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ORIGINAL RESEARCH

Mid- to Late-Life Traditional Cardiovascular Risk Factor Exposure and Zero Coronary Artery Calcium

The ARIC (Atherosclerosis Risk in Communities) Study

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ABSTRACT

BACKGROUND Our understanding of traditional atherosclerotic risk factors is based predominantly on one-time measurements and associations with adverse cardiovascular outcomes.

OBJECTIVES The aim of this study was to evaluate the contribution of mid- to late-life cumulative risk factor exposure to healthy arterial aging, represented by a persistent coronary artery calcium (CAC) score of zero.

METHODS Among 2,044 community-dwelling, participants free of coronary heart disease from the ARIC (Atherosclerosis Risk in Communities) study, the associations of ~30-year time-weighted average mid- to late-life (starting at a median age of 49 years in 1987-1989) traditional atherosclerotic risk factors (cholesterol, systolic blood pressure, fasting glucose, and smoking) with late-life (median age 80 years in 2018-2019) CAC 0 were evaluated.

RESULTS A total of 204 participants (10.0%) had CAC 0, and they tended to have more favorable mid- to late-life average risk factor profiles than those with CAC: lower total cholesterol, especially <160 mg/dL; lower systolic blood pressure, especially <125 mm Hg; and higher high-density lipoprotein cholesterol, especially >45 mg/dL. The association was less evident for fasting glucose, with no increased probability of CAC 0 at <95 mg/dL. Never smoking was associated with a 5.7 (95% CI: 2.3-16.7) times greater odds of CAC 0 vs smoking throughout mid- to late-life. Within sex-race groups, average modifiable risk factors predicted substantial differences in CAC 0 probability (eg, for a Black woman, 53% vs 0.4% for a low vs high risk factor profile, respectively).

CONCLUSIONS Favorable average risk factor profiles at mid- to late-life were associated with a greater probability of CAC 0 at older age. These results highlight the importance of maintaining a healthy risk factor profile from mid- to late-life, with implications for public health promotion and policy. (JACC Cardiovasc Imaging. 2025;■:■-■) © 2025 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CAC = coronary artery calcium

CHD = coronary heart disease

HbA_{1c} = glycated hemoglobin

HDL-C = high-density lipoprotein cholesterol

LDL-C = low-density lipoprotein cholesterol

SBP = systolic blood pressure

Although age is one of the strongest risk factors for cardiovascular disease, vascular disease burden is very heterogeneous among older adults.[1] Traditionally, studies have focused on the unhealthy end of the arterial aging spectrum, namely, advanced atherosclerosis, vascular stiffening, or adverse outcomes such as cardiovascular death and myocardial infarction. However, the focus of public health and clinical research has expanded beyond avoiding cardiovascular disease toward optimizing long-term healthy arterial aging in the population (eg, the AHA [American Heart Association] 2030 goals to extend health-adjusted life expectancies).[2] Knowledge of cardiovascular health profiles linked to healthy arterial aging is important for understanding how to optimize cardiovascular health and extend cardiovascular disease-free healthy life expectancy in the general population.

Although various measures of healthy arterial aging have been proposed or explored,[1,3-5] a coronary artery calcium (CAC) score of zero has especially attracted attention, including in recent clinical guidelines,[6-9] as one of the strongest negative predictors of cardiovascular disease and mortality.[10-17] For example, even in the 75-and-older age group, a prior study demonstrated that the risk for mortality over a 5.6-year follow-up period in those with CAC 0 was 2% compared with 19% in those with CAC scores >400.[18] Thus, maintenance of CAC 0 into older adulthood is a logical and clinically important marker of healthy arterial aging to help us further understand lifelong contributors to optimal arterial aging.

Leveraging >30 years of data on traditional cardiovascular risk factors from the ARIC (Atherosclerosis Risk in Communities) study, we assessed the association between average risk factor exposures from mid- to late-life with CAC 0. We also contrasted the associations of midlife vs late-life risk factors with CAC 0. Additionally, we examined these associations with a broader definition of low CAC, including CAC scores of 1-10. Thus, our overarching aim was to understand optimal cardiovascular risk factor profiles across mid- to late-life for maintaining low CAC into old age.

