

CLINICAL RESEARCH

Predicting Long-Term Absence of Coronary Artery Calcium in Metabolic Syndrome and Diabetes

The MESA Study

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ABSTRACT

OBJECTIVES The purpose of this study was to identify predictors of healthy arterial aging (long-term coronary artery calcification [CAC] of 0) among individuals with metabolic syndrome (MetS) or type 2 diabetes (T2D), which may improve primary prevention strategies.

BACKGROUND Individuals with MetS or T2D have a heterogeneously increased risk of atherosclerotic cardiovascular disease and not all have a high-intermediate risk.

METHODS We included 574 participants from the MESA (Multi-Ethnic Study of Atherosclerosis) with MetS or T2D who had CAC=0 at baseline and a repeat CAC scan 10 years later. Multivariable logistic regression assessed the association of traditional and novel atherosclerotic cardiovascular disease risk factors and the MetS severity score (based on the 5 MetS criteria) with healthy arterial aging.

RESULTS The mean age of participants was 58.9 years, 67% were women, 422 participants had MetS, and 152 had T2D. The proportion with long-term CAC=0 was similar for MetS (42%) and T2D (44%). A younger age was the only individual low/normal traditional risk factor associated with an increased likelihood of long-term CAC=0 (odds ratio [OR]: 1.50; 95% confidence interval [CI]: 1.22 to 1.85 per 10-years younger). The strongest associations of nontraditional risk factors were observed for an absence of thoracic calcification (OR: 2.42; 95% CI: 1.24 to 4.72), absence of carotid plaque (OR: 1.81; 95% CI: 1.25 to 2.61), and among persons with a high sensitivity troponin <3 ng/ml (OR: 1.55; 95% CI: 1.01 to 2.38). In addition, persons with the lowest quartile MetS severity score had a substantially higher odds of healthy long-term CAC=0 (OR: 2.71; 95% CI: 1.27 to 5.76).

CONCLUSIONS More than 40% of adults with MetS or T2D and baseline CAC=0 had long-term absence of CAC, which was most strongly associated with an absence of extracoronary atherosclerosis and a low MetS score. An optimal overall cardiovascular profile appears to be more important than an ideal value of any individual risk factor to maintain healthy arterial aging. (J Am Coll Cardiol Img 2020;■:■-■) © 2020 by the American College of Cardiology Foundation.

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**ABBREVIATIONS
AND ACRONYMS****ASCVD** = atherosclerotic
cardiovascular disease**CAC** = coronary artery
calcification**CI** = confidence interval**hs-cTnT** = high-sensitivity
cardiac troponin T**eGFR** = estimated glomerular
filtration rate**HDL-C** = high-density
lipoprotein cholesterol**Lp(a)** = lipoprotein a**MetS** = metabolic syndrome**NT-proBNP** = N-terminal pro-
brain natriuretic peptide**OR** = odds ratio**PCE** = Pooled Cohort Equations**T2D** = type 2 diabetes

The prevalences of metabolic syndrome (MetS) and type 2 diabetes (T2D) disease have increased sharply during the past 3 decades (1,2) and they now currently affect 115 million (35%) (3) and 30 million (9%) (4) individuals in the United States, respectively. Although both of these conditions are often considered atherosclerotic cardiovascular disease (ASCVD) risk equivalents (5,6), there is significant heterogeneity in the risk for a future ASCVD event (7). In particular, approximately 40% of individuals with MetS and/or T2D do not have coronary artery calcium (CAC=0) (8–10). The absence of CAC, as measured using noncontrast computed tomography, is associated with a very low risk for incident ASCVD (11), with a long-term event rate of <7/1,000 person-years of follow-up (8). These observations underline a need to further understand

the predictors of healthy arterial aging (persistent long-term CAC=0) among individuals with MetS and/or T2D to develop a more precise approach for the primary prevention of ASCVD.

CAC, or the lack thereof, reflects the contribution of cumulative risk factor exposure, genetics, and susceptibility (12). Although the risk factors associated with CAC progression are well-established (13), the predictors associated with persistent long-term CAC=0 remain largely unexplored. Furthermore, prospective studies of CAC conducted among individuals with MetS or T2D have been limited to relatively short follow-up times and focused solely on CAC progression and traditional ASCVD risk factors (8,14). Understanding the risk predictors, or absence of risk factors, associated with persistent CAC=0 among individuals with MetS or T2D may provide insight into: 1) the predictors of healthy arterial aging in this patient group that is otherwise considered at high risk for ASCVD; and 2) which patients with MetS or T2D are most likely to have long-term healthy arterial aging.

METHODS

STUDY POPULATION. MESA (Multi-Ethnic Study of Atherosclerosis) is a community-based, multiethnic

cohort study of 6,814 men and women free of clinical ASCVD 45 to 84 years of age at baseline, which has been described in detail elsewhere (15). Participants with CAC >0 at Visit 1 (n = 3,398), participants without a repeat CAC scan at Visit 5 (n = 1,566), and those who did not have MetS or diabetes at baseline (n = 1,276) were excluded resulting in a cohort of 574 individuals with CAC=0 and MetS or T2D at MESA Visit 1 (2000 to 2002) (Supplemental Figure 1). This group of 574 individuals was compared with participants with CAC=0 at baseline who had MetS or T2D that were not randomized to a follow-up CAC scan (n = 559) (Supplemental Table 1). T2D was defined by a fasting blood glucose level >126 mg/ml (hemoglobin A1c was not measured at MESA Visit 1), reported use of insulin and/or oral hypoglycemic agents, or self-reported diabetes. MetS was defined using the National Cholesterol Education Program Adult Treatment Panel III guidelines (16), characterized by any 3 of the 5 following traits: 1) waist circumference >102 cm in men or >88 cm in women; 2) serum triglycerides ≥150 mg/ml or drug treatment for elevated triglycerides; 3) serum high-density lipoprotein cholesterol (HDL-C) <40 mg/dl in men or <50 mg/dl in women; 4) blood pressure ≥130/85 mm Hg or drug treatment for elevated blood pressure; and 5) fasting blood glucose ≥100 mg/dl or drug treatment for elevated blood glucose.

All study participants provided written informed consent at each examination, and study protocols were approved by site-specific Institutional Review Boards at respective MESA-participating institutions.

MEASUREMENT OF CORONARY AND THORACIC CALCIFICATION.

