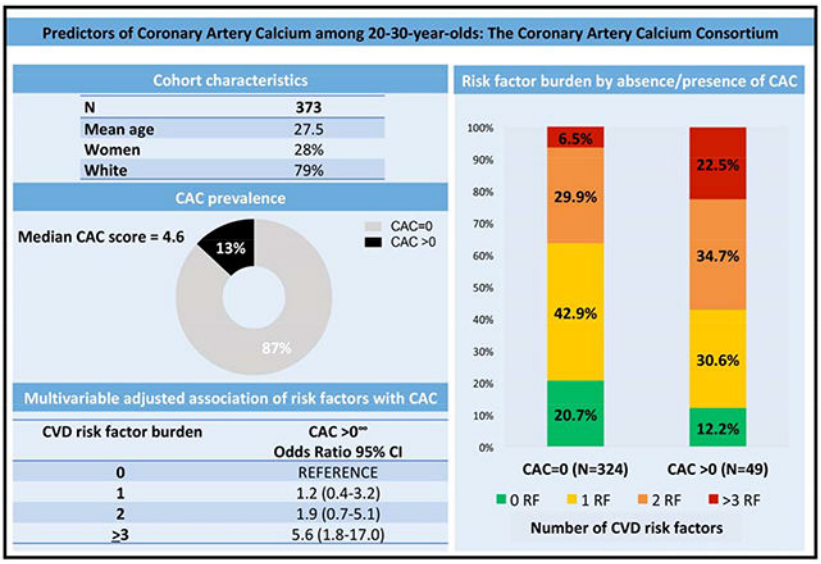
Background and aims—We sought to understand the risk factor correlates of very early coronary artery calcium (CAC), and the potential investigational value of CAC phenotyping in adults aged 20–30 years.

Methods—We studied all participants aged 20–30 years at baseline (N=373) in the Coronary Artery Calcium Consortium, a large multi-center cohort study of patients aged 18 years or older without known atherosclerotic cardiovascular disease (ASCVD) at baseline, referred for CAC scoring for clinical risk stratification. We described the prevalence of CAC in men and women, the frequency of risk factors by the presence of CAC (CAC=0 *vs* CAC >0), and assessed the association between traditional non-demographic CVD risk factors (hypertension, hyperlipidemia, smoking, family history of CHD, and diabetes) and prevalent CAC, using age- and sex-adjusted logistic regression models.

Results—The mean age of the study participants was 27.5±2.4 years; 324 (86.9%) had CAC=0, and 49 (13.1%) had CAC >0. Among the 49 participants with CAC, 38 (77.6%) were men, and median CAC score was low at 4.6. In age- and sex-adjusted models, there was a graded increase in the odds of CAC >0 with increasing traditional cardiovascular disease (CVD) risk factor burden (p=0.001 for linear trend). Participants with ≥3 traditional risk factors had a statistically significant higher odds of having prevalent CAC (OR 5.57, 95% CI; 1.82–17.03) compared to participants with no risk factors.

Conclusions—Our study demonstrates the non-negligible prevalence of CAC among very high-risk young US adults, reinforcing the critical importance of traditional risk factors in the earliest development of detectable subclinical ASCVD.

Graphical Abstract



Keywords

Coronary Artery Calcium; Predictors; Cardiovascular risk factors; Young adults; Prevention

Introduction

CAC, a direct marker of coronary atherosclerosis, is an important risk stratification tool with guideline endorsement for shared clinical decision making regarding preventive CVD medications allocation in asymptomatic individuals 40–75 years old with 5–20% 10-year estimated risk of atherosclerotic cardiovascular disease (ASCVD).[1–5]While there is emerging data on CAC burden and CAC utility in identification of younger individuals aged 30–49 years at higher risk for CVD,[6] almost no data are available on the determinants of CAC among very young adults ≤30 years with risk factors, who may benefit from aggressive therapy for risk mitigation.

Understanding CAC at its earliest onset is important given recent data suggesting that young adults aged 30–49 years who had already developed elevated CAC had markedly higher 10-year rates of ASCVD and total mortality.[6] Importantly, observational data links early ASCVD risk factor exposure to early atherosclerosis and lifetime risk of ASCVD events, suggesting the need to detect risk factors well before age 30–40 years.[7,8] To further understand the risk factor correlates of very early CAC, and the potential investigational value of CAC phenotyping at very young ages, we studied CAC testing in at-risk adults aged 20–30 years from the CAC Consortium.

