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Journal

JACC Cardiovascular Imaging, 8(12)

ISSN

1936-878X

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Publication Date

2015-12-01

DOI

10.1016/j.jcmg.2015.06.019

Peer reviewed

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JACC: CARDIOVASCULAR IMAGING VOL. ■, NO. ■, 2015
© 2015 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER INC. http://dx.doi.org/10.1016/j.jcmg.2015.06.019

Predictors of Long-Term Healthy Arterial Aging

Coronary Artery Calcium Nondevelopment in the MESA Study

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ABSTRACT

OBJECTIVES This study sought to determine the predictors of healthy arterial aging.

BACKGROUND Long-term nondevelopment of coronary artery calcification (persistent CAC = 0) is a marker of healthy arterial aging. The predictors of this phenotype are not known.

METHODS We analyzed 1,850 participants from MESA (Multi-Ethnic Study of Atherosclerosis) with baseline CAC = 0 who underwent a follow-up CAC scan at visit 5 (median 9.6 years after baseline). We examined the proportion with persistent CAC = 0 and calculated multivariable relative risks and area under the receiver operating characteristic curve for prediction of this healthy arterial aging phenotype.

RESULTS We found that 55% of participants (n = 1,000) had persistent CAC = 0, and these individuals were significantly more likely to be younger, female, and have fewer traditional risk factors (RF). Participants with an ASCVD (Atherosclerotic Cardiovascular Disease Risk Score) risk score <2.5% were 53% more likely to have healthy arterial aging than were participants with an ASCVD score ≥7.5%. There was no significant association between the Healthy Lifestyle variables (body mass index, physical activity, Mediterranean Diet, and never smoking) and persistent CAC = 0. The area under the receiver operating characteristic curve incorporating age, sex, and ethnicity was 0.65, indicating fair to poor discrimination. No single traditional RF or combination of other risk factors increased the area under the receiver operating characteristic curve by more than 0.05.

CONCLUSIONS Whereas participants free of traditional cardiovascular disease RF were significantly more likely to have persistent CAC = 0, there was no single RF or specific low-risk RF phenotype that markedly improved the discrimination of persistent CAC = 0 over demographic variables. Therefore, we conclude that healthy arterial aging may be predominantly influenced by the long-term maintenance of a low cardiovascular disease risk profile or yet to be determined genetic factors rather than the absence of any specific RF cluster identified in late adulthood. (J Am Coll Cardiol Img 2015;■:■-■) © 2015 by the American College of Cardiology Foundation.

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Manuscript received March 27, 2015; revised manuscript received June 2, 2015, accepted June 11, 2015.

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ABBREVIATIONS AND ACRONYMS

AUC = area under the receiver operating characteristic curve

BMI = body mass index

CAC = coronary artery calcium

CHD = coronary heart disease

CI = confidence interval

CVD = cardiovascular disease

HR = hazard ratio

Traditionally, aging has been thought of as a linear, chronological process. However, genetics and cumulative risk factor exposure can lead to significant variations in biological age for individuals of the same chronological age (1-3). This has prompted some to suggest substituting an individual's biological or vascular age in place of chronological age for risk prediction models (4-6). Although the predictors of unhealthy arterial aging are well established, the predictors of healthy arterial aging are less certain, and it is unclear whether there are specific protective factors or a low-risk phenotype that exist for the maintenance of healthy arterial aging.

A finding of no coronary artery calcium (CAC) in a middle age or older adult is a marker of healthy arterial aging that is a powerful predictor of long-term all-cause survival and very low risk of cardiovascular disease (CVD) (7-9). In contrast, compared with an individual without CAC, individuals with a CAC score as low as 1 to 10 Agatston units are at more than 3× the risk for a hard coronary heart disease (CHD) event (10). Moreover, elderly patients without CAC have a better survival rate than do younger individuals with an elevated CAC score (11). As such, long-term, persistent maintenance of CAC = 0 can be considered an extreme manifestation of healthy arterial aging.

Just as it is important to clearly define high-risk phenotypes, it is also important to understand the predictors of healthy arterial aging in order to promote continued healthy aging. In this analysis, we sought to identify a phenotype for healthy arterial aging using routinely collected clinical variables.