All MESA participants underwent a CAC scan at Visit 1, whereas one-half of MESA participants at Visit 5 were randomized to a CAC scan. Calcium scores were computed using the Agatston method and standardization of results among field centers was achieved using calcium phantoms scanned alongside participants (17,18). The phantom had 4 bars of known calcium density and was used to calibrate the level of brightness between study subjects and sites. The Chicago, Los Angeles, and New York field centers used electron beam computed tomography scanners and the Baltimore, Forsyth County, and

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St. Paul field centers used multidetector computed tomography scanners to acquire CAC scans.

Rescan agreement was robust for both electron beam computed scanners and multidetector computed tomography scanners with a Kappa statistic for interobserver and intraobserver agreement of 0.93 and 0.90, respectively (11,19). Using the Agatston method, the ascending aorta (aortic annulus to the lower edge of pulmonary artery) and descending aorta (lower edge of pulmonary artery to the cardiac apex) were evaluated for the presence (Agatston score ≥ 1) or absence (Agatston score = 0) of thoracic aortic calcification (20).

GENERAL CLINICAL EXAMINATION, ASCVD RISK FACTORS, AND ASCVD EVENTS. Standardized survey methods were used to collect demographic and clinical information, including sex, race, education status, smoking status, and medication use history (15). Resting blood pressure was measured in triplicate on the right arm after 5 min in the seated position and the average of the second and third readings was used in analyses. Waist circumference was measured at the level of the umbilicus using a Gullick II 150 cm anthropometric steel measuring tape with standard 4-ounce tension (Sammons Preston, Chicago, Illinois) (21). Fasting blood glucose was measured using the Vitros 950 analyzer (Johnson & Johnson, Rochester, New York) (22). Fasting lipid values were measured using the cholesterol oxidase method (Roche Diagnostics) (22) and low-density lipoprotein cholesterol was calculated using the Friedewald equation (23). Using the 5 traditional MetS components of: 1) waist circumference; 2) systolic blood pressure; 3) HDL-C; 4) serum triglycerides; and 5) fasting blood glucose, we calculated sex- and race-specific MetS severity scores for each study participant (24–26). As previously described in greater detail (24), a confirmatory factor analysis was performed to establish the weighted contribution of each component to a latent MetS factor on a sex- and race-specific basis. For each of the 8 subgroups based on sex and race (White, African American, Hispanic, and Chinese) factor loadings from the 5 MetS components were determined and used to produce equations for calculating a MetS severity score for each subgroup (24–26). The MetS severity scores were initially derived from adults aged 20 to 64 years participating in the National Health and Nutrition Examination Survey (24) and have been since used in several cohorts, including the Atherosclerosis Risk In Communities, Jackson Heart Study, Bogalusa Heart Study, and Princeton Lipid Research cohorts (27–29). The resulting score

has a standard normal distribution that functions as a z-score. Serum creatinine was quantified using the Kinetic Jaffe method and was used to calculate estimated glomerular filtration rate (eGFR) via the Chronic Kidney Disease Epidemiology Collaboration equation (30). Semiquantitative urine protein dipstick analysis was performed on collected urine samples. The presence of a carotid artery atherosclerotic plaque was defined by a distinct, focal wall thickening >1.5 cm or focal thickening $>50\%$ than the surrounding intima-media thickness and was measured using an M12L transducer (General Electric Medical Systems, Waukesha, Wisconsin; common carotid artery frequency, 13 MHz) (31,32). Serum levels of high-sensitivity C-reactive protein (hs-CRP) were measured using the BNIII nephelometer (Dade Behring, Deerfield, Illinois) (33). Cardiac biomarkers, N-terminal pro-brain natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin T (hs-cTnT), were quantified in ethylenediaminetetraacetic acid plasma and were measured on the Cobas e601 (Roche Diagnostics, Indianapolis, Indiana) (34). Lipoprotein a (Lp(a)) concentration was quantified using a latex-enhanced turbidimetric immunoassay (Denka Seiken, Tokyo, Japan) (35). Carotid plaque ($n = 545$), NT-proBNP ($n = 474$), and Lp(a) ($n = 303$) were measured among a subset of all study participants ($n = 574$).

ASCVD events were defined as incident coronary heart disease, incident stroke, or other incident ASCVD and adjudicated per a previously described MESA protocol (15). To examine differences in ASCVD event rates between participants with and without long-term persistent CAC=0, Visit 5 served as the baseline for follow-up time for all ASCVD event analyses.

STATISTICAL ANALYSIS. Study population characteristics are presented as mean \pm SD for continuous variables, whereas percentages are used for categorical variables. Normality of continuous variable distribution was assessed via the Kolmogorov-Smirnov test. The Student's *t*-test and Wilcoxon signed-rank test were used to assess differences in normally and non-normally distributed continuous variables, respectively. Differences between categorical variables were evaluated using the chi-square test.

We categorized continuous predictor variables as normal or elevated to assess their association with long-term absence of CAC using the following interval values: waist circumference <102 cm for men and <88 cm for women, systolic and diastolic blood pressure <130 mm Hg and <80 mm Hg, fasting blood glucose <100 mg/dl, fasting serum triglycerides

TABLE 1 Characteristics of 574 MESA Participants With Metabolic Syndrome and/or Type 2 Diabetes Mellitus