Materials and methods

Study population

The CAC Consortium is a large multi-center cohort study of 66,636 asymptomatic patients aimed at determining the association of CAC with long-term, cause-specific mortality. The consortium consists of patients aged 18 years or older without known ASCVD at baseline, who were referred for CAC scoring for clinical risk stratification. Patients with cardiovascular symptoms at baseline were excluded. Four institutions from three states within the US participated (California, Minnesota, and Ohio).[1,9] CAC testing was generally performed in individuals with CVD risk factor(s) and/or with uncertainty about absolute risk of CVD. Additional details about specific clinical indications were not systematically recorded. However, as many patients had CAC testing associated with history of hyperlipidemia or family history of CVD, it can be concluded that referral patterns followed general clinical perception of potential premature risk.

All patients in the study provided written informed consent for participation in research at all centers and institutional review board approval for coordinating center activities was obtained at Johns Hopkins University School of Medicine.[9] Data on risk factors were collated during routine clinical visit for CAC testing and/or from a semi-structured in-person interview at time of CAC scan. Smoking was based on self-report. Diabetes and hypertension were defined by a prior clinical diagnosis or treatment with glucose-lowering or antihypertensive therapy. Family history of CHD was determined by the presence of a first-degree relative with a history of CHD at any age. Dyslipidemia was defined as prior diagnosis of primary hyperlipidemia, prior diagnosis of dyslipidemia (elevated triglycerides and/or low HDL-C), or treatment with any lipid-lowering drug. Among patients with concomitant laboratory data, dyslipidemia was additionally considered present if LDL-C >

160mg/dL, HDL-C < 40mg/dL in men and <50mg/dL in women, or fasting triglycerides >150mg/dL.[6,9]

Statistical analysis

For this analysis, we included all participants aged 20–30 years at baseline (N=373). Baseline characteristics are presented stratified by prevalent CAC. Continuous variables are summarized as mean ± standard deviation (SD) and categorical variables are described as number (%). In cross sectional analysis, we first described the prevalence of CAC in men and women. Then, we described the frequency of risk factors by the presence of CAC (CAC=0 *vs* CAC >0), and assessed the association between traditional non-demographic CVD risk factors (hypertension, hyperlipidemia, smoking, family history of CHD, and diabetes) and prevalent CAC, using age- and sex-adjusted logistic regression models. Additional analyses were conducted to assess the association between each traditional non-demographic CVD risk factor and prevalent CAC, using age- and sex-adjusted logistic regression models. All *p* values were from 2-sided tests and results were considered statistically significant at $p < 0.05$. Analyses were conducted using Stata statistical software (version 15.1).

Results

The mean age of the study participants was 27.5±2.4 years; 324 (86.9%) had CAC=0, and 49 (13.1%) had CAC >0 (Table 1). Among the 49 participants with CAC, 38 (77.6%) were men, 10.1% had CAC >100, and median CAC score was low at 4.6. The average Body Mass Index (BMI) was 26.6 kg/m^2 and 28.7 kg/m^2 among participants with no CAC and CAC, respectively. Among participants with CAC >0, 18.4% were obese (BMI ≥ 30 kg/m^2) as compared to 13% participants with CAC=0.

Among those with CAC >0, 22.4% had ≥3 risk factors, while this was true for only 6.5% of the 324 participants with CAC=0 (Figure 1). The prevalence of CAC was 9.7%, 14.9%, and 34.4% in those with 1, 2, and ≥3 risk factors, respectively.

Among 43 participants with CAC >0 who reported at least 1 risk factor, 34.9% had hypertension, 69.8% had hyperlipidemia, 7.0% had diabetes, 62.8% had a family history of CHD, and 20.9% were current smokers. Among 97 (26%) participants with the combination of hyperlipidemia and family history of CHD, 22% had CAC >0.

In age- and sex-adjusted models, there was a graded increase in the odds of CAC >0 with increasing traditional CVD risk factor burden (p=0.001 for linear trend). Participants with ≥3 traditional risk factors (32 patients, 8.6% of the total sample) had a statistically significant higher odds of having prevalent CAC (OR 5.57, 95% CI; 1.82–17.03) compared to participants with no risk factors (Table 2). Additional analyses assessing the association between each traditional non-demographic CVD risk factor and prevalent CAC are available in Supplementary Data.

Discussion

In this study, we examined the risk factor correlates of very early CAC, and the potential investigational value of CAC phenotyping in adults aged 20–30 years. We found a graded increase in the odds of CAC >0 with increasing traditional CVD risk factors. Participants with ≥3 traditional risk factors had a statistically significant higher odds of having prevalent CAC compared to participants with no risk factors.