METHODS

We used data from the MESA (Multi-Ethnic Study of Atherosclerosis): a community-based, multiethnic, cohort free of CVD at baseline, which has been described in greater detail elsewhere (12).

CAC was measured in all participants at MESA visit 1 (2000 to 2002) and one-half of the participants were selected randomly for a CAC scan at MESA visit 5 (2010 to 2012). We excluded participants with any CAC at MESA visit 1 (n = 3,399) and those without a repeat CAC scan at MESA visit 5 (n = 1,566) for a total of 1,850 participants included in this analysis.

CAC scans were performed using an electron beam computed tomography scanner at the Chicago, Los Angeles, and New York field centers and using multidetector computed tomography at the Baltimore, Forsyth County, and St. Paul field centers. Participants were scanned twice during MESA visit 1 and once during MESA visit 5. Calcium scores were calculated using the Agatston method and calcium phantoms scanned alongside the participants were used to standardize results between field centers (13,14). Scans were uploaded and read at the Harbor-University of California, Los Angeles Research and Education Institute. There was an interobserver kappa value of 0.90 and interscan kappa value of 0.92 for the presence of coronary artery calcification (15).

Participant covariates were obtained from the baseline MESA clinical examination. We defined hypertension as a systolic blood pressure ≥140 mm Hg, a diastolic blood pressure ≥90 mm Hg, or use of a blood pressure-lowering medication; diabetes was defined as a fasting blood glucose ≥126 mg/dl, self-report of diabetes mellitus, or use of a blood glucose-lowering medication; smoking was classified as current, former, or never. Optimal body mass index (BMI) was defined as ≥18.5 kg/m^2 to <25 kg/m^2. Regular physical activity was defined as more than 150 min per week of moderate intensity physical activity or more than 75 min per week of vigorous intensity physical activity. We used a Mediterranean Diet score as previously defined by Trichopoulou et al. (16). A family history of CHD was classified as a parent, sibling, or child with a history of CHD at any age. We defined socioeconomic status based on the highest level of achieved education and household income. The Lifestyle Score is the sum of optimal BMI, regular physical activity, adherence to a Mediterranean Diet, and never smoking (17).

Persistent CAC = 0, our definition of healthy arterial aging, was the primary outcome for this analysis. In order to determine whether we could identify a healthy arterial aging phenotype, we calculated the absolute number and percentage of participants with persistent CAC = 0 stratified by high- and low-risk groups. We also used hazard ratios (HRs) and associated 95% confidence intervals (CIs) to assess whether these relationships were independent of other associated cardiovascular risk factors. The proportional hazards assumption was assessed using Schoenfeld residual testing and was not violated (18). Model 1 was adjusted for age, sex, and race. Model 2 was adjusted for age, sex, race, BMI, waist circumference, systolic and diastolic blood pressure, antihypertensive medication use, smoking status, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, lipid-lowering medication use, family history of CHD, household income, educational attainment, and reported physical activity. In addition, we calculated the area under the receiver operating characteristic curve (AUC) to further investigate whether we

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could identify and predict a persistent CAC = 0 phenotype.

We also performed sensitivity analyses incorporating the following novel risk factors to determine whether they helped identify a CAC = 0 phenotype: high-sensitivity C-reactive protein, N-terminal pro-B-type natriuretic peptide, creatinine, microalbuminuria, homocysteine, and fibrinogen.

RESULTS

Participants had a mean age of 57.1 ± 8.6 years, 37% were men, and there was a median of 9.6 years between CAC scans. We found that 55% of participants (n = 1,000) had persistent CAC = 0. Participants with persistent CAC = 0 were more likely to be younger, female, have a lower burden of CVD risk factors, and a lower ASCVD (Atherosclerotic Cardiovascular Disease) score (Table 1). They also were more likely to have an optimal BMI, never smoked cigarettes, and a higher Healthy Lifestyle score, but were not significantly more likely to report regular physical activity or consume a Mediterranean Diet. Among the 45.9% of participants with CAC = 0 who developed incident CAC, the median CAC score was 25 (interquartile range: 9 to 65). There were 2 (0.2%) hard CHD events among participants with persistent CAC = 0 and 11 (1.3%) hard CHD events among participants with incident CAC.