	All (N = 574)	Long-Term CAC=0 (n = 240)	Incident CAC (n = 334)	p Value§
Sociodemographic				
Age, yrs	58.9 ± 9.1	56.8 ± 8.9	60.3 ± 8.9	<0.0001
Female, %	66.6	68.8	65.0	0.34
Race, %				0.98
White	29.5	29.2	29.6	
Chinese	8.5	8.7	8.4	
African American	33.6	32.9	34.1	
Hispanic	28.4	29.2	27.9	
Traditional ASCVD Factors				
Systolic blood pressure, mm Hg	130.3 ± 20.3	129.1 ± 19.9	131.1 ± 20.6	0.23
Diastolic blood pressure, mm Hg	73.1 ± 10.1	72.9 ± 10.5	73.2 ± 9.9	0.67
Antihypertensive medication, %	44.1	40.4	46.7	0.13
Total cholesterol, mg/dl	195.4 ± 36.7	192.7 ± 35.8	197.3 ± 37.3	0.15
HDL cholesterol, mg/dl	44.5 ± 10.8	44.5 ± 10.9	44.5 ± 10.7	0.94
Serum triglycerides, mg/dl†	162.0 (105.0, 212.0)	159.0 (107.0, 205.0)	162.0 (104.0, 213.0)	0.69
Lipid-lowering medication, %	17.1	12.5	20.5	0.01
Type 2 diabetes mellitus, %	26.5	26.3	26.7	0.92
Fasting blood glucose, mg/dl	107.6 ± 37.9	102.7 ± 28.2	111.2 ± 43.2	<0.001
Glucose-lowering medication, %	17.3	15.4	18.6	0.33
Waist circumference, cm	104.4 ± 12.4	103.9 ± 12.4	104.7 ± 12.4	0.48
Never smokers, %	56.9	57.7	56.3	0.88
10-yr ASCVD risk	8.5 (3.7, 15.4)	6.9 (2.7, 12.6)	9.5 (4.8, 16.6)	<0.001
Cardiovascular imaging				
CAC score at Visit 5†	6.8 (0.0, 35.9)	0.0 (0.0, 0.0)	29.3 (12.2, 75.5)	<0.001
Presence of carotid plaque, %‡	43.3	33.8	50.3	0.0001
Presence of thoracic calcification, %	14.5	7.5	19.5	<0.001
Novel CVD risk factors				
hs-C-reactive protein, mg/l	5.1 ± 6.4	4.9 ± 5.8	5.1 ± 6.8	0.79
hs-cardiac troponin T, pg/dl †	4.0 (2.9, 6.5)	3.3 (2.9, 5.5)	4.4 (2.9, 6.9)	<0.001
NT-proBNP, pg/dl †‡	44.4 (19.9, 89.4)	39.1 (19.3, 77.3)	49.9 (20.6, 91.2)	0.10
Lipoprotein a, mg/dl‡	25.7 ± 30.2	23.1 ± 18.7	27.9 ± 31.3	0.12
Metabolic syndrome severity z-score	1.8 ± 1.1	1.7 ± 0.9	1.8 ± 1.2	0.13
eGFR, ml/min/1.73 m ²	81.2 ± 15.9	82.8 ± 15.7	80.1 ± 16.1	0.04
Presence of urine protein, %	9.9	9.2	10.6	0.60

Values are mean ± SD, unless otherwise noted. †Median (Q1, Q3). ‡Measured in subset of population (carotid plaque, n = 545; NT-proBNP, n = 474; Lp(a), n = 303). §p for comparison between long-term CAC=0 and incident CAC.

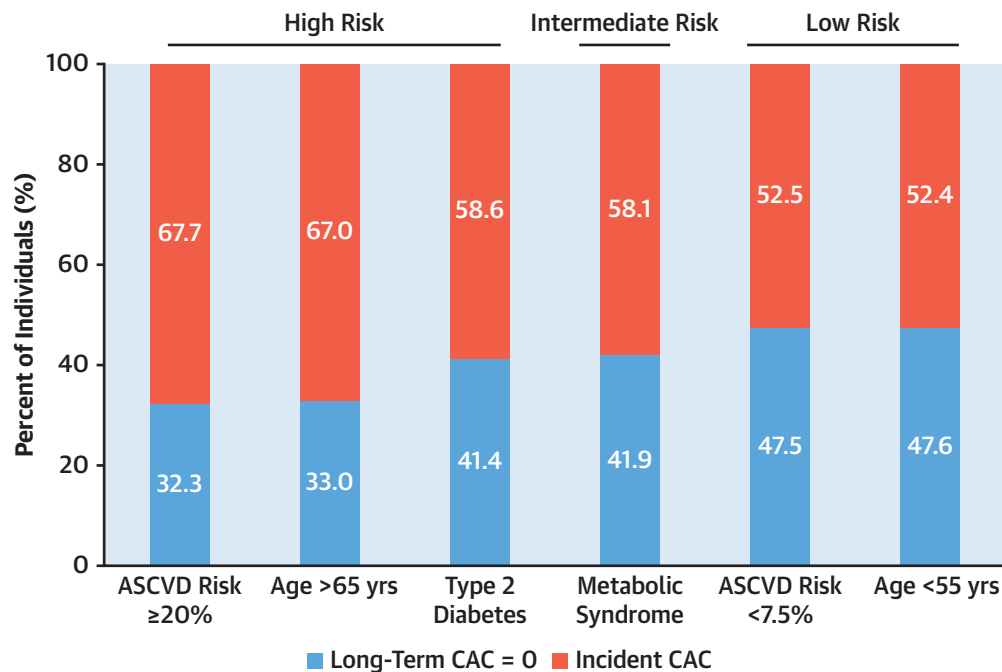
ASCVD = atherosclerotic cardiovascular disease; CAC = coronary artery calcium; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; hs = high-sensitivity; MESA = multi-ethnic study of atherosclerosis; NT-proBNP = n-terminal pro-brain natriuretic peptide.

<150 mg/dl (37), total cholesterol/HDL-C ratio <3.5 (38), NT-proBNP <125 pg/ml (39), hs-cTnT <3 ng/ml, Lp(a) <50 mg/dl for non-Hispanic white, Hispanic, and Chinese and <30 mg/dl for non-Hispanic black (35), eGFR ≥60 ml/min/1.73 m², absence of urine protein, hs-CRP <2 mg/l (33), and absence of thoracic calcification. Lastly, individuals were categorized into quartiles based on their MetS severity score consistent with prior publications (28,40), and the highest quartile was compared with the lowest quartile.

The association of ASCVD predictor variables with persistent CAC=0 was assessed through multivariable logistic regression adjusting for age, sex, race, education, antihypertensive medication, lipid-lowering medication, glucose-lowering medication,

cigarette smoking, waist circumference, blood pressure, fasting blood glucose, fasting serum triglycerides, and total cholesterol/HDL-C ratio. The association between the MetS severity score and persistent CAC=0 was assessed in the latter fully adjusted model and a model containing only age, sex, race, education, antihypertensive medication, lipid-lowering medication, glucose-lowering medication, and cigarette smoking. The association between the Pooled Cohort Equations (PCE) ASCVD risk score and persistent CAC=0 was assessed in a bivariate logistic regression analysis using a cutoff of 7.5%. To investigate if there was a phenotype or specific group of risk predictors most strongly associated with persistent CAC=0, we examined the

CENTRAL ILLUSTRATION Proportion of Participants With Long-Term CAC=0 Versus Incident CAC Stratified by Baseline Risk



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Similar proportion of participants with long-term CAC=0 among persons with metabolic syndrome and/or type 2 diabetes. ASCVD = atherosclerotic cardiovascular disease; CAC = coronary artery calcification.

discriminative ability of groups of continuous ASCVD predictor variables using the concordance statistic via multivariable logistic regression modeling. The nonparametric approach developed by DeLong et al. (41) was used to compare receiver-operating characteristic curves between models. ASCVD events were expressed as absolute numbers and proportions for each respective study sample. The total number of events was divided by person-years to calculate ASCVD rates (per 1,000-year follow-up). For the main study sample, 23 of 574 people experienced an event in between MESA Visit 1 and the follow-up CAC scans at Visit 5 and, thus, were excluded from the events analysis.