METHODS

STUDY POPULATION. The ARIC study is a prospective cohort designed to study the etiology of cardiovascular disease that originally recruited 15,792 participants 45-64 years of age between 1987 and 1989 (visit 1) from 4 communities in the United States: Forsyth County, North Carolina; Jackson, Mississippi; suburban Minneapolis, Minnesota; and Washington County, Maryland.[19] Participants were subsequently followed up in 1990-1992 (visit 2), 1993-1995 (visit 3), 1996-1998 (visit 4), 2011-2013 (visit 5), 2016-2017 (visit 6), and 2018-2019 (visit 7), when CAC was measured.

In our cumulative time-weighted average exposure analyses, we assessed risk factor exposure from visit 1 to visit 6 to maximize average exposure duration and have 2 time points of exposure assessment in older adulthood (visits 5 and 6), while also allowing a lag time for CAC development by visit 7. For single-time point analyses, we used visit 1 as the midlife time point, as it was the first visit available, and visit 5, rather than visit 6, as the late-life time point because the 2 visits were only 4 years apart, and visit 5 had significantly less missingness.

At visit 7, a total of 2,288 participants without prevalent coronary heart disease (CHD), defined as having either a medical history or self-reported myocardial infarction or coronary revascularization prior to December 31, 2015, underwent noncontrast computed tomographic scanning to evaluate CAC. Of these participants, we excluded those who were not of Black or White race (n = 7) or had missing covariates at midlife visit 1 or late-life visit 5 (n = 237), yielding a final study sample of 2,044 participants. In sensitivity analyses, we included 388 additional visit 7 participants who were excluded from CAC scanning because of a clinical history of CHD. All participants in the present study provided informed consent, and the Institutional Review Board at each of the sites approved the study.

EXPOSURE ASCERTAINMENT. Our exposures of interest were traditional, modifiable atherosclerotic risk factors: total cholesterol, high-density lipoprotein cholesterol (HDL-C), systolic blood pressure (SBP), fasting glucose, and smoking. Total cholesterol and HDL-C were measured using enzymatic methods following National Cholesterol Education Program standards.[20,21] Seated SBP was measured 3 times, and the mean of the last 2 measurements was recorded, except for visit 4, when only 2 SBP measures were taken. Smoking status was self-reported at the time of each study visit. Fasting glucose was measured using standard hexokinase assay methods. In secondary analyses, we also evaluated glycated hemoglobin (HbA_{1c}) (including nonfasters), which was measured in accordance with the NGSP (National Glycohemoglobin Standardization Program) criterion at only ARIC visit 2 (n = 1,998) and visit 5 (n = 2,041).[22]

The primary exposure was mid- to late-life averages (from visit 1 to visit 6) of each of the risk factors.

Average risk factor exposure was calculated by multiplying the time duration between each 2 consecutive measures (weights) with the average of the 2 consecutive measures, divided by the total time between the first and last measure (total weights). Further details on this method are provided in the Supplemental Methods. As secondary exposures, associations with single-time point exposures at midlife (visit 1, 45-64 years of age) and late-life (visit 5, 66-90 years of age) were also evaluated.

COVARIATES AND PARTICIPANT CHARACTERISTICS. At each study visit, participant demographics and health behaviors were collected through a standardized questionnaire administered by a trained interviewer. Age, race, and sex were self-reported. Body mass index was calculated as weight in kilograms divided by the square of height in meters. When describing participant characteristics, hypertension was defined as SBP ≥130 mm Hg, diastolic blood pressure ≥80 mm Hg, or using antihypertensive medications. Diabetes was defined as a fasting glucose ≥126 mg/dL, nonfasting glucose ≥200 mg/dL, using diabetes medications, or a self-reported prior medical diagnosis of diabetes. Participants brought the medications they used to each study visit, and medication use was coded by trained study personnel.