Table 2 shows the percentage of participants with persistent CAC = 0 stratified by risk factors groups. In the fully adjusted model, participants <55 years of age at baseline were 39% more likely to have persistent CAC = 0 than were participants ≥65 years of age ($p < 0.001$) and women were 18% more likely to have persistent CAC = 0 than were men ($p < 0.004$) (Table 2). Participants with no traditional CVD risk factors were more likely to have persistent CAC = 0 and had a HR of 0.69 (95% CI: 0.54 to 0.90) than were participants with ≥3 risk factors. Individuals without diabetes mellitus were more likely to have persistent CAC = 0 and had a HR of 0.80 (95% CI: 0.68 to 0.94) than were individuals with diabetes mellitus. In the fully adjusted model, there was no significant difference in the likelihood of persistent CAC = 0 for any of the individual lifestyle score components or for the Lifestyle Score: HR 1.06 (95% CI: 0.88 to 1.27).

There was significant heterogeneity in persistent CAC = 0 of individuals who would be traditionally classified as having a high or low CVD risk. Among participants who would traditionally be classified as high risk for the development of CVD: 38% of participants age ≥65 years old, 36% of participants with an ASCVD ≥7.5%, and 36% of participants with ≥3 CVD risk factors had persistent CAC = 0 (Table 3). Conversely, among participants who would traditionally be classified as low risk for the development of CVD, 35% of participants were <55 years old; 40% had a low ASCVD of <2.5%; and 30% of participants with no traditional CVD risk factors did develop CAC (Figure 1).

Age, sex, and race were moderately predictive for persistent CAC = 0 with a C-statistic of 0.65 (Table 4). The addition of a participant's ASCVD score or their CVD risk factors had a small improvement in the C-statistic of 0.011 ($p < 0.001$) and 0.051 ($p < 0.001$), respectively. There was no significant change after adding the Lifestyle score ($p = 0.07$). When added individually, the absence of any single CVD risk factor did not significantly increase the C-statistic

TABLE 1 Participant Characteristics at Visit 1 Stratified by Persistent CAC = 0

	Persistent CAC = 0 (n = 1,000)	Incident CAC (n = 850)	p Value
Demographics			
Age, yrs	55.4 ± 8.1	59.2 ± 8.7	<0.001
Male	32.5	42.1	<0.001
Ethnicity			
White	32.6	37.2	0.039
Black	12.7	9.9	0.500
Hispanic	30.5	29.1	0.873
Chinese	24.2	23.9	0.057
Traditional risk factors			
SBP, mm Hg	118.1 ± 18.7	124.8 ± 20.1	<0.001
DBP, mm Hg	70.3 ± 10.2	72.4 ± 9.8	<0.001
Total cholesterol, mg/dl	192.0 ± 34.8	196.6 ± 34.4	0.004
LDL, mg/dl	114.2 ± 29.5	119.9 ± 30.0	<0.001
HDL, mg/dl	53.7 ± 15.4	50.6 ± 14.3	<0.001
Triglycerides, mg/dl	121.2 ± 85.9	131.8 ± 78.4	0.006
Non-HDL, mg/dl	138.3 ± 35.0	146.1 ± 34.2	<0.001
Antihypertensive medication	21.8	35.0	<0.001
Lipid-lowering medication	7.8	14.7	<0.001
Diabetes	5.0	9.9	<0.001
ASCVD risk			
0%–<2.5%	39.8	18.0	<0.001
2.5%–<7.5%	33.7	36.1	0.28
≥7.5%	26.5	45.9	<0.001
ASCVD risk score	5.7 ± 7.0	9.3 ± 8.5	<0.001
No. of risk factors	1.2 ± 0.9	1.5 ± 0.9	<0.001
Lifestyle score variables			
Optimal BMI	31.7	22.8	<0.001
Regular physical activity	21.1	18.0	0.099
Mediterranean diet	48.2	49.4	0.627
Never smoker	58.5	54.0	0.050
Lifestyle score	1.6 ± 1.0	1.4 ± 0.9	0.012
CAC score at visit 5	0	24.8 (9.4–64.8)	<0.001

Values are mean ± SD, %, or median (interquartile range).

ASCVD = Atherosclerotic Cardiovascular Disease Risk Score; BMI = body mass index; CAC = coronary artery calcium; DBP = diastolic blood pressure; HDL = high-density lipoprotein; LDL = low-density lipoprotein; SBP = systolic blood pressure.