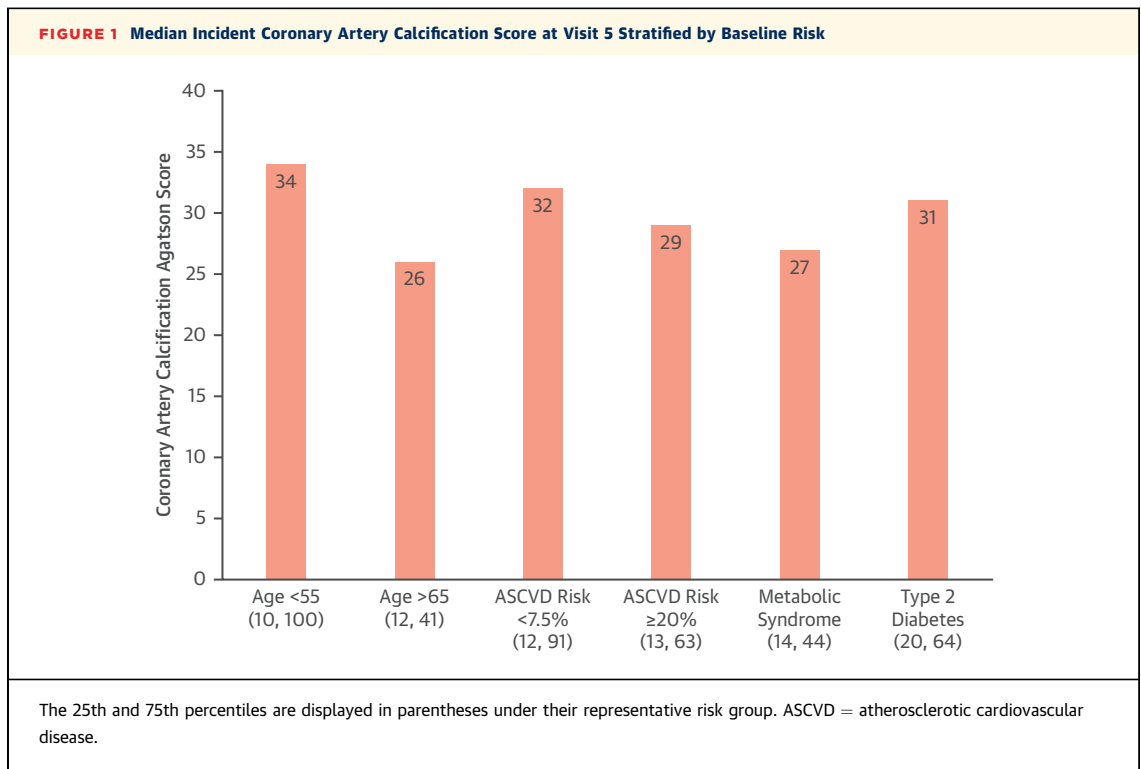
We performed 3 separate sensitivity analyses controlling for diabetes duration (insulin use at Visit 1), diabetes control (glycated hemoglobin measured at Visit 2), and changes in metabolic health over time to examine how these additional measures of risk may impact our results. Changes in metabolic health over time were assessed by averaging the MetS severity score from MESA Visit 1 (2000 to 2002), Visit 2 (2002

to 2004), and Visit 3 (2004 to 2005). We also conducted a sensitivity analysis calculating the ASCVD event rates for: 1) participants with baseline CAC=0 and MetS or diabetes, but without randomization to a follow-up CAC scan at Visit 5 (n = 342); and 2) participants with baseline CAC=0, but without MetS or T2D who were and were not randomized to a follow-up CAC scan (n = 1,988).

Statistical analyses were performed using SAS 9.3 (SAS Institute, Cary, North Carolina). All hypothesis tests were 2-sided. We used an alpha threshold of 0.05 for detecting differences in descriptive statistics and for detecting significant odds ratios in logistic regression models.

RESULTS

The average age of the study population was 58.9 ± 9.1 years and two thirds of individuals were female (Table 1). There were 422 participants with MetS and 152 with T2D at baseline. Individuals with long-term absence of CAC were significantly younger, had



lower fasting blood glucose, had lower hs-cTnT, had a higher eGFR, and were less likely to be prescribed a lipid-lowering medication compared with CAC progressors. Those with persistent CAC=0 were also significantly less likely to have a carotid artery plaque or thoracic aortic calcification. Among participants with MetS or T2D and baseline CAC=0, individuals randomized to follow-up CAC scans were younger and had a lower prevalence of diabetes compared with those who were not randomized to follow-up CAC scans ([Supplemental Table 1](#)).

There was a similar proportion of individuals with persistent CAC=0 for participants with T2D (41.5%) and MetS (41.9%) ([Central Illustration](#)). Approximately one third of individuals classified as having a high ASCVD risk ($\geq 20\%$) by traditional scoring had a long-term absence of CAC, whereas nearly 50% of low-risk individuals ($< 7.5\%$) had a long-term absence of CAC. Among participants who developed incident CAC, there was no significant difference in the median Agatston score at Visit 5 between groups classified as high or low risk by traditional ASCVD scoring ([Figure 1](#)).

After adjusting for traditional ASCVD risk factors, participants had 50% higher odds of persistent long-term CAC=0 per every 10-years younger age (odds ratio [OR]: 1.50; 95% confidence interval [CI]: 1.22 to 1.85; $p < 0.01$), but no significant associations with

other individual traditional ASCVD risk factors were found ([Table 2](#)). In bivariate analysis, individuals with a low 10-year ASCVD risk of $< 7.5\%$ had 51% higher odds of maintaining CAC=0 compared with those with an intermediate or higher risk (OR: 1.51; 95% CI: 1.08 to 2.11; $p = 0.02$).

