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FULL RESEARCH PAPER
Imaging

Impact of coronary artery calcium on mortality and cardiovascular events in metabolic syndrome and diabetes among younger adults

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See the editorial comment for this article 'Does coronary artery calcium screening help cardiovascular risk stratification in asymptomatic young patients with diabetes mellitus? A knowledge gap', by A. Carbone *et al.*, https://doi.org/10.1093/eurjpc/zwae101.

Aims Whether coronary artery calcium (CAC) testing in younger individuals with metabolic syndrome (MetS) and diabetes mellitus (DM) helps predict cardiovascular disease (CVD) and death independent of traditional risk factors (RFs) remains less clear.

Methods and results We pooled data obtained from 5174 individuals aged 38–55 years from the CARDIA (Coronary Artery Risk Development in Young Adults; $n = 3047$, year 20) and MESA (Multi-Ethnic Study of Atherosclerosis; $n = 2127$, Visit 1) studies who completed computed tomography of CAC. The mean age (SD) of participants (44.7% men) was 47.3 (4.2) years. Multivariable Cox proportional hazards regression models were used to estimate hazard ratios (HRs) of CVD, coronary heart disease (CHD), and all-cause death. There were 1085 participants (21.0%) with prevalent CAC at baseline. A total of 461 (8.9%) had DM, 1025 (19.8%) had MetS without DM, and 3688 (71.3%) had neither condition. Over a median follow-up of 14.2 years, 256 (5.0%) participants died, and 304 (5.9%) CVD and 188 (3.6%) CHD events occurred. The CAC score was independently associated with incident CVD in those with DM (HR: 95% CI; 1.22: 1.08–1.38), MetS (1.18: 1.08–1.31), and neither condition (1.36: 1.26–1.46). The corresponding HRs for CAC ≥ 100 were 2.70 (1.25–5.83), 3.29 (1.87–5.79), and 6.30 (4.02–9.86), respectively. Similar associations for CHD and death were found. The impact of CAC ≥ 100 on CVD and CHD was lower in the presence of DM (P interaction < 0.05). The association of CAC with all outcomes in individuals with DM remained significant after adjusting with haemoglobin A1c levels.

Conclusion Coronary artery calcium score is independently associated with cardiovascular events and death over nearly 15 years after screening at ages 38–55 years, with a less pronounced impact on CVD and CHD events in the presence of DM.

Lay summary

- In this pooled cohort, we aimed to analyse the relationship between coronary artery calcium (CAC) and incidence of cardiovascular disease (CVD), coronary heart disease (CHD), and all-cause mortality among younger individuals with diabetes mellitus (DM), metabolic syndrome (MetS), and neither condition.
- The CAC score was independently associated with incident CVD, CHD, and all-cause mortality in those with DM, MetS, and neither condition.
- The impact of CAC ≥ 100 on CVD and CHD events was lower in the presence of DM.
- The association of CAC with all outcomes in individuals with DM remained significant after adjusting with haemoglobin A1c levels.

Keywords Coronary artery calcification • Cardiovascular events • Diabetes • Metabolic syndrome • Cardiovascular imaging

Introduction

As a marker of atherosclerotic burden, coronary artery calcium (CAC) is more prevalent in individuals with metabolic syndrome (MetS) and diabetes mellitus (DM).[1] Among adults aged 30 to 50 years, compared with individuals without risk factors, those with diabetes are prone to developing CAC 6.4 years earlier on average.[2]

Coronary artery calcium is a well-established predictor of future cardiovascular disease (CVD) events in individuals with MetS or DM, as reported in prospective studies.[3–5] According to the 2018 AHA/ACC/Multi-Society Cholesterol Guidelines and the 2023 ESC Guidelines

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for managing CVD in patients with diabetes, insufficient robust evidence exists supporting CAC assessment to reclassify cardiovascular risk in asymptomatic individuals with DM.[6,7]

Current cardiovascular guidelines recommend using 10-year absolute atherosclerotic cardiovascular disease (ASCVD) risk estimates to guide treatment and allocation of preventive therapies.[8–11] Accordingly, the 2019 ACC/AHA guidelines for primary prevention recommend CAC scoring for further risk assessment in borderline to intermediate-risk individuals—typically middle-aged—in whom management is uncertain.[12] Atherosclerotic cardiovascular disease risk equations are heavily influenced by age; this means that many younger individuals often show a low risk of ASCVD over a 10-year period, even if they have suboptimal risk factor control and may have a high lifetime risk for CVD.[13,14]

While CAC studies have primarily focused on the yield of testing middle to older-aged adults with MetS and DM,[3,4,15,16] the utility of CAC testing for identification of high-risk individuals for CVD, coronary heart disease (CHD), and death in younger populations with MetS and DM remains less clear. Considering recent data suggesting a higher risk of clinical CHD, CVD, and mortality among younger adults with any CAC, even within very low ranges,[17–19] we analysed pooled data from individuals free of CVD from the CARDIA (Coronary Artery Risk Development in Young Adults) and MESA (Multi-Ethnic Study of Atherosclerosis) studies to determine what role, if any, CAC detection in young individuals aged 38 to 55 years might play in the presence of MetS or DM.

Methods

The data used for this study were obtained from the National Heart, Lung, and Blood Institute BioLINCC Data Repository and is available at https://biolincc.nhlbi.nih.gov/home/.