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TABLE 2 Percentage of Individuals With Persistent CAC = 0 Stratified by Low- and High-Risk Groups With the Multivariable Adjusted Relative Risk of Persistent CAC = 0

	N	% Persistent CAC = 0	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Demographics				
Age, yrs				
<55	856	64.8	0.56 (0.50–0.63)	0.61 (0.53–0.71)
≥65	426	38.3	Ref.	Ref.
Sex				
Female	1,167	57.8	0.78 (0.71–0.85)	0.82 (0.71–0.94)
Male	683	47.6	Ref.	Ref.
Traditional risk factors				
No. of risk factors				
0 RF	338	70.1	0.48 (0.39–0.57)	0.69 (0.54–0.90)
≥3 RF	193	35.8	Ref.	Ref.
ASCVD score				
0%–<2.5%	551	72.2	0.47 (0.40–0.54)*	
2.5%–<7.5%	644	52.3	0.80 (0.72–0.89)*	
≥7.5%	655	40.5	Ref.	
Diabetes				
Yes	134	37.3	Ref.	Ref.
No	1,716	55.4	0.75 (0.65–0.88)	0.80 (0.68–0.94)
Lifestyle score variables				
Optimal BMI				
Yes	511	62	0.77 (0.68–0.88)	0.94 (0.80–1.09)
No	1,339	51	Ref.	Ref.
Regular physical activity				
Yes	363	57.9	0.87 (0.76–0.99)	0.95 (0.83–1.09)
No	1,484	53	Ref.	Ref.
Mediterranean diet				
Yes	872	46.6	0.99 (0.90–1.10)	0.98 (0.88–1.09)
No	916	45.4	Ref.	Ref.
Never smoker				
Yes	1,042	56	0.95 (0.86–1.04)	0.94 (0.85–1.04)
No	804	51.4	Ref.	Ref.
Healthy Lifestyle score				
0	260	53.5	Ref.	Ref.
≥3	419	57.5	0.97 (0.83–1.11)	1.06 (0.91–1.24)

Model 1: age, sex, race. Model 2: = Model 1 + BMI, waist circumference, SBP, DBP, antihypertensive medication, smoking, LDL-C, HDL-C, triglycerides, lipid-lowering medication, family history of CHD, household income, educational attainment, physical activity. *Unadjusted model.

CHD = coronary heart disease; CI = confidence interval; HDL-C = high-density lipoprotein cholesterol; HR = hazard ratio; LDL-C = low-density lipoprotein cholesterol; Ref. = reference value; RF = risk factors; other abbreviations as in Table 1.

($p > 0.05$). Adding high-sensitivity C-reactive protein and other novel CVD risk factors to the model had a small, but statistically significant improvement in the C-statistic of 0.027 ($p < 0.001$).

There was no association between persistent CAC = 0 and a carotid intima-medial thickness <75% percentile; HR 0.95 (95% CI: 0.85 to 1.06) (Table 5). However, participants without carotid plaque by ultrasound were 11% more likely to have persistent CAC = 0 than were those with a carotid plaque (HR: 0.89; 95% CI: 0.80 to 0.99) and participants without thoracic artery calcification were 18% more likely to have persistent CAC = 0 than were individuals with extracoronary calcification of HR 0.82 (95% CI: 0.73 to 0.92).

In our sensitivity analyses we found was no significant difference in high-sensitivity C-reactive protein levels between participants with and without persistent CAC = 0 (Online Tables 1). In addition, using the visit 5 variables in place of the baseline variables, the AUC estimates were essentially the same (Online Table 2).

DISCUSSION

Our analysis demonstrates that participants with persistent CAC = 0 had an overall lower cardiovascular risk factor profile. The healthy arterial aging group had a significantly lower level for all of the individual cardiovascular risk factors and a higher level for all of the healthy lifestyle factors, except Mediterranean diet. The absence of traditional CVD risk factors was also associated with persistent CAC = 0 when compared with participants with ≥3 CVD risk factors. However, there was no single modifiable traditional cardiovascular risk factor whose absence was strongly associated with healthy arterial aging. This is similar to a large cross-sectional cohort study of almost 17,000 participants by Boutouyrie et al. (19) in which sex, dyslipidemia, and smoking were not significantly associated with arterial aging, which was classified as an increased central arterial stiffness. In addition, Lehmann et al. (20) found a significant inverse trend between the number of cardiovascular risk factors and healthy arterial aging.