Participants with the lowest quartile MetS severity score had nearly 3-fold higher odds of persistent CAC=0 compared with individuals in the upper quartile (OR: 2.71; 95% CI: 1.27 to 5.76; $p < 0.01$) ([Table 3](#)). This association was especially strong among individuals with T2D, because people in the lowest quartile had nearly 6-fold higher odds of maintaining an absence of CAC versus those in the highest quartile (OR: 5.96; 95% CI: 1.27 to 28.07; $p = 0.02$). ORs and significance for the MetS severity score were consistent when comparing the fully adjusted model with a model without traditional biological ASCVD risk factors (OR: 2.29; 95% CI: 1.33 to 5.26; $p < 0.01$). In addition, individuals with a serum hs-cTnT concentration < 3 mg/dl had 55% higher odds of long-term absence of CAC compared with those with a hs-cTnT concentration ≥ 3 mg/dl ($p = 0.04$). People without thoracic calcification had more than double the odds of maintaining long-term absence of CAC in the overall sample (OR: 2.42; 95% CI: 1.24 to 4.72; $p < 0.01$). Similarly, absence of carotid plaque was associated with 81% higher odds

TABLE 2 Association Between Traditional ASCVD Risk Factors and Long-Term CAC=0 Among Persons With Metabolic Syndrome and/or Type 2 Diabetes

	All		Metabolic Syndrome Alone		Type 2 Diabetes	
	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value
Demographic						
Female	1.25 (0.83-1.89)	0.28	1.29 (0.80-2.09)	0.29	1.22 (0.52-2.84)	0.65
Age, per 10 yrs younger	1.50 (1.22-1.85)	<0.01	1.70 (1.33-2.17)	<0.0001	1.11 (0.72-1.70)	0.64
Traditional ASCVD risk factors*						
Never cigarette smoker	1.07 (0.75-1.55)	0.70	0.96 (0.63-1.47)	0.85	1.67 (0.76-3.68)	0.20
Waist circumference	1.10 (0.66-1.82)	0.73	1.02 (0.54-1.92)	0.94	1.45 (0.54-3.89)	0.46
Blood pressure	1.14 (0.71-1.83)	0.58	1.15 (0.67-1.98)	0.61	0.81 (0.27-2.43)	0.70
Fasting blood glucose	1.27 (0.84-1.91)	0.26	1.18 (0.75-1.87)	0.47	5.22 (0.89-30.59)	0.07
Triglycerides	0.98 (0.63-1.53)	0.92	1.04 (0.60-1.81)	0.89	0.83 (0.34-2.01)	0.68
Total cholesterol/HDL-cholesterol	1.27 (0.73-2.21)	0.40	1.34 (0.65-2.79)	0.43	1.02 (0.40-2.63)	0.96
ASCVD risk <7.5%†	1.51 (1.08-2.11)	0.02	1.68 (1.13-2.48)	<0.01	1.11 (0.53-2.31)	0.78

Adjusted for age, sex, race, education, antihypertensive medication, lipid-lowering medication, glucose-lowering medication, cigarette smoking, waist circumference, blood pressure, fasting blood glucose, fasting serum triglycerides, and total cholesterol/HDL-C ratio. *Waist circumference <40 inches in males, <35 inches in females; blood pressure <130/<80 mm Hg; fasting blood glucose <100 mg/dl; triglycerides <150 mg/dl; total cholesterol/HDL-cholesterol ratio <3.5. †Bivariate analysis.

CI = confidence interval; OR = odds ratio; other abbreviations as in Table 1.

of persistent CAC=0 among persons with MetS or diabetes (OR: 1.81; 95% CI: 1.25 to 2.61; $p < 0.01$). Parameter estimates and significance values of ASCVD risk factors with long-term CAC=0 remained consistent after additionally controlling for diabetes duration, diabetes control, and after further adjustment of metabolic health over time, leveraging an averaged MetS severity score through MESA Visit 3.

The addition of traditional ASCVD risk factors to demographic information yielded a higher C-statistic of 0.671 compared with a model that included the PCEs risk score, C-statistic of 0.599 (Table 4). The addition of the MetS severity score had a similar improvement in the predictive ability for long-term absence of CAC (C-statistic = 0.673), whereas the addition of novel serum biomarkers (C-statistic = 0.686) and absence of extracoronary atherosclerosis (C-statistic = 0.698) had higher predictive values.

There were 28 (5.1%) ASCVD events over a median follow-up time of 4.8 years. The overall event rate for persons with MetS or T2D with baseline CAC=0 was similar for those who underwent follow-up CAC scans (10.9 events per 1,000 person-years) versus those who did not undergo a repeat CAC scan (11.7 events per 1,000 person-years), whereas individuals without MetS or T2D who were and were not randomized to a follow-up CAC scan had an ASCVD event rate of 5.9 per 1,000 person-years (Supplemental Table 2). Compared with incident CAC, long-term CAC=0 conferred a 62% and 66% lower risk of an ASCVD event among persons with MetS (4.9 events per 1,000 person-years) and T2D (7.1 events per 1,000 person-years), respectively (Supplemental Figure 2).

DISCUSSION

This is one of the first population-based studies to assess the predictors of healthy arterial aging, defined here by persistent CAC=0, in persons with MetS or T2D. We found that among the approximately 40% of MESA participants with MetS or T2D who have baseline CAC=0, 42% had long-term absence of CAC during a 10-year follow-up period. Aside from a lower age, the absence of any specific individual traditional ASCVD risk factor was not associated with an increased likelihood of healthy arterial aging, whereas a low MetS severity score and absence of thoracic aortic calcification were associated with an approximately 2.5-fold greater likelihood of healthy arterial aging. Overall, our results suggest that future studies are required to determine the risk/benefit of primary prevention pharmacotherapy among younger persons with diabetes who have a low metabolic severity score because they are most likely to maintain healthy arterial aging.

Although the absence of individual traditional ASCVD risk factors were not associated with long-term CAC=0, a normal hs-cTnT level (<3 mg/dl) emerged as a novel predictor for this protective phenotype. Elevated hs-cTnT is a marker of subclinical myocardial damage that is associated with myocardial fibrosis and alterations in left ventricular structure among adults without ASCVD. Additionally, hs-cTnT is also associated with higher pulse wave velocity in persons with T2D (42), suggesting that elevated hs-cTnT may reflect both subclinical myocardial injury and systemic arterial stiffness in persons with metabolic disease. Accordingly, further

TABLE 3 Association Between Novel ASCVD Risk Factors and Long-Term CAC=0 Among Persons With Metabolic Syndrome and/or Type 2 Diabetes

Novel ASCVD Risk Factors*	All		Metabolic Syndrome Alone		Type 2 Diabetes	
	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value
hs-CRP	1.23 (0.80-1.89)	0.34	1.14 (0.69-1.88)	0.62	1.43 (0.59-3.47)	0.43
hs-cardiac troponin T	1.55 (1.01-2.38)	0.04	1.37 (0.84-2.24)	0.21	3.35 (1.22-9.15)	0.02
NT-proBNP	1.20 (0.66-2.18)	0.55	0.92 (0.46-1.82)	0.80	3.06 (0.70-13.47)	0.14
Lipoprotein (a)	1.85 (0.92-3.71)	0.08	1.73 (0.79-3.80)	0.17	3.22 (0.58-17.76)	0.18
eGFR	1.67 (0.70-3.97)	0.25	1.40 (0.53-3.65)	0.50	4.63 (0.45-47.67)	0.20
Absence of urine protein	1.05 (0.53-2.09)	0.88	0.75 (0.26-2.18)	0.59	1.51 (0.56-4.03)	0.41
Absence of thoracic calcification	2.42 (1.24-4.72)	<0.01	2.72 (1.23-6.02)	0.01	2.42 (0.59-9.81)	0.22
Absence of carotid plaque	1.81 (1.25-2.61)	<0.01	1.61 (1.04-2.49)	0.03	2.86 (1.37-5.98)	<0.01
Metabolic syndrome severity score†	2.71 (1.27-5.76)	<0.01	2.25 (0.87-5.87)	0.09	5.96 (1.27-28.07)	0.02