Study population and definitions

The participant-level data were pooled from two prospective cohort studies: (1) the CARDIA (Coronary Artery Risk Development in Young Adults)[20] and (2) the MESA (Multi-Ethnic Study of Atherosclerosis)[21] studies. Briefly, the CARDIA study enrolled 5115 African American and White men and women aged 18–30 years from 1985 to 1986 across four urban sites, including Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA. The MESA is a multi-ethnic (White, African American, Hispanic, and Chinese) cohort study that enrolled 6814 participants aged 45 to 84 years without any known CVD between 2000 and 2002 in six US communities (Baltimore City and Baltimore County, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; New York, NY; and St Paul, MN). In this study, we included participants from the two cohorts who were free of CVD at baseline and had CAC scores available; we included the data from year 20 of CARDIA (baseline for this analysis) and Visit 1 of MESA (*Figure 1*). Given the study's objective to assess the role of CAC on CVD, CHD, and all-cause death among younger adults across metabolic states, we excluded individuals older than 55 years from MESA. Each study protocol was approved by the institutional review committee of each site participating in the studies. The institutional review boards of each site approved the studies, and all participants provided written informed consent. All methods were carried out following relevant guidelines and regulations. Approval for undertaking the current project was also obtained from the Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Diabetes mellitus was defined as diagnosed diabetes, use of diabetes medications, or fasting plasma glucose (FPG) levels ≥ 126 mg/dL,[22] and MetS was based on having ≥3 of the following characteristics: (1) waist circumference ≥ 88 cm (35 inches) for women and ≥102 cm (40 inches) for men; (2) high-density lipoprotein cholesterol (HDL-C) < 40 mg/dL (1.0 mmol/L) for men and <50 mg/dL (1.3 mmol/L) for women; (3) fasting triglycerides (TG) ≥ 150 mg/dL (1.7 mmol/L) or the use of lipid-lowering medications; (4) systolic blood pressure (SBP) ≥ 130 mmHg or diastolic blood pressure (DBP) ≥ 85 mmHg or the use of anti-hypertensive medications; and (5) FPG ≥ 100 mg/dL (5.55 mmol/L) but without DM (as defined above). Body mass index (BMI) was defined as weight in kilograms divided by the square of the height in metres (kg/m^2) and general obesity was defined as BMI ≥ 30 kg/m^2. Hypertension was defined as SBP ≥ 130 mmHg, or DBP ≥ 80 mmHg, or taking anti-hypertensive medications. Dyslipidaemia was defined as total cholesterol (TC) ≥ 200 mg/dL, or TG ≥ 150 mg/dL, or low-density lipoprotein cholesterol (LDL-C) ≥ 130 mg/dL, or HDL-C < 40 mg/dL (for men) and <50 mg/dL (for women), or taking lipid-lowering medications.

Risk factor measurement

Trained interviewers with standardized questionnaires obtained information on demographics, smoking, and medical history. Descriptions of anthropometric measurements, TC, HDL-C, TG, LDL-C, and FPG levels have been published previously.[23–25] Resting SBP and DBP were measured three times, and the average of the last two measurements was used. The use of blood pressure, cholesterol, and diabetes medications was determined by questionnaire, and participants brought in medications for verification.

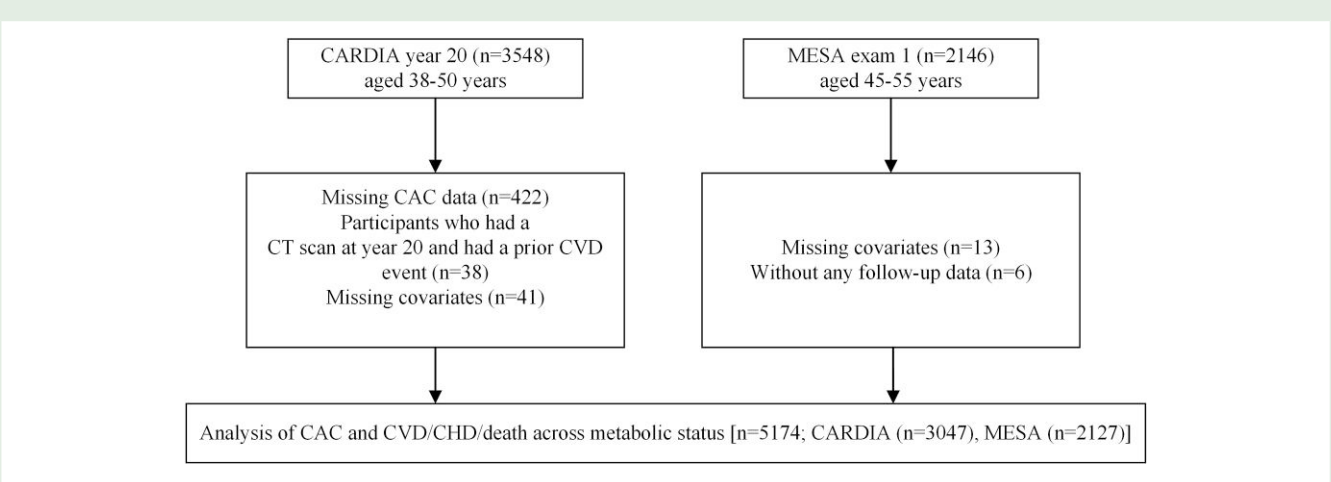

Figure 1 Flow chart of the study participants' selection. CARDIA, Coronary Artery Risk Development in Young Adults; MESA, Multi-Ethnic Study of Atherosclerosis; CAC, coronary artery calcium; CVD, cardiovascular disease; CHD, coronary heart disease.

Coronary artery calcium measurement

The CAC assessment protocols for participants of CARDIA and MESA studies have been previously reported.[17,26,27] Coronary artery calcium scores were available for all individuals included in the current analysis. Coronary artery calcium was measured using non-contrast cardiac computed tomography (CT) and scored using the Agatston method, calculated for each calcified lesion. The scores were summed across all lesions within a given artery and all arteries (left main, left anterior descending, left circumflex, and right coronary artery) to calculate the total CAC score. For the current analyses, CAC was categorized as either absent or present (CAC = 0 vs. CAC > 0) or as CAC score categories of 0, >0 to 99, and ≥100 for all participants.

Study outcomes

Details on the definitions and ascertainment methods for events used in each cohort have been published previously and were similar across studies.[21,28,29] Briefly, In CARDIA, participants were contacted each year to inquire about interim hospitalizations; death certificates and autopsy reports were also collected. For each event, medical records were reviewed and adjudicated by two trained physician members of the CARDIA Endpoints Surveillance and Adjudication Subcommittee.[29] MESA obtained information from medical records from hospitalization, death certificates, autopsy reports, as well as interviews with individuals, and each event was reviewed by two trained physician reviewers.[21] The study outcomes were the incidence of any CVD, any CHD, and all-cause mortality during the follow-up period. The CVD events endpoint of interest included all CVD events, defined as CHD, peripheral vascular disease, stroke, transient ischaemic attack, heart failure, and cardiovascular death (secondary to stroke, CHD, or atherosclerotic or non-atherosclerotic cardiac disease); all CHD events included any of—myocardial infarction (MI), non-MI acute coronary syndrome, coronary revascularization, resuscitated cardiac arrest, and coronary death.