Although our results did not identify an individual predictor or specific phenotype of healthy arterial aging, it is important to understand that this does not exclude the existence of such predictors or phenotypes. Our analysis focused on using traditional CVD risk factors measured in late adulthood to examine healthy arterial aging. These risk factors are well established to be individually and collectively predictive of CVD events. Our analysis showed that the absence of these risk factors collectively was associated with healthy arterial aging, but that the absence of the risk factors individually was not associated with healthy arterial aging.

This finding suggests that although modifying CVD risk factors individually may lead to a lower burden of CAC and, hence, risk of CVD; we did not identify a specific CVD risk factor measured in late adulthood in which an improvement would be expected to predict continued healthy arterial aging. This does not preclude the existence of a predictor of healthy arterial aging, but it suggests that there may be other factors that we did not examine, such as genetics.

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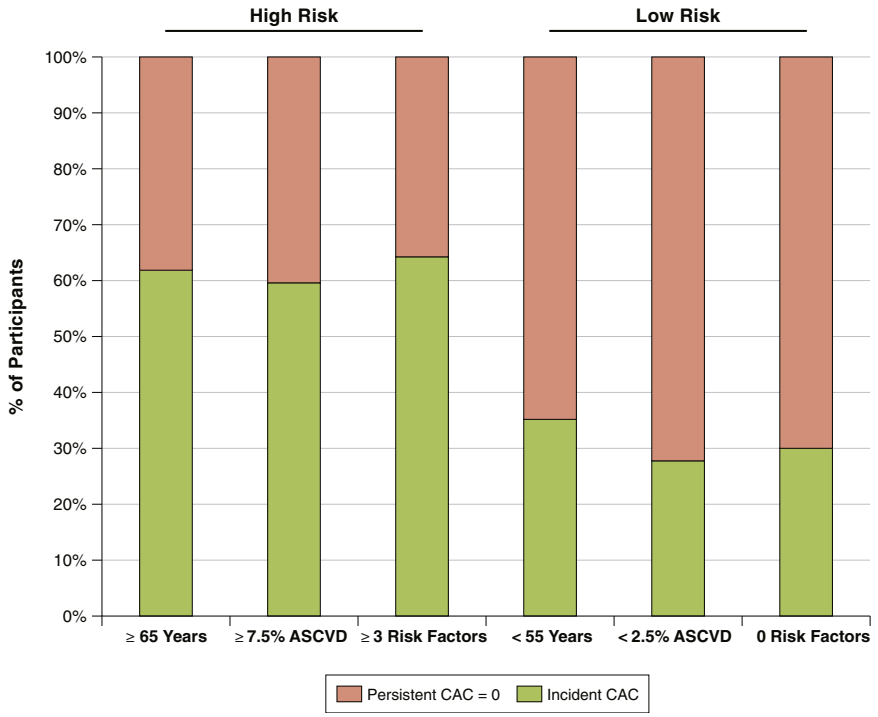
TABLE 3 Description of Traditional High-Risk and Low-Risk Phenotypes Stratified by Individuals With Persistent CAC = 0 Versus Incident CAC