Adjusted for age, sex, race, education, antihypertensive medication, lipid-lowering medication, glucose-lowering medication, cigarette smoking, waist circumference, blood pressure, fasting blood glucose, fasting serum triglycerides, and total cholesterol/HDL-C ratio. *Each novel risk factor was evaluated independently and added to model 1: hs-CRP <2 mg/L; hs-cardiac troponin T <3 ng/mL; NT-proBNP <125 pg/mL; Lp(a) <50 mg/dL in Whites, Chinese, and Hispanics; Lp(a) <30 mg/dL in Blacks; eGFR >60 mL/min/1.73 m². †Quartile 1 (lowest) vs. quartile 4 (reference).

hs-CRP = high sensitivity C-reactive protein; other abbreviations as in Tables 1 and 2.

studies evaluating whether long-term normal hs-cTnT values improve the prediction of healthy arterial aging are warranted.

An absence of carotid plaque was associated with an 81% higher likelihood of persistent CAC=0 among individuals with MetS or T2D. This association was more prominent among individuals with diabetes because an absence of carotid plaque conferred a nearly 3-fold higher odds of persistent CAC=0 among this subgroup. Our findings build on previous studies that have demonstrated similar associations between carotid and coronary atherosclerosis because the presence of a carotid plaque identified through ultrasound is associated with a 37% higher risk of incident CAC among individuals without clinical ASCVD (43). However, <15% of patients harboring carotid artery plaque(s) go on to develop CAC (43), suggesting differences in the pathobiology of atherosclerosis between the 2 sites. Thus, the fairly modest associations between the 2 imaging modalities underline that assessment and treatment of additional risk factors outside of carotid atherosclerosis may be required to successfully prevent incident CAC.

Overall, the absence of individual traditional and novel risk factors was not strongly associated with persistent CAC=0, and these findings may have been sensitive to how continuous variables were categorized or dichotomized. In contrast to individual ASCVD risk factors, we observed strong and consistent associations of persistent CAC=0 with composite risk scores, including the PCEs and MetS severity scores. The MetS severity score was more robustly associated with CAC=0 compared with 10-year ASCVD risk because individuals in the lowest quartile of MetS severity score had over 2-fold higher odds

of maintaining CAC=0 compared with those in the highest quartile. This latter association was nearly 6-fold among those with diabetes. However, differences in the strength of association of the PCE and MetS severity score with persistent CAC=0 may have also been due to the methods of categorizing independent variables. The MetS severity score OR compared extremes in the distribution (first quartile vs. fourth quartile), whereas the PCE OR compared those <7.5% versus those with ≥7.5% 10-year ASCVD predicted risk. The MetS severity score and PCEs collectively incorporate and define risk factor burden, which may explain why these scores perform significantly better than any individual risk factor alone. Thus, given the heterogeneity and inconsistent associations of individual risk factors with CAC, the MetS severity score represents a powerful supplemental tool for the prediction of healthy arterial aging in individuals with MetS or T2D.

Although T2D is often considered an ASCVD risk equivalent, our results fit into a broader context of research that demonstrates considerable heterogeneity in risk among individuals with diabetes and MetS (44). We observed that >40% of individuals with T2D or MetS have a persistent absence of CAC during a 10-year period.

Furthermore, our results underline the “power of zero” (45) and the concept that individual traditional ASCVD risk markers have a limited utility for derisking individuals compared with atherosclerosis imaging modalities, especially CAC imaging. An absence of extracoronary atherosclerosis, carotid or thoracic, was the strongest individual negative risk markers and similar in strength compared with a combination of risk factors as integrated by the MetS

TABLE 4 AUC Analysis For Prediction Of Long-Term CAC=0 Among Individuals With Metabolic Syndrome Or Type 2 Diabetes

	C-Statistic (95% CI)	Model p Value	Change in C-Statistic*	AUC Contrast p Value*
Demographics				
Age, sex, race	0.625 (0.577-0.673)	<0.001	-	-
Traditional risk factors/risk scoring				
Individual risk factors†	0.671 (0.625-0.718)	<0.0001	+0.046	<0.01
Pooled cohort equations ASCVD risk	0.599 (0.551-0.648)	<0.01	-0.026	0.17
Novel risk factors/risk scoring				
Individual risk factors + metabolic syndrome severity score	0.673 (0.627-0.719)	<0.001	+0.048	<0.01
Individual risk factors + hs-cTnT, NT-proBNP, Lp(a), hs-CRP, eGFR, absence of urine protein	0.686 (0.625-0.747)	0.05	+0.061	0.12
Imaging				
Individual risk factors + absence of extra-coronary atherosclerosis‡	0.698 (0.650-0.740)	<0.0001	+0.073	<0.01
Demographics, traditional risk factors, novel risk factors, and imaging§	0.709 (0.650-0.768)	<0.01	+0.084	0.03

All models, except pooled cohort equations model, include age, sex, and race as covariates. *ROC curves were compared with the reference model including age, sex, and race. †Systolic blood pressure, diastolic blood pressure, total cholesterol, HDL cholesterol, fasting blood glucose, waist circumference, triglycerides, antihypertensive medication, glucose-lowering medication, and lipid-lowering medication. ‡Carotid plaque and thoracic calcification. §All individual risk factors listed above, except the pooled cohort equations ASCVD risk and the metabolic syndrome severity score.

AUC = area-under-the-curve; hs-cTnT = high-sensitivity cardiac troponin T; Lp(a) = lipoprotein a; other abbreviations as in Tables 1 to 3.

score. We observed no significant association of hs-CRP, Lp(a), nor NT-proBNP with persistent CAC=0. These findings support data that demonstrate little reduction in the post-test versus pre-test ASCVD risk for a low/normal finding of traditional and novel risk factors, including hs-CRP, Lp(a), and NT-proBNP⁽⁴⁶⁾. On the other hand, a finding of CAC=0 has up to an 80% reduction in post-test compared with pre-test risk for coronary heart disease⁽⁴⁶⁾. Thus, intrinsic differences between risk enhancers and risk reducers may be a further explanation for our observation that individual ASCVD risk factors were not significantly associated with healthy arterial aging.