Statistical analysis

Descriptive statistics [mean (SD) or percentages] of baseline characteristics across different metabolic states [individuals with DM (DM group), those with MetS and without DM (MetS group), and those with neither condition (reference group)] were compared using χ^2 tests and ANOVA. Kaplan–Meier plots were used to compute the cumulative incidence of death, CVD, and CHD events across different combinations of the presence of CAC and metabolic states. Multivariable logistic regression models were used to estimate odds ratios (ORs) and their respective 95% confidence intervals (CIs) to determine the relations between the prevalence of CAC (defined as either CAC > 0 or CAC ≥ 100) and the prevalence of MetS and DM (independent variable). We also compared the ORs for prevalent CAC between the MetS and DM groups. Multivariable Cox proportional hazards regression models were used to estimate the hazard ratio (HR) and 95% CIs of all-cause death, new-onset CVD, and CHD for CAC score, both as a continuous and categorical variable, in each group separately (MetS, DM, and neither). Multivariable models were adjusted for age, sex, and ethnicity as demographic variables (Model 1). Model 2 included Model 1 plus variables in the Pooled Cohort Equation (PCE), including TC, HDL-C, SBP, use of anti-hypertensive medication, and current smoking. Because haemoglobin A_{1c} measurements were unavailable at baseline for the MESA study, but were available in Visit 2 (~2 years after the baseline), we conducted a secondary analysis with haemoglobin A1c levels in the model and other covariates. Finally, to examine potential modification effects, we tested interactions between CAC score and metabolic status groups on the risk of outcomes by adding interaction terms to the multivariable-adjusted model. Statistical analyses were performed using Stata version 14 SE (StataCorp, College Station, TX, USA), and a two-tailed *P* value of <0.05 was considered statistically significant.

Results

The baseline characteristics of individuals from each cohort included in this study are shown in Supplementary material online, *Table S1*. As expected, participants from the CARDIA study were younger, included more women, Caucasian and African American subjects, had generally better cardiometabolic status, and lower prevalence of any CAC compared to those from the MESA study; however, the prevalence of high FPG component was higher among individuals from the CARDIA study. The baseline characteristics of individuals among the total population and across metabolic groups are shown in *Table 1*. Of the 5174 participants (mean age, SD: 47.3 years, 4.2) included in this analysis, 44.7% were men. Of the entire study cohort, there were 47.8% White, 37.5% African American, 10.0% Hispanic, and 4.7% Chinese individuals. Among the participants, 28.7% had MetS or DM (8.9% had the latter). In the total population, the prevalence of current smoking, general obesity, dyslipidaemia, and hypertension were 19.1%, 36.3%, 65.6%, and 35.5%, respectively. The prevalence of MetS components ranged from 25.0% for high FPG to 42.6% for high waist circumference. Individuals in the MetS or DM groups had a higher CAC prevalence than the reference group ($P < 0.001$; *Table 1*).

We evaluated the odds of having subclinical atherosclerosis among participants with neither MetS nor DM (reference), MetS and no DM, and those with DM (*Table 2*). Those with MetS had 34% higher odds of having any CAC (OR: 95% CI; 1.34: 1.10–1.64) and 50% higher odds of CAC ≥ 100 (1.50: 1.05–2.15) after adjustment for age, sex, ethnicity, and traditional risk factors from the PCE risk score. Similarly, individuals with DM had higher odds of having any CAC and CAC ≥ 100 with ORs of 1.86 (1.45–2.40) and 2.30 (1.52–3.50) in Model 2. In addition, participants in the DM group had 38% (1.38: 1.06–1.80) and 54% (1.54: 1.01–2.36) significantly higher odds of having any CAC and CAC ≥ 100 compared with those in the MetS group (data not shown).

During 69 266 person-years of follow-up, 256 (5.0%) participants died, and there were 304 (5.9%) and 188 (3.6%) CVD and CHD events, respectively (*Table 3*). The overall CVD rate for those with DM was 10.0/1000; for those with MetS, it was 6.7/1000 person-years; and for those without neither condition, it was 3.1/1000. The lowest crude rate for CVD, 2.0/1000 person-years, was for those with neither condition and a CAC score of 0. Among those with either MetS or DM with CAC scores of 0, there was a higher rate of CVD (4.9 and 6.7 per 1000 person-years, respectively). The highest rates for CVD were in the highest CAC categories for each group. Similar relationships were observed for CHD and death events (*Table 3*).

Participants with CAC > 0 and DM had a higher cumulative incidence of subsequent CVD/CHD/death than those in other groups. The lowest cumulative incidence for all outcomes was observed among those with CAC scores of 0 and with neither DM nor MetS (*Figure 2*).

Table 4 depicts the association of CAC with incident CVD, CHD, and all-cause death among individuals with MetS, DM, or neither condition. Coronary artery calcium score was significantly associated with incident CVD, CHD, and death across all metabolic groups; specifically, HRs of CVD/CHD/death ranged from 1.26 to 1.32 in individuals with DM. In those with MetS, HRs ranged from 1.15 to 1.35. Additionally, HRs ranged from 1.20 to 1.56 among individuals with neither condition. These associations remained significant in Model 2, except for the association of CAC score with death among those with MetS (HR: 95% CI; 1.13: 0.99–1.30, $P = 0.073$).

In the Cox proportional hazards model, adjusting for age, sex, and ethnicity, we found that any CAC was predictive of CVD events in those with neither MetS nor DM (HR: 95% CI; 3.98: 2.83–5.56), those with MetS without DM (1.95: 1.27–3.03), and those with DM (2.42: 1.38–4.25). The corresponding HRs for CHD events were 5.72 (3.78–8.67), 3.18 (1.76–5.75), and 2.41 (1.12–5.17). Regarding death, the corresponding HRs were 1.95 (1.37–2.81), 1.41 (0.80–2.49, $P = 0.229$), and 2.49 (1.34–4.65). After further adjustment with traditional risk factors from the PCE risk score, the associations remained significant, except for the association of any CAC with CHD events among those with DM, which reached marginally significant levels (2.09: 0.97–4.54, $P = 0.060$) (*Table 4*).