Few other studies are available on CAC in adults ≤30 years. A cross-sectional study of 96,166 Koreans undergoing routine health examination showed that higher blood pressure categories were associated with higher CAC in both young (20–39 years) and middle-aged adults.[10] This healthy participant Korean study reported a CAC prevalence of 3.9% among young adults aged 20–39 years; in contrast, we noted a 13.1% CAC prevalence among American adults aged 20–30 years, known to be enriched in cardiovascular risk factors.

A recent study of young adults aged 30–49 years with very low estimated 10-year ASCVD risk (<5%) observed that 34.4% of patients had any CAC and 7.2% had significantly elevated CAC scores (>100).[6] In the Coronary Artery Risk Development in Young Adults (CARDIA) study, the presence of CAC among individuals aged between 32 and 46 years was associated with increased risk of fatal and non CHD during 12.5 years of follow-up.[11] The authors report a CAC prevalence of 10.2% at year 15 of the study. Carr et al. concluded that adults younger than 50 years with any CAC, even with very low scores, are at elevated risk and the selective use of screening for CAC might be considered in individuals with risk factors in early life to inform primary prevention strategies.[11]

Our study demonstrates that the prevalence of CAC in even younger US adults referred for CAC scoring is not negligible, confirming a potential investigational value of CAC in this select population. It is notable that with known rates of CAC progression of ~25% per year,[12–14] a CAC=5 at age 30 may be similar to CAC~50 at age 40 and CAC~400 at age 50, highlighting the importance of noting any CAC>0 at very young age for estimating risk of higher CAC in middle adulthood. The exponential nature of CAC increase is poorly understood by many clinicians and may lead to underestimation of the early time point at which CAC could have theoretically been detected in patients with high CAC at middle age.

Importantly, any CAC in young adults -- even scores as low as 1–10 -- should be considered very abnormal. In a study on the 10-year prognostic value of zero and minimal CAC, Joshi et al. showed higher overall ASCVD event rates of 5.4 in 1000 person-years in participants with CAC score of 1–10 compared to those with CAC=0 score, with an event rate of 2.9 in 1000 person-years (correlating to nearly twice the unadjusted hazard for ASCVD compared to CAC=0).[15] A study on the absence of CAC and all-cause mortality also showed that individuals with low CAC score of 1–10 are at increased risk above those with CAC=0 score and could be considered a distinct risk group by physicians and investigators.[16]

Our study has a few limitations. Our sample size is small, reflecting known clinical referral patterns, as for example >60% of participants had a family history of CHD. As such, prevalence estimates of CAC>0 must not be generalized to the broader healthy young adult population. In addition, severity of risk factors (i.e. precise blood pressure values, LDL-C

measurements, etc.) was not systematically collected; for example, we expect that in many cases of hyperlipidemia with family history (26% of cohort), familial hypercholesterolemia could have been present. We cannot rule out obesity being associated with low CAC via increased image noise; however, our data is highly consistent with a large body of evidence pointing to obesity being a strong etiologic risk factor for CAC in young adults. Additionally, details about specific clinical indications for CAC testing were not systematically recorded at the individual patient level. Impaired kidney function may be a potential confounder of the relationship between risk factors and CAC; unfortunately, data on kidney function were not available to examine this association. However, we do not suspect that many of our study participants in the 20–30 age group had chronic kidney disease.

Conclusion

Despite the limitations, our analysis is an important first step demonstrating the non-negligible prevalence of CAC among very high-risk young US adults, reinforcing the critical importance of traditional risk factors in the earliest development of detectable subclinical ASCVD. Our data may inform researchers about CAC prevalence in early life and may encourage additional research on CAC progression and risk mitigation in this important phenotype.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Financial support

M.J. Blaha has received support from National Institutes of Health award L30 HL110027 for this project.

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Highlights

- Coronary Artery Calcium (CAC), a direct marker of coronary atherosclerosis, is an important risk stratification tool.
- Almost no data are available on the determinants of CAC among very young adults ≤30 years with risk factors who may benefit from aggressive therapy for risk mitigation.
- We demonstrate the non-negligible prevalence of CAC among very high-risk young US adults, reinforcing the critical importance of traditional risk factors in the earliest development of detectable subclinical ASCVD.