Strengths of this study include the longitudinal measurement of CAC in a diverse population during a 10-year follow-up period. Consistent with previous studies of healthy arterial aging⁽⁴⁷⁾, two thirds of our study sample were women and the participants were ethnically diverse, giving our results wider generalizability. Similarly, 62% of individuals with CAC=0 in MESA are women, and women are more likely to have an absence of CAC compared with men of the same age⁽⁴⁸⁾. In addition, we examined both traditional and novel ASCVD risk factors, underlining potential new risk stratification tools that may help improve prediction of healthy arterial aging, including hs-cTnT and the MetS severity score.

Limitations of our analysis include the heterogeneity within metabolic disease as well as different definitions of the MetS. However, all definitions are based on similar risk factors and we used the most widely recognized MetS definition⁽¹⁶⁾ to overcome this limitation and related ambiguity. Overall, our study also had a relatively small

sample size and there were only 152 participants with diabetes at baseline. Accordingly, differences in risk markers for long-term CAC=0 between participants with MetS or diabetes should be interpreted with caution. A larger sample size would help to determine whether the observed differences in individual risk factors for the prediction of healthy arterial aging between those with MetS and T2D may have been due to either low statistical power or true biologic heterogeneity. Furthermore, there were 559 individuals with MetS or T2D and CAC=0 at baseline who did not have a CAC measurement 10 years later, and thus were not included in the current analysis. Aside from a slightly older mean age and higher prevalence of diabetes, this group had a similar cardiovascular risk profile and ASCVD event rates were similar when comparing persons who underwent follow-up CAC scans compared with those who were not randomized to a follow-up CAC scan. However, long-term ASCVD event rates were lower for participants without MetS or T2D. Similar findings have previously been reported by Valenti et al.⁽⁴⁹⁾ who found that among individuals with baseline CAC=0, the 5-year cumulative mortality rate was similar for persons with and without diabetes, but at 15 years follow-up the cumulative mortality rate was significantly higher for persons with diabetes (11.7%) compared with persons without diabetes (4.5%; $p < 0.05$). In our cohort, the difference in ASCVD rates between years 10 and 15 of follow-up after a baseline CAC score of 0 may be at least partially explained by the higher 10-year ASCVD risk of 12.4% among participants with MetS or T2D

compared with 5.9% for participants without MetS or T2D.

In conclusion, among individuals with MetS or T2D and baseline CAC=0, approximately 40% maintained long-term absence of CAC during at least 10 years. Younger individuals, those with a lower MetS severity score, and those with an absence of extracoronary atherosclerosis were the most likely to maintain a healthy arterial aging phenotype of long-term CAC=0. These results emphasize the significant ASCVD heterogeneity within these 2 groups of participants and highlight the significant heterogeneity in arterial aging among patients with MetS and diabetes. Our findings suggest that an optimal overall cardiovascular profile may be more important than an ideal value of any individual risk factor for the maintenance of healthy arterial aging.

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AUTHOR RELATIONSHIP WITH INDUSTRY

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE:

Among the approximately 40% of MESA participants with MetS or T2D who have baseline CAC = 0, 42% had long-term absence of CAC during a 10-year follow-up period. Younger age, a lower MetS severity score, and absence of extracoronary atherosclerosis serve as key predictors for the long-term absence of CAC among persons with MetS or T2D.

TRANSLATIONAL OUTLOOK: Future studies are required to determine the risk/benefit of primary prevention pharmacotherapy among younger persons with diabetes who have a low metabolic severity score because they are most likely to maintain healthy arterial aging.

REFERENCES

- Geiss LS, Wang J, Cheng YJ, et al. Prevalence and incidence trends for diagnosed diabetes among adults aged 20 to 79 years, United States, 1980-2012. *JAMA* 2014;312:1218-26.
- Saklayen MG. The global epidemic of the metabolic syndrome. *Curr Hypertens Rep* 2018;20:12.
- Moore JX, Chaudhary N, Akinyemiju T. Metabolic syndrome prevalence by race/ethnicity and sex in the United States, national health and nutrition examination survey, 1988-2012. *Prev Chronic Dis* 2017;14:160287.
- Centers for Disease Control and Prevention. Prevention C for DC and National Diabetes Statistics Report, 2017. 2018. Estimates of diabetes and its burden in the United States Background 2018. Available at: <https://www.cdc.gov/diabetes/data/index.html>. Accessed February 1, 2020.
- Wilson PWF, D'Agostino RB, Parise H, Sullivan L, Meigs JB. Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. *Circulation* 2005;112:3066-72.
- Haffner SM, Lehto S, Rönkämaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 1998;339:229-34.
- Sarkar S, Orimoloye OA, Nass CM, Blumenthal RS, Martin SS. Cardiovascular risk heterogeneity in adults with diabetes: selective use of coronary artery calcium in statin use decision-making. *J Gen Intern Med* 2019;34:2643-7.
- 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;2:1332-40.
- Bertoni AG, Wong ND, Shea S, et al. Insulin resistance, metabolic syndrome, and subclinical atherosclerosis: the Multi-Ethnic Study of Atherosclerosis (MESA). *Diabetes Care* 2007;30:2951-6.
- Wong ND, Sciammarella MG, Polk D, et al. The metabolic syndrome, diabetes, and subclinical atherosclerosis assessed by coronary calcium. *J Am Coll Cardiol* 2003;41:1547-53.
- Detrano R, Guerci AD, Carr JJ, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. *N Engl J Med* 2008;358:1336-45.
- Greenland P, Blaha MJ, Budoff MJ, Erbel R, Watson KE. Coronary calcium score and cardiovascular risk. *J Am Coll Cardiol* 2018;72:434-47.
- Gassett AJ, Sheppard L, McClelland RL, et al. Risk factors for long-term coronary artery calcium progression in the multi-ethnic study of atherosclerosis. *J Am Heart Assoc* 2015;4:e001726.
- Wong ND, Nelson JC, Granston T, et al. Metabolic syndrome, diabetes, and incidence and

progression of coronary calcium: The Multiethnic Study of Atherosclerosis (MESA). *J Am Coll Cardiol Img* 2012;5:358.

15. Bild DE, Bluemke DA, Burke GL, et al. Multi-ethnic study of atherosclerosis: objectives and design. *Am J Epidemiol* 2002;156:871-81.

16. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002;106:3143-421.