We also examined the relation of clinical CAC categories (0, 1–99, and ≥100) to CVD, CHD, and death events (*Table 4*). Among

Table 1 Baseline characteristics of participants with diabetes, metabolic syndrome, or neither condition

Clinical characteristics	Total ($n = 5174$)	No MetS or DM ($n = 3688$)	MetS without DM ($n = 1025$)	DM ($n = 461$)	*P* value
Age, years	47.3 (4.2)	47.0 (4.2)	48.0 (4.2)	47.7 (4.3)	<0.001
Women, no. (%)	2863 (55.3)	2053 (55.7)	539 (52.6)	271 (58.8)	0.063
Ethnicity, no. (%)					<0.001
Caucasian	2475 (47.8)	1851 (50.2)	475 (46.3)	149 (32.3)	
African American	1942 (37.5)	1330 (36.1)	381 (37.2)	231 (50.1)	
Chinese	242 (4.7)	193 (5.2)	35 (3.4)	14 (3.0)	
Hispanic	515 (10.0)	314 (8.5)	134 (13.1)	67 (14.5)	
Body mass index, kg/m^2	28.9 (6.0)	27.3 (5.2)	33.0 (5.5)	33.1 (6.8)	<0.001
Waist circumference, cm	93.5 (14.9)	89.0 (12.9)	105.4 (12.1)	103.4 (15.9)	<0.001
Fasting plasma glucose, mg/dL	95.7 (27.2)	88.8 (9.3)	97.2 (11.4)	148.6 (64.4)	<0.001
Total cholesterol, mg/dL	189.6 (35.6)	188.6 (33.8)	195.8 (40.1)	184.2 (37.4)	<0.001
HDL cholesterol, mg/dL	52.5 (15.9)	56.2 (15.8)	41.5 (10.3)	47.5 (14.7)	<0.001
Triglycerides, mg/dL	119.0 (86.6)	96.7 (59.4)	186.6 (112.9)	147.1 (112.8)	<0.001
LDL cholesterol, mg/dL	113.7 (32.0)	113.2 (31.2)	118.1 (33.7)	108.6 (33.8)	<0.001
Blood pressure, mmHg					
Systolic	116.2 (15.8)	113.5 (14.3)	123.8 (16.6)	121.0 (17.8)	<0.001
Diastolic	72.1 (10.7)	70.5 (10.1)	77.0 (11.0)	74.3 (10.7)	<0.001
Current smoking, no. (%)	990 (19.1)	674 (18.3)	224 (21.9)	92 (20.0)	0.032
General obesity, no. (%)	1876 (36.3)	882 (23.9)	694 (67.7)	300 (65.1)	<0.001
MetS components, no. (%)					
High waist circumference	2205 (42.6)	1018 (27.6)	868 (84.7)	319 (69.2)	<0.001
High fasting plasma glucose	1292 (25.0)	363 (9.8)	468 (45.7)	461 (100)	<0.001
Low HDL cholesterol	1731 (33.5)	718 (19.5)	785 (76.6)	228 (49.5)	<0.001
High triglycerides	1473 (28.5)	517 (14.0)	726 (70.8)	230 (49.9)	<0.001
High blood pressure	1586 (30.7)	695 (18.8)	643 (62.7)	248 (53.8)	<0.001
Dyslipidaemia, no. (%)	3396 (65.6)	2038 (55.3)	985 (96.1)	373 (80.9)	<0.001
Lipid-lowering medication use, no. (%)	426 (8.2)	149 (4.0)	169 (16.5)	108 (23.4)	<0.001
Hypertension, no. (%)	1838 (35.5)	876 (23.8)	690 (67.3)	272 (59.0)	<0.001
Anti-hypertensive medication use, no. (%)	942 (18.2)	342 (9.3)	408 (39.8)	192 (41.7)	<0.001
CAC score, Agatston units	21.8 (130.4)	16.0 (122.5)	29.6 (123.3)	50.7 (189.4)	<0.001
CAC score category (%)					<0.001
CAC 0	4089 (79.0)	3046 (82.6)	722 (70.5)	321 (69.6)	
CAC 1–99	837 (16.2)	510 (13.8)	229 (22.3)	98 (21.3)	
CAC ≥ 100	248 (4.8)	132 (3.6)	74 (7.2)	42 (9.1)	

Data are shown as percentage or mean (SD).
MetS, metabolic syndrome; DM, diabetes mellitus; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CAC, coronary artery calcium.

Table 2 Odds of the prevalent CAC among participants with diabetes, metabolic syndrome, or neither condition

Any CAC	No MetS or DM	MetS without DM			DM		
		OR	95% CI	*P* value	OR	95% CI	*P* value
Model 1	Reference	**1.90**	**1.61–2.25**	**<0.001**	**2.30**	**1.80–2.88**	**<0.001**
Model 2	Reference	**1.34**	**1.10–1.64**	**0.004**	**1.86**	**1.45–2.40**	**<0.001**
CAC ≥ 100							
Model 1	Reference	**1.88**	**1.40–2.54**	**<0.001**	**2.73**	**1.86–4.00**	**<0.001**
Model 2	Reference	**1.50**	**1.05–2.15**	**0.028**	**2.30**	**1.52–3.50**	**<0.001**

Model 1: Adjusted for age, sex, and ethnicity. Model 2: Model 1 plus variables included in the Pooled Cohort Equation (PCE) including total cholesterol, HDL cholesterol, systolic blood pressure, use of anti-hypertensive medication, and current smoking. Bold values are statistically significant.
MetS, metabolic syndrome; DM, diabetes mellitus; CAC, coronary artery calcium; OR, odds ratio; CI, confidence interval; HDL, high-density lipoprotein.