CAC EVALUATION. CAC was measured using noncontrast cardiac-gated multidetector computed tomographic scanning at each of the field centers. All CAC scans from the 4 sites were interpreted at a centralized reading center at Harbor-UCLA Medical Center in Los Angeles, California, USA. CAC was calculated using the Agatston scoring method and reported in Agaston units.[23]

STATISTICAL ANALYSIS. Participant characteristics at midlife and late-life were described for those with CAC 0, 1-10, and >10. The associations between midlife and late-life levels of each risk factor were evaluated using either Pearson's correlation coefficient (r) or the kappa statistic.

We evaluated the association of average risk factor exposures, as well as single-time point midlife and late-life exposures individually, with CAC 0. To evaluate potential nonlinearity, we modeled the continuous risk factors as restricted cubic splines with knots at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles. In the main analysis, adjusted multinomial regressions were used to calculate ORs of CAC 0 and CAC 1-10 vs CAC >10. All models were adjusted by age, race, sex, use of diabetes, hypertension, and cholesterol-lowering medication, and all other listed cardiovascular risk factors (total cholesterol, HDL-C, SBP, and fasting glucose). As CAC 0 is a stronger marker of healthy vascular aging, we used multivariable logistic regressions to quantify ORs for having zero vs any CAC according to risk factors of interest. C-statistics were used to evaluate the performance of midlife, late-life, and average risk factors for predicting CAC 0. Likelihood ratio tests were used to test whether the combination of midlife and late-life risk factors added to the prediction of CAC 0 over that of each time point alone. We also estimated the probability of CAC 0 at 75 years of age according to average risk factor exposures from a multivariable logistic regression. In this analysis, to efficiently present the data as a heatmap, we followed the approach of the 2021 ESC (European Society of Cardiology) clinical guidelines on cardiovascular disease prevention and modeled non-HDL-C, instead of total cholesterol and HDL-C.[24]

As sensitivity analyses, multivariable logistic regressions were constructed using expanded definitions of: 1) healthy arterial aging as CAC <10; and 2) unhealthy arterial aging as those with CAC >0 along with individuals with prevalent CHD (388 additional cases). We also conducted sensitivity analyses excluding participants with prevalent stroke at visit 7. As a final sensitivity analysis, we also reconducted the modeling analyses using standard inverse probabilities of attrition weighting methods.[25,26] First, we built a multivariable logistic regression model on the basis of the entire ARIC visit 1 study population without missing covariates (n = 13,057) to estimate the attrition weight. Predictors included in the generation of the attrition weights were age, race, sex, use of diabetes, hypertension, and cholesterol-lowering medication, total cholesterol, HDL-C, SBP, and fasting glucose, and the dependent variable was missingness in the present study vs the entire ARIC visit 1 cohort. Second, the inverses of these attrition weights were added to the multivariable logistic regression models used in the main analysis (detailed earlier) to evaluate the ORs and z-scores for having zero vs any CAC by risk factors of interest.

All analyses were performed using R version 4.0.2 (R Foundation for Statistical Computing). Statistical significance was defined as a 2-sided value of $P < 0.05$.

RESULTS

DESCRIPTIVE STATISTICS. In the 2,044 study participants, the median age was 49 years (Q1-Q3: 47-53 years) at midlife visit 1, 73 years (Q1-Q3: 71-77 years) at late-life visit 5, and 80 years (Q1-Q3: 77-83 years) at visit 7 (time of CAC scanning), with 20% Black and 39% male individuals. In midlife, 34% of participants had hypertension, 3% had diabetes, and 2% were on

TABLE 1 Midlife and Late-Life Participant Characteristics by CAC Score (0, 1-10, and >10)