	High Risk						Low Risk					
	Age ≥65 Years		≥7.5% ASCVD		≥3 Risk Factors		Age <55 Years		<2.5% ASCVD		0 Risk Factors	
	Persistent CAC = 0 (n = 163)	Incident CAC (n = 263)	Persistent CAC = 0 (n = 265)	Incident CAC (n = 390)	Persistent CAC = 0 (n = 69)	Incident CAC (n = 124)	Persistent CAC = 0 (n = 555)	Incident CAC (n = 301)	Persistent CAC = 0 (n = 398)	Incident CAC (n = 153)	Persistent CAC = 0 (n = 237)	Incident CAC (n = 101)
Demographics												
Age, yrs	69.3	69.8	62.9	65.0*	58.8	59.4	49.4	49.9*	50.2	50.4	54.5	58.8*
Male, %	25.2	37.6*	48.3	50.8	37.7	38.7	34.6	47.8*	11.3	17.6*	30.0	43.6*
Traditional risk factors												
No. risk factors	1.4	1.5	1.9	1.9	3.1	3.1	1.1	1.5*	0.8	0.9	0	0
ASCVD score	15.0	16.4	14.6	16.0*	16.4	16.5	2.9	4.1*	1.2	1.4*	2.9	5.3*
Diabetes, %	11.0	11.0	15.1	16.2	44.9	48.4	3.6	8.6*	1.0	2.6	0	0
Lifestyle score variables												
Optimal BMI	33.1	24.7	19.6	19.0	0	2.0	32.6	20.3*	41.2	34.6	94.5	95.0
Regular physical activity	20.2	16.7	20.6	18.7	23.2	14.5	20.8	19.3	20.6	19.0	26.6	23.8
Mediterranean Diet	44.0	51.4	47.7	50.5	43.1	41.9	49.5	46.9	47.5	51.7	44.2	51.0
Never smoker	63.2	55.5	51.7	47.0	42.0	34.7	57.3	54.2	66.3	64.1	74.7	59.4*
Healthy Lifestyle score	1.7	1.5	1.4	1.4	1.1	0.9	1.5	1.4	1.7	1.7	2.4	2.3

*p < 0.05 compared with nondevelopment participants.
Abbreviations as in Table 1.

FIGURE 1 Persistent CAC = 0 Stratified by Baseline Risk Factor Profile



Percentage of participants with and without persistent CAC = 0 stratified by baseline risk factor profile. ASCVD = Atherosclerosis Cardiovascular Disease Risk Score; CAC = coronary artery calcium.

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TABLE 4 AUC for the Prediction of Persistent CAC = 0

	AUC	Change in AUC	p Value
Demographics			
Age, sex, race	0.650	N/A	N/A
Traditional risk factors			
ASCVD score	0.656	0.013	<0.001
Risk factors, continuous*	0.695	0.051	<0.001
Lifestyle score variables			
No. variables	0.657	0.008	0.074
Novel biomarkers			
hsCRP	0.645	0.004	0.029
All†	0.665	0.027	<0.001

*SBP, DBP, LDL-C, HDL-C, antihypertensive medication, lipid-lowering medication, diabetes. †hsCRP, NT-proBNP, creatinine, microalbuminuria, homocysteine, fibrinogen.

AUC = area under the curve; hsCRP = high-sensitivity C-reactive protein; NT-proBNP = N-terminal pro-B-type natriuretic peptide; other abbreviations as in Tables 1 and 2.

We did not observe the same consistent difference in the Lifestyle score variables between the healthy and nonhealthy arterial aging groups. Neither the individual Lifestyle score variables nor the aggregate Healthy Lifestyle score were significantly associated with healthy arterial aging after multivariable adjustment. It is possible that these variables measured at MESA visit 1 may not be representative of the participants' true lifetime risk status or the self-reported physical activity, and Mediterranean Diet variables may incompletely define those variables. However, CVD risk factors earlier in life are predictive of CAC in middle age and a lower Healthy Lifestyle was associated with a reduced risk of CHD in a separate analysis (17,21).

Our analysis showed that whereas a lower overall CVD risk profile was associated with healthy arterial aging, there was still a large amount of heterogeneity within individuals who would traditionally be classified as low or high risk for CVD. For example, among participants with no CVD risk factors, approximately one-third did not have continued healthy arterial aging over the course of the almost 10-year follow-up, and among participants with ≥3 cardiovascular risk factors, more than one-third had healthy arterial aging during the same follow-up. Furthermore, among individuals ≥65 years old more than one-third had persistent CAC = 0 during follow-up, at which time they had a mean age of approximately 79 years compared with approximately one-third of participants <55 years old who had unhealthy arterial aging by the mean age of 59 years at MESA visit 5.

Regardless of the definition of high and low risk, approximately one-third of the high-risk participants had healthy arterial aging versus one-third of low-risk participants who had unhealthy arterial aging. Within the majority of each high- and low-risk group there were also minimal differences in the number of CVD risk factors, mean ASCVD scores, and Lifestyle score variables. Further emphasizing the challenge of predicting healthy arterial aging, we found that age, sex, and race provided the vast majority of the prediction in AUC models, although with an AUC of 0.65 these demographic variables were only poorly predictive of healthy arterial aging. The addition of further traditional and novel variables to the models provided statistically significant improvements, but the absolute improvements were small enough that the models remained poorly predictive.