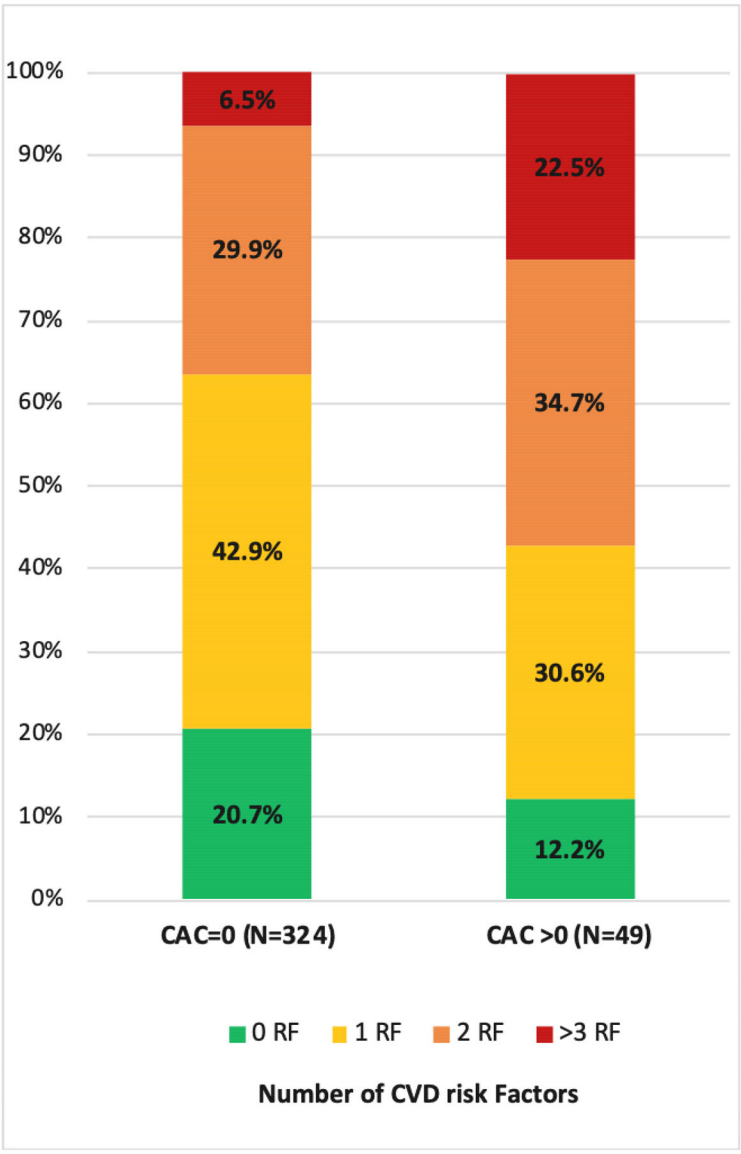

Figure 1:
Risk factor burden by CAC

Table 1:

Baseline characteristics by CAC presence among 20–30-year-olds

Characteristics	**CAC=0 (N=324)**	**CAC >0 (N=49)**
Age, mean (SD), y	27.5(2.4)	27.5(2.6)
Men, No. (%)	229 (70.7)	38 (77.6)
Race/ethnicity, No. (%) (N=241)		
White	167 (80.7)	23 (67.7)
Asian	14 (6.8)	3 (8.8)
Black	6 (2.9)	3 (8.8)
Hispanic	16 (7.7)	2 (5.9)
Other	4 (1.9)	3 (8.8)
Hypertension, No. (%)	42 (13)	15 (30.6)
Hyperlipidemia, No. (%)	127 (39.2)	30 (61.2)
Diabetes, No. (%)	9 (2.8)	3 (6.1)
Family history of CHD, No. (%)	174 (53.7)	27 (55.1)
Current smoker, No. (%)	46 (14.2)	9 (18.4)
Statin use, No. (%) (N=185)	13 (8.0)	4 (17.4)
Body Mass Index (BMI), mean (SD), kg/m^2 (N=211)	26.6 (5.3)	28.7 (6.3)

Table 2:

The association of traditional risk factors with CAC in very young adults (age 20–30) in the CAC Consortium.

	CAC >0 Odds ratio 95% CI (unadjusted model)	**CAC >0[a] Odds ratio 95% CI (adjusted model)**
CVD risk factor burden[b]		
0	REFERENCE	REFERENCE
1	1.21 (0.45–3.25)	1.17 (0.43–3.16)
2	1.95 (0.73–5.22)	1.90 (0.71–5.08)
≥3	5.85 (1.93–17.73)	5.57 (1.82–17.03)

[a]Adjusted for age and sex

[b]Hypertension, hyperlipidemia, smoking, family history of CHD, and diabetes *p* value for trend association of risk factor burden with the presence of CAC - 0.001