	Midlife (1987-1989) Characteristics				Late-Life (2011-2013) Characteristics			
		CAC at Visit 7				CAC at Visit 7		
	Overall (N = 2,044)	0 (n = 204)	1-10 (n = 138)	>10 (n = 1,702)	Overall (N = 2,044)	0 (n = 204)	1-10 (n = 138)	>10 (n = 1,702)
Age, y	49 (47-53)	48 (46-50)	49 (46-52)	50 (47-53)	73 (71-77)	72 (70-74)	73 (70-76)	73 (71-77)
White	1,634 (79.9)	147 (72.1)	100 (72.5)	1,387 (81.5)	–	–	–	–
Male	786 (38.5)	35 (17.2)	25 (18.1)	726 (42.7)	–	–	–	–
BMI, kg/m^2	26.0 (23.4-29.1)	24.5 (21.9-27.1)	25.8 (22.6-28.5)	26.1 (23.7-29.4)	28.1 (25.1-31.6)	26.9 (23.8-30.8)	28.2 (24.9-31.7)	28.2 (25.4-31.7)
SBP, mm Hg	112 (103-122)	107 (101-115)	109 (102-117)	113 (104-123)	128 (117-139)	124 (116-136)	128 (119-137)	128 (117-139)
DBP, mm Hg	71 (65-78)	69 (63-76)	70 (64-76)	72 (66-78)	67 (60-74)	67 (61-74)	67 (61-74)	67 (60-74)
Hypertension	693 (34.0)	60 (29.4)	39 (28.5)	594 (35.0)	1,678 (82.3)	147 (72.1)	109 (79.0)	1,422 (83.8)
Antihypertensive medication	341 (16.7)	33 (16.2)	25 (18.1)	283 (16.6)	1,402 (68.6)	118 (57.8)	87 (63.0)	1,197 (70.3)
Current smoking	310 (15.2)	17 (8.3)	16 (11.6)	277 (16.3)	100 (4.9)	5 (2.5)	6 (4.3)	89 (5.2)
Fasting glucose, mg/dL	96 (91-102)	94 (89-99)	96 (89-101)	97 (91-102)	105 (97-117)	101 (94-109)	104 (97-113)	106 (98-118)
Diabetes	55 (2.7)	3 (1.5)	2 (1.4)	50 (2.9)	533 (26.1)	33 (16.2)	23 (16.7)	477 (28.0)
Diabetes medication	19 (0.9)	3 (1.5)	1 (0.7)	15 (0.9)	305 (14.9)	18 (8.8)	15 (10.9)	272 (16.0)
Total cholesterol, mg/dL	202 (180-227)	189 (165-208)	193 (172-212)	206 (182-229)	184 (159-211)	197 (168-219)	188 (167-221)	182 (157-209)
HDL-C, mg/dL	52 (43-64)	61 (50-71)	57 (49-67)	50 (41-63)	51 (43-61)	57 (48-68)	55 (47-62)	50 (43-60)
Cholesterol-lowering medication	32 (1.6)	1 (0.5)	1 (0.7)	30 (1.8)	1,022 (50.0)	64 (31.4)	51 (37.0)	907 (53.3)

Values are median (Q1-Q3) or n (%).

BMI = body mass index; CAC = coronary artery calcium; DBP = diastolic blood pressure; HDL-C = high-density lipoprotein cholesterol; SBP = systolic blood pressure.