Table 3 Incidence of coronary and cardiovascular events and all-cause death

Characteristics	Cardiovascular disease		Coronary heart disease		Death	
	Events/ total	Incidence rate per 1000 person-years	Events/ total	Incidence rate per 1000 person-years	Events/ total	Incidence rate per 1000 person-years
No MetS or DM						
All	156/3688	3.12	104/3688	2.07	153/3688	2.97
CAC 0	85/3046	2.04	44/3046	1.04	106/3046	2.48
CAC 1–99	40/510	5.98	31/510	4.60	31/510	4.40
CAC ≥ 100	31/132	19.44	29/132	18.03	16/132	8.83
MetS without DM						
All	90/1025	6.69	52/1025	3.80	56/1025	3.94
CAC 0	47/722	4.88	19/722	1.94	34/722	3.40
CAC 1–99	22/229	7.33	16/229	5.27	13/229	4.06
CAC ≥ 100	21/74	25.09	17/74	19.83	9/74	9.04
DM						
All	58/461	10.00	32/461	5.36	47/461	7.50
CAC 0	28/321	6.74	14/321	3.30	22/321	5.01
CAC 1–99	19/98	16.15	11/98	8.89	13/98	9.75
CAC ≥ 100	11/42	23.60	7/42	14.30	12/42	22.13

MetS, metabolic syndrome; DM, diabetes mellitus; CAC, coronary artery calcium.

participants with neither MetS nor DM, compared with a CAC score of 0, CAC scores of 1–99 were associated with an increased CVD, CHD, and death risk with HRs ranging from 1.65 to 3.86; the corresponding values for CAC ≥ 100 ranged from 3.66 to 13.94, respectively (All $P < 0.05$, Model 1). All the associations remained statistically significant in Model 2, except for the association of CAC scores of 1–99 with death (1.47: 0.96–2.23, $P = 0.074$).

Regarding those in the MetS group, CAC scores of ≥100 were associated with 3.29- and 5.57-fold significantly greater risk of CVD and CHD events in Model 2, respectively. Regarding death, CAC scores of ≥100 were associated with a 2.13-fold greater risk (2.13: 0.97–4.72, $P = 0.062$).

For the participants in the DM group, in Model 2, CAC scores of 1–99 and ≥100 were associated with increased CVD risk of 1.89- and 2.70-fold, respectively; CAC scores of ≥100 were associated with a 2.97-fold significantly greater CHD risk (2.97: 1.09–8.10, $P = 0.033$). Regarding death, a 3.68-fold significantly greater risk was observed among those with CAC ≥ 100 (*Table 4*). Moreover, in Model 2, the impact of CAC scores of ≥100, on CVD and CHD among those with DM was significantly lower than those with neither MetS nor DM (*P* for interaction 0.018 and 0.009 for CVD and CHD, respectively).

Finally, we evaluated the association of DM or MetS with incident CVD, CHD, and death in the presence of subclinical atherosclerosis. Only DM remained a significant predictor of the events after adjustment with age, sex, ethnicity, risk factors in the PCE risk score, and subclinical atherosclerosis. More specifically, in Model 2, those with DM had 1.89 (1.35–2.46), 1.53 (0.98–2.38, $P = 0.059$), and 1.96 (1.37–2.81) folds increase in the hazard of CVD, CHD, and death, respectively (*Table 5*).

In a secondary analysis among individuals with DM and available haemoglobin A_{1c} data, after further adjusting for haemoglobin A_{1c}, the association of CAC score with CVD, CHD, and death remained significant (see Supplementary material online, *Table S2*).

Discussion

In this diverse sample of US adults aged 38 to 55 years, with a median 14.2-year follow-up, after multivariable adjustment for risk factors and in the presence of CAC, individuals with DM but not those with MetS had 1.5 to 2-fold greater risk of CVD, CHD, and all-cause death. We found that, in general, a CAC score of zero was associated with low event rates across all metabolic groups. Coronary artery calcium scores of ≥100, irrespective of the presence of MetS or DM, were independently associated with incident CVD, CHD, and death. Further adjustment with $HbA1_c$ did not modify these associations among those with DM. More importantly, the association of CAC scores of ≥100 with CVD and CHD events was less pronounced among individuals with DM.

In the current analysis, the presence of DM in contrast to MetS with no DM was directly associated with incident CVD and all-cause death, regardless of subclinical atherosclerosis. Xanthakis *et al.*[4] showed that these groups are both associated with an elevated risk of incident CVD in the presence of subclinical disease, including CAC scores of ≥100. However, in contrast to their study, we adjusted for risk factors included in the ASCVD risk score.

In a prior study, among participants with a mean age of 62.2 years from the MESA study, CAC testing refined risk estimation of CVD and CHD in individuals with MetS and DM over a decade.[5] In line with our findings, Xanthakis *et al.*,[4] among 4416 African Americans with a mean age of 54 years from the Jackson Heart Study, reported a direct association of CAC ≥ 100 with incident CVD events among individuals with MetS, DM, or with neither condition. Regarding all-cause death, similar to a previous analysis in the Diabetes Heart Study,[16] we found a significantly higher risk of death for CAC scores of ≥100 among individuals with DM.[16]

Additionally, the absence of CAC has been found to be associated with low CHD, ASCVD, and death risk among those with DM.[5,16] Similarly, we found an ~50% significantly lower risk of CVD and death among individuals with DM and in the absence of CAC (data not shown).

In the current analysis among younger individuals, CAC, especially CAC scores of ≥100, predicted cardiovascular risk and all-cause death across all metabolic groups (MetS, DM, neither). In those with DM, these associations were independent of haemoglobin A_{1c} levels. In general, data on CAC in younger individuals are limited.