Even when we examined imaging of other vasculature as a predictor of healthy arterial aging there was still significant heterogeneity as 42% of participants with any carotid plaque had persistent CAC = 0 and only 59% of those without carotid plaque had healthy arterial aging. Although we found that the association between imaging of other vasculature beds was more strongly associated with healthy arterial aging than traditional risk factors, the imaging variables had a smaller improvement in the AUC score than did traditional risk factors as a continuous variable.

Thus, the heterogeneity of arterial aging was one of the most important findings of this analysis. It may be attributable to the fact that even though the presence of a CVD risk factor is associated with the development of CVD, its absence is not necessarily associated with healthy arterial aging. This is reflected in most cardiovascular risk scores by the virtue that CVD risk factors add points, but typically only an elevated high-density lipoprotein cholesterol is used to subtract points. It may also be that despite using

TABLE 5 Percentage of Individuals With Persistent CAC = 0 Stratified by Low- and High-Risk Imaging Groups With the Multivariable Adjusted Relative Risk of Persistent CAC = 0

	n	% Without CAC Development	Model 1 HR (95% CI)	Model 2 HR (95% CI)
CIMT ≥75%				
Yes	462	42.6	Ref.	Ref.
No	1,388	57.9	0.86 (0.78–0.96)	0.95 (0.85–1.06)
Carotid plaque				
Yes	492	41.9	Ref.	Ref.
No	1,358	58.5	0.79 (0.72–0.88)	0.89 (0.80–0.99)
Thoracic calcification				
Yes	187	30.5	Ref.	Ref.
No	1,663	56.7	0.76 (0.67–0.85)	0.82 (0.73–0.93)

Model 1: age, sex, race. Model 2: Model 1 + BMI, SBP, DBP, antihypertensive medication, smoking, LDL-C, HDL-C, lipid-lowering medication, family history of CHD, household income, educational attainment, physical activity.

CIMT = carotid intima-medial thickness; other abbreviations as in Tables 1 and 2.

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nontraditional cardiovascular risk factors including noninvasive imaging methods, we may not be measuring the true determinants of arterial aging.

Strengths of this analysis include that participants in this analysis were middle to older age at baseline and there was a nearly 10-year median follow-up time allowing for the investigation of long-term arterial aging. In addition, we examined both traditional and novel cardiovascular risk factors and noninvasive imaging modalities.

STUDY LIMITATIONS. One limitation of this study is that the follow-up CAC scans were performed approximately 10 years apart, and we do not know precisely when during the follow-up time individuals developed CAC. We also did not examine the initiation of new medications or directly investigate incident CVD. However, <2% of participants had a CVD event over the nearly 10-year follow-up and the goal of our analysis was to identify predictors of long-term healthy arterial aging measured by CAC.

CONCLUSIONS

Whereas the risk factors for the development of CVD are firmly established, the predictors of healthy arterial aging are less well defined. In this analysis we demonstrate that a low CVD risk factor burden is associated with an increased likelihood of healthy arterial aging as measured by CAC. However, the absence of any one individual CVD risk factor was not strongly predictive of healthy arterial again and there was significant heterogeneity among the participants with healthy arterial aging. Consequently, healthy arterial aging may be predominantly influenced by the long-term maintenance of a low CVD risk profile rather than the absence of any specific RF or low-risk phenotype identified in adulthood. The prediction of individuals who will continue to have healthy arterial aging remains elusive given the current available risk factors and further work using other markers such as genetics is needed to determine whether a healthy aging phenotype can be identified.

ACKNOWLEDGMENTS The authors thank the other investigators, the staff, and the participants of the MESA study for their valuable contributions. A full list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The long-term nondevelopment of CAC is a marker of healthy arterial aging. Participants without a single traditional cardiovascular risk factor were more likely to have healthy arterial aging, although there was no single risk factor whose absence significantly improved the predication of healthy arterial aging.

TRANSLATIONAL OUTLOOK: There was no single traditional cardiovascular risk factor or group of risk factors whose absence significantly improved the prediction of healthy arterial aging. Future studies are needed to determine whether there are other factors such as genetics that may improve the prediction of healthy arterial aging.

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KEY WORDS arterial aging, cardiovascular disease, cardiac computed tomography, coronary artery calcium

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

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