17. McClelland RL, Chung H, Detrano R, Post W, Kronmal RA. Distribution of coronary artery calcium by race, gender, and age. *Circulation* 2006;113:30-7.

18. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol* 1990;15: 827-32.

19. Budoff MJ, McClelland RL, Chung H, et al. Reproducibility of coronary artery calcified plaque with cardiac 64-MDCT: the multi-ethnic study of atherosclerosis. *Am J Roentgenol* 2009;21:613-7.

20. Takasu J, Katz R, Nasir K, et al. Relationships of thoracic aortic wall calcification to cardiovascular risk factors: the Multi-Ethnic Study of Atherosclerosis (MESA). *Am Heart J* 2008;155:765-71.

21. Ostchega Y, Seu R, Sarafrazi N, Zhang G, Hughes JP, Miller I. Waist circumference measurement methodology study: national health and nutrition examination survey, 2016. *Vital Health Stat* 2 2019;182:1-20.

22. Levin G, Kestenbaum B, Ida Chen Y, Der, et al. Glucose, insulin, and incident hypertension in the multi-ethnic study of atherosclerosis. *Am J Epidemiol* 2010;172:1144-54.

23. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 1972;18: 499-502.

24. Gurka MJ, Lilly CL, Oliver MN, DeBoer MD. An examination of sex and racial/ethnic differences in the metabolic syndrome among adults: a confirmatory factor analysis and a resulting continuous severity score. *Metabolism* 2014;63:218-25.

25. Lee AM, Gurka MJ, DeBoer MD. A metabolic syndrome severity score to estimate risk in adolescents and adults: current evidence and future potential. *Expert Rev Cardiovasc Ther* 2016;14:411-3.

26. Low S, Khoo KCJ, Wang J, et al. Development of a metabolic syndrome severity score and its association with incident diabetes in an Asian population—results from a longitudinal cohort in Singapore. *Endocrine* 2019;65:1-8.

27. DeBoer MD, Gurka MJ, Morrison JA, Woo JG. Inter-relationships between the severity of metabolic syndrome, insulin and adiponectin and their

relationship to future type 2 diabetes and cardiovascular disease. *Int J Obes* 2016;40:1353-9.

28. Gurka MJ, Golden SH, Musani SK, et al. Independent associations between a metabolic syndrome severity score and future diabetes by sex and race: the Atherosclerosis Risk In Communities Study and Jackson Heart Study. *Diabetologia* 2017;60:1261-70.

29. Wang LX, Filipp SL, Urbina EM, Gurka MJ, DeBoer MD. Longitudinal associations of metabolic syndrome severity between childhood and young adulthood: the Bogalusa Heart Study. *Metab Syndr Relat Disord* 2018;16:208-14.

30. Levey AS, Stevens LA. Estimating GFR using the CKD Epidemiology Collaboration (CKD-EPI) creatinine equation: more accurate GFR estimates, lower CKD prevalence estimates, and better risk predictions. *Am J Kidney Dis* 2010;55:622.

31. Stein JH, Korcarz CE, Hurst RT, et al. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force endorsed by the Society for Vascular Medicine. *J Am Soc Echocardiogr* 2008;93-111.

32. Tattersall MC, Gassett A, Korcarz CE, et al. Predictors of carotid thickness and plaque progression during a decade: the Multi-Ethnic Study of Atherosclerosis. *Stroke* 2014;45:3257-62.

33. Cainzos-Achirica M, Miedema MD, McEvoy JW, et al. The prognostic value of high sensitivity C-reactive protein in a multi-ethnic population after > 10 years of follow-up: the Multi-Ethnic Study of Atherosclerosis (MESA). *Int J Cardiol* 2018;264: 158-64.

34. Seliger SL, Hong SN, Christenson RH, et al. High-sensitive cardiac troponin T as an early biochemical signature for clinical and subclinical heart failure: MESA (Multi-Ethnic Study of Atherosclerosis). *Circulation* 2017;135: 1494-505.

35. Guan W, Cao J, Steffen BT, et al. Race is a key variable in assigning lipoprotein(a) cutoff values for coronary heart disease risk assessment: the Multi-Ethnic Study of Atherosclerosis. *Arterioscler Thromb Vasc Biol* 2015;35:996-1001.

36. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2018;71: 2199-269.

37. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease. *J Am Coll Cardiol* 2019;74:e177-232.

38. Millán J, Pintó X, Muñoz A, et al. Lipoprotein ratios: physiological significance and clinical usefulness in cardiovascular prevention. *Vasc Health Risk Manag* 2009;5:757-65.

39. Gustafsson F, Steensgaard-Hansen F, Badskjaer J, Poulsen AH, Corell P, Hildebrandt P. Diagnostic and prognostic performance of N-terminal ProBNP in primary care patients with suspected heart failure. *J Card Fail* 2005;11:S15-20.

40. DeBoer MD, Filipp SL, Musani SK, Sims M, Okusa MD, Gurka M. Metabolic syndrome severity and risk of CKD and Worsened GFR: the Jackson Heart Study. *Kidney Blood Press Res* 2018;43: 555-67.

41. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988;44: 837-45.

42. Yiu KH, Zhao CT, Chen Y, et al. Association of subclinical myocardial injury with arterial stiffness in patients with type 2 diabetes mellitus. *Cardiovasc Diabetol* 2013;12:94.

43. Polak JF, Tracy R, Harrington A, Zavadni AEH, O'Leary DH. Carotid artery plaque and progression of coronary artery calcium: the Multi-Ethnic Study of Atherosclerosis. *J Am Soc Echocardiogr* 2013; 26:548-55.

44. Ahlqvist E, Storm P, Käräjämäki A, et al. Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables. *Lancet Diabetes Endocrinol* 2018;6:361-9.

45. 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: 849-58.

46. Mortensen MB, Fuster V, Muntendam P, et al. Negative risk markers for cardiovascular events in the elderly. *J Am Coll Cardiol* 2019;74:1-11.

47. Whelton SP, Silverman MG, McEvoy JW, et al. Predictors of long-term healthy arterial aging. *J Am Coll Cardiol Img* 2015;8:1393-400.

48. McClelland RL, Chung H, Detrano R, Post W, Kronmal RA. Distribution of coronary artery calcium by race, gender, and age: results from the Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation* 2006;113:30-7.

49. Valenti V, Hartaigh B, Cho I, et al. Absence of coronary artery calcium identifies asymptomatic diabetic individuals at low near-term but not long-term risk of mortality: a 15-year follow-up study of 9715 patients. *Circ Cardiovasc Imaging* 2016;9: e003528.

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APPENDIX For supplemental tables and figures, please see the online version of this paper.