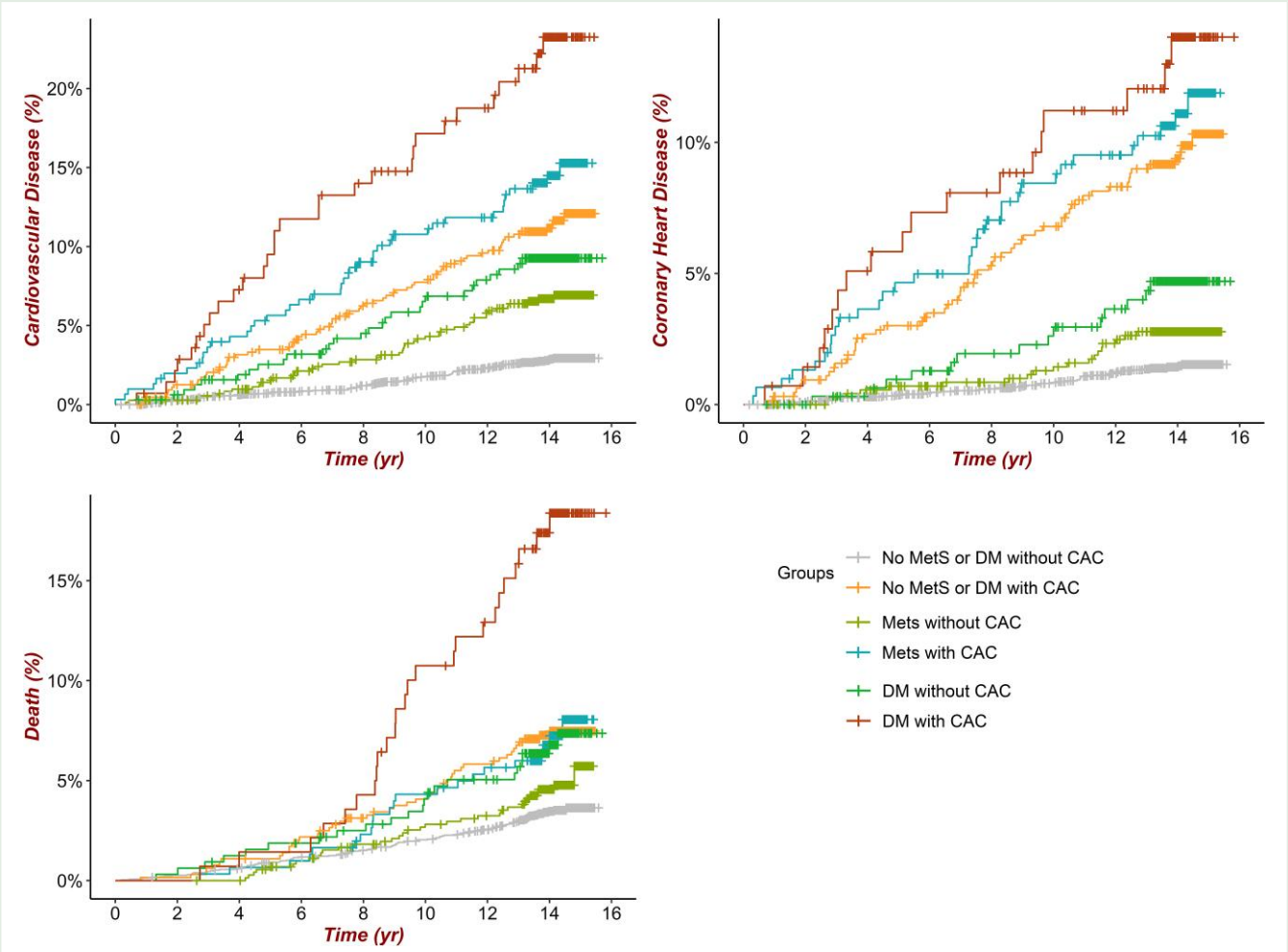

Figure 2 Kaplan–Meier estimated cumulative incidence of CVD, CHD, and death by CAC and metabolic status categories. MetS, metabolic syndrome; DM, diabetes mellitus; CAC, coronary artery calcium.

In population-based cohorts, most asymptomatic adults aged <55 years have a CAC score of 0.[17,30,31] However, among young adults aged 30–49 years, having CAC scores of ≥100 associates with a higher risk of total, CVD, and CHD death.[18] It is of note that about one-half of individuals with DM at ages 40 to 49 years already have intermediate ASCVD risk,[32] and whether the presence of CAC is associated with greater risk of CVD and death in younger patients with DM is less clear. According to the 2023 Standards of Care in Diabetes[33] and the 2023 ESC Guidelines for managing CVD in patients with DM,[6] any benefit of CT calcium scanning to identify patient subgroups for different treatment strategies remains unproved in asymptomatic people with diabetes. Our study revealed that both DM and CAC ≥ 100 are associated with a higher risk of CVD, CHD, and all-cause death among individuals younger than 55 years, independently. However, the association of CAC ≥ 100 with cardiovascular events among individuals with DM was significantly lower than those with neither MetS nor DM. Although an elevated CAC score has been shown to predict clinical outcomes in several cohorts, including various proportions of participants with DM,[34] the ACC/AHA elaborates that clinicians should not down-classify risk in patients with DM who have a CAC score of 0 due to the potential presence of non-calcified plaques.[35] In our study, although the risk of all-cause death for CAC score across different metabolic groups was comparable, regarding CVD risk, the presence of DM had a significant impact on the association between CAC with cardiovascular and coronary events. Our findings among younger individuals complement the current guidelines[6,33] that CAC screening may be less helpful in refining CVD risk estimation beyond ASCVD RFs in the presence of DM among asymptomatic individuals.

The practical aspects of CAC measurement in younger individuals are debateable as screening low-risk individuals younger than 55 years for CAC is not desirable and the negative findings could be accompanied by the negative consequences of screening, including associated cost and time, and radiation exposure, consequently limiting benefit in most individuals. However, it is noteworthy that the significance of chronological age diminishes once the CAC score is known. The presence of CAC among individuals with low CVD risk is not uncommon; in a large US observational study of 13 397 young adults aged 30–49 years (76% with ≤1 CVD risk factor), the number needed to scan to detect CAC was 5 and the assessment of CAC predicted future CVD and all-cause mortality events more accurately than traditional CVD risk factors alone.[36] Meanwhile reducing the number needed to scan required to identify a young individual with any CAC using a selective CAC screening strategy may provide rationale for CAC testing; a previous analysis from the CARDIA study showed that compared with a strategy in which all individuals aged 32–46 years are screened, an approach using assessment of risk factors in early adulthood may have potential

Table 4 Hazard of coronary and cardiovascular events and all-cause death associated with coronary artery calcium by metabolic status

	No MetS or DM			MetS without DM			DM		
	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
Cardiovascular disease									
Model 1									
Log (CAC + 1)	**1.44**	**1.34–1.55**	**<0.001**	**1.25**	**1.13–1.38**	**<0.001**	**1.26**	**1.12–1.42**	**0.001**
Any CAC vs. 0	**3.98**	**2.83–5.56**	**<0.001**	**1.95**	**1.27–3.03**	**0.002**	**2.42**	**1.38–4.25**	**0.002**
CAC 1–99 vs. 0	**2.88**	**1.96–4.27**	**<0.001**	1.34	0.80–2.26	0.261	**2.18**	**1.18–4.02**	**0.013**
CAC ≥ 100 vs. 0	**8.65**	**5.56–13.47**	**<0.001**	**4.35**	**2.49–7.57**	**<0.001**	**3.21**	**1.49–6.94**	**0.003**
Model 2									
Log (CAC + 1)	**1.36**	**1.26–1.46**	**<0.001**	**1.18**	**1.08–1.31**	**0.001**	**1.22**	**1.08–1.38**	**0.001**
Any CAC vs. 0	**3.18**	**2.27–4.45**	**<0.001**	**1.67**	**1.08–2.60**	**0.022**	**2.09**	**1.19–3.68**	**0.010**
CAC 1–99 vs. 0	**2.38**	**1.60–3.52**	**<0.001**	1.18	0.70–2.01	0.529	**1.89**	**1.02–3.51**	**0.040**
CAC ≥ 100 vs. 0	**6.30**	**4.02–9.86**	**<0.001**	**3.29**	**1.87–5.79**	**<0.001**	**2.70**	**1.25–5.83**	**0.012**
Coronary heart disease									
Model 1									
Log (CAC + 1)	**1.56**	**1.44–1.70**	**<0.001**	**1.35**	**1.20–1.54**	**<0.001**	**1.26**	**1.07–1.48**	**0.005**
Any CAC vs. 0	**5.72**	**3.78–8.67**	**<0.001**	**3.18**	**1.76–5.75**	**<0.001**	**2.41**	**1.12–5.17**	**0.024**
CAC 1–99 vs. 0	**3.86**	**2.40–6.24**	**<0.001**	**2.18**	**1.10–4.30**	**0.025**	2.11	0.92–4.88	0.078
CAC ≥ 100 vs. 0	**13.94**	**8.37–23.21**	**<0.001**	**6.82**	**3.34–13.94**	**<0.001**	**3.27**	**1.20–8.92**	**0.020**
Model 2									
Log (CAC + 1)	**1.50**	**1.38–1.63**	**<0.001**	**1.31**	**1.15–1.49**	**<0.001**	**1.22**	**1.04–1.45**	**0.013**
Any CAC vs. 0	**4.64**	**3.06–7.04**	**<0.001**	**2.75**	**1.51–4.99**	**0.001**	2.09	0.97–4.54	0.060
CAC 1–99 vs. 0	**3.20**	**1.98–5.17**	**<0.001**	1.90	0.97–3.79	0.067	1.80	0.77–4.20	0.178
CAC ≥ 100 vs. 0	**10.80**	**6.44–18.10**	**<0.001**	**5.57**	**2.71–11.45**	**<0.001**	**2.97**	**1.09–8.10**	**0.033**
Death									
Model 1									
Log (CAC + 1)	**1.20**	**1.10–1.31**	**<0.001**	**1.15**	**1.01–1.32**	**0.040**	**1.32**	**1.16–1.51**	**<0.001**
Any CAC vs. 0	**1.95**	**1.37–2.81**	**<0.001**	1.41	0.80–2.49	0.229	**2.49**	**1.34–4.65**	**0.004**
CAC 1–99 vs. 0	**1.65**	**1.09–2.50**	**0.018**	1.13	0.59–2.18	0.405	1.91	0.94–3.91	0.076
CAC ≥ 100 vs. 0	**3.66**	**2.11–6.33**	**<0.001**	**2.40**	**1.10–5.23**	**0.029**	**4.44**	**1.99–9.91**	**<0.001**
Model 2									
Log (CAC + 1)	**1.17**	**1.07–1.28**	**0.001**	1.13	0.99–1.30	0.073	**1.28**	**1.12–1.46**	**<0.001**
Any CAC vs. 0	**1.74**	**1.20–2.51**	**0.003**	1.38	0.78–2.43	0.278	**2.10**	**1.12–3.98**	**0.021**
CAC 1–99 vs. 0	1.47	0.96–2.23	0.074	1.13	0.59–2.19	0.712	1.61	0.78–3.35	0.196
CAC ≥ 100 vs. 0	**2.77**	**1.60–4.81**	**<0.001**	2.13	0.97–4.72	0.062	**3.68**	**1.63–8.34**	**0.002**

Model 1: Adjusted for age, sex, and ethnicity. Model 2: Model 1 plus variables included in the Pooled Cohort Equation (PCE), including total cholesterol, HDL cholesterol, systolic blood pressure, use of anti-hypertensive medication, and current smoking. Bold values are statistically significant.
MetS, metabolic syndrome; DM, diabetes mellitus; HDL, high-density lipoprotein; CAC, coronary artery calcium; HR, hazard ratio; CI, confidence interval.

to reduce the number of people scanned for CAC by 50% and reduce the number of people needed to screen to find an individual with CAC from 3.5 to 2.2 in midlife.[17] Generally, whether CAC testing in younger adults with low CVD risk is justified needs to be assessed in the context of societal priorities, the general population's willingness, as well as available prevention resources.

In our analyses, we categorized participants into three groups—those with DM, those with MetS but without DM, and those with neither condition—to examine the association between CAC and outcomes across these metabolic profiles. Given inconsistent evidence on long-term CVD risk with metabolically healthy obesity,[37–40] our main analyses' focus was on the three-group categorization based on established definitions of DM and MetS, similar to previous studies.[3,4,41] Further research is needed to clarify CVD risk associated with the presence of CAC for metabolically healthy obesity and address these associations in individuals with MetS and with/without transition to DM over follow-up, especially among younger adults.

Limitations

This study has several limitations that must be acknowledged. First, although we adjusted for age, sex, ethnicity, and a number of risk factors in the models, potential residual confounding could still be present. Further, the effects of CAC scoring on incident changes to medical therapy and lifestyle behaviours are unknown in the current study, and their mitigating impact on clinical outcomes is unknown. However, we believe that would lead to under-, rather than overestimation, of the effect sizes of this study. Our model did not assess the association of CAC with cause-specific mortality. Thus, our analysis cannot offer information regarding the impact of CAC, specifically on

Table 5 Hazard of coronary and cardiovascular events and all-cause death by metabolic status and presence of coronary artery calcium

	Cardiovascular disease			Coronary heart disease			Death		
	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
(A) Risks associated with MetS and DM, not adjusting for subclinical atherosclerosis									
Model 1									
No MetS or DM	1			1			1		
MetS without DM	**1.99**	**1.53–2.57**	**<0.001**	**1.68**	**1.21–2.36**	**0.002**	1.24	0.91–1.69	0.169
DM	**2.96**	**2.18–4.01**	**<0.001**	**2.56**	**1.71–3.82**	**<0.001**	**2.28**	**1.64–3.18**	**<0.001**
Model 2									
No MetS or DM	1			1			1		
MetS without DM	1.25	0.92–1.70	0.152	1.10	0.75–1.62	0.926	1.22	0.86–1.75	0.322
DM	**2.20**	**1.58–3.08**	**<0.001**	**1.97**	**1.27–3.06**	**0.002**	**2.16**	**1.51–3.10**	**<0.001**
(B) Risks associated with MetS and DM, adjusting for subclinical atherosclerosis									
Model 1									
No MetS or DM	1			1			1		
MetS without DM	**1.74**	**1.33–2.26**	**<0.001**	1.37	0.99–1.93	0.061	1.13	0.83–1.55	0.409
DM	**2.36**	**1.73–3.21**	**<0.001**	**1.80**	**1.20–2.70**	**0.004**	**2.01**	**1.44–2.81**	**<0.001**
CAC 1–99 vs. 0	**2.22**	**1.68–2.93**	**<0.001**	**3.09**	**2.16–4.40**	**<0.001**	**1.54**	**1.13–2.12**	**0.001**
CAC ≥ 100 vs. 0	**5.77**	**4.20–7.93**	**<0.001**	**9.12**	**6.19–13.44**	**<0.001**	**3.17**	**2.16–4.66**	**<0.001**
Model 2									
No MetS or DM	1			1			1		
MetS without DM	1.16	0.86–1.59	0.323	0.97	0.65–1.44	0.887	1.16	0.81–1.67	0.395
DM	**1.89**	**1.35–2.46**	**<0.001**	1.53	0.98–2.38	0.059	**1.96**	**1.37–2.81**	**<0.001**
CAC 1–99 vs. 0	**1.87**	**1.42–2.48**	**<0.001**	**2.62**	**1.83–3.75**	**<0.001**	**1.42**	**1.04–1.95**	**0.030**
CAC ≥ 100 vs. 0	**4.31**	**3.13–5.95**	**<0.001**	**7.36**	**4.98–10.86**	**<0.001**	**2.71**	**1.83–3.99**	**<0.001**

Model 1: Adjusted for age, sex, and ethnicity. Model 2: Model 1 plus variables included in the Pooled Cohort Equation (PCE) including total cholesterol, HDL cholesterol, systolic blood pressure, use of anti-hypertensive medication, and current smoking. Bold values are statistically significant.
MetS, metabolic syndrome; DM, diabetes mellitus; HDL, high-density lipoprotein; CAC, coronary artery calcium; HR, hazard ratio; CI, confidence interval.

cardiovascular mortality among individuals with and without diabetes. However, we believe that all-cause mortality is the most relevant endpoint that can be examined in epidemiological studies.[42] In this regard, future studies with longer follow-ups are warranted to help confirm our findings and to ascertain whether CAC scoring aids in reclassifying young individuals with and without diabetes in terms of cardiovascular events and death. Another potential limitation is the pooling of individuals included from two cohorts with differences in their age (38–50 years for CARDIA and 45–55 years for MESA individuals), where there may be differences both in comorbidities and the effects of CAC on CVD, CHD, and mortality risk. Realizing that the mean age of individuals from the MESA study cohort was higher than those of the CARDIA study, it is not surprising that the CARDIA study had a lower prevalence of comorbidities and CAC. Although longer follow-up certainly would have resulted in more incident events to perform the analyses in each cohort separately, the number of events in the pooled cohorts provided sufficient power to detect statistically significant differences in CVD, CHD events, and death within and between pre-defined groups. We also included interaction terms of this cohort effect with CAC score as the main exposure as well as covariates used in the main analyses, which were all generally non-significant, indicating that the effect of CAC or covariates on the outcomes may not differ significantly by cohort (data not shown).

However, this study has considerable strengths, including the multi-ethnic nature of this study, the large study sample from two landmark prospective cohorts from the USA, and the use of CAC categories of 0, 1–99, and ≥100 according to ACC/AHA guideline recommendations.[12]

Conclusions

In this study from over 5000 adults aged 38–55 years from the CARDIA and MESA cohorts, we found that the presence and severity of CAC were associated with a significantly higher risk of CVD, CHD, and all-cause mortality nearly 15 years after screening, across all metabolic groups (DM, MetS, neither). However, the association of CAC ≥ 100 with CVD and CHD events was less pronounced in the presence of DM.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

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Author contribution

S.M., F.H., and M.D.S. contributed to the conceptualization of the study and design; S.M. analysed and interpreted the data and provided the study figures; F.H. and M.D.S. contributed to the project administration and methodology; S.M. wrote the initial manuscript; F.H. and M.D.S. did the final approval of the manuscript; D.K. reviewed the manuscript.

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Ethical approval

Each study protocol was approved by the institutional review committee of each site participating in the studies. The institutional review boards of each site approved the studies, and all participants provided written informed consent. All methods were carried out following relevant guidelines and regulations. Approval for undertaking the current project was also obtained from the Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Conflict of interest: M.D.S. is on the scientific advisory boards of Amgen, Agepha, Ionis, New Amsterdam, Novartis, Precision BioScience, and Novo Nordisk, and is a consultant for Ionis, Novartis, Regeneron, Aidoc, and Shanghai Pharma Biotherapeutics. All other authors declare that they have nothing to disclose.

Data availability

The data used for this study are available at https://biolincc.nhlbi.nih.gov/home/.

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