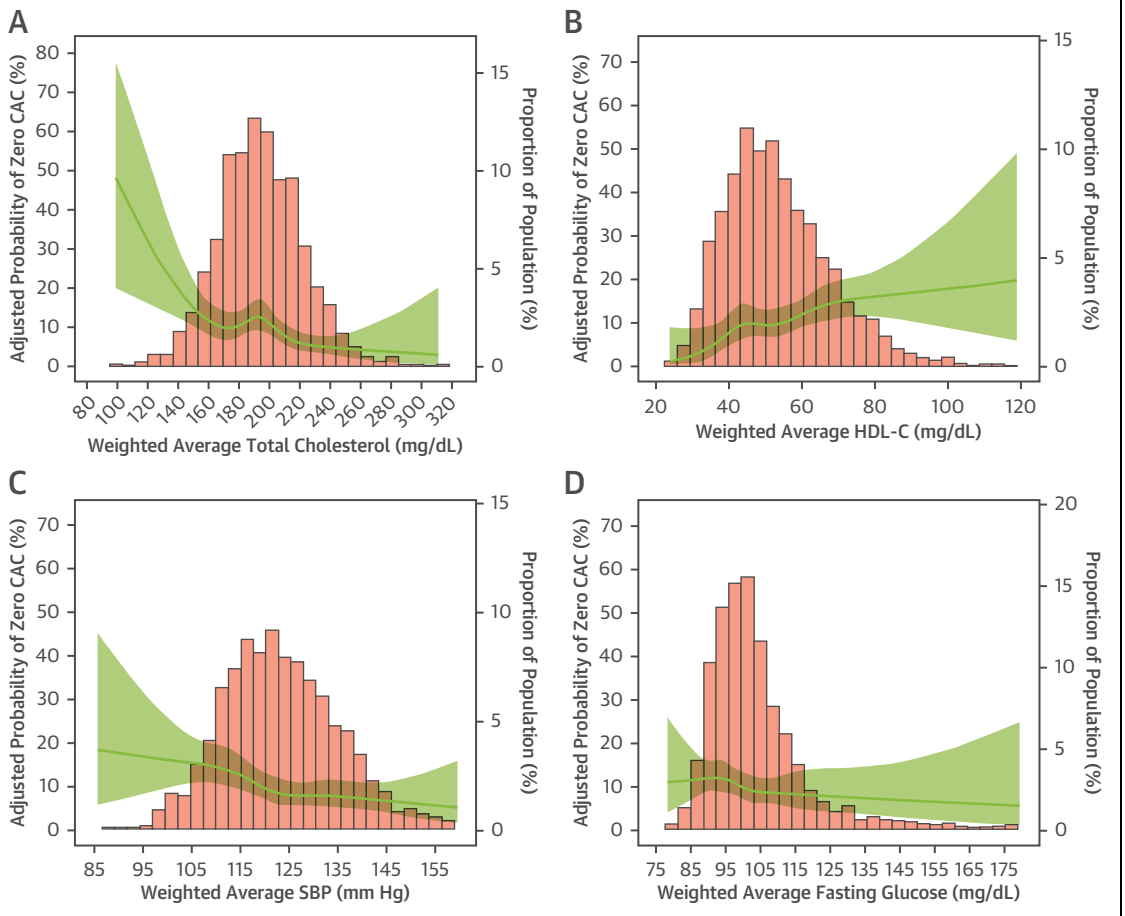
cholesterol-lowering medications (Table 1). By late-life, 82% of participants had hypertension, 26% had diabetes, and 50% were on cholesterol-lowering medications.

The prevalence of CAC 0 at visit 7 was 10% (204 participants), and the prevalence of CAC 1 to 10 was 7% (138 participants). There were higher proportions of participants who were Black, were female, did not smoke, did not have hypertension, did not have diabetes, and had lower body mass index with CAC 0 than among those with CAC > 10 in both mid- and late-life (Table 1). Those with CAC 0 were also more likely to have lower total cholesterol in midlife and not be taking cholesterol-lowering medication in late-life. Further midlife and late-life demographics are presented by sex-race group (Supplemental Tables 1 and 2).

CORRELATIONS OF TRADITIONAL MODIFIABLE RISK FACTORS AT MIDLIFE AND LATE-LIFE. Within participants, the correlations between mid- and late-life HDL-C were strongest (r = 0.70) (Supplemental Figure 1). The mid- and late-life correlations were modest for SBP and fasting glucose levels (r = 0.23 and r = 0.34, respectively), with an overall shift to higher SBP and fasting glucose levels in late-life. The correlation between mid- and late-life was weakest for total cholesterol (r = 0.16). For smoking, most midlife nonsmokers (98%) remained nonsmokers in late-life, and the majority of midlife smokers (78%) had stopped smoking by late-life (Supplemental Figure 2).

ASSOCIATIONS OF 30-YEAR AVERAGE EXPOSURES OF TRADITIONAL MODIFIABLE RISK FACTORS WITH LOW CAC. Figure 1 demonstrates the adjusted probability of CAC 0 at visit 7 by average risk factor exposure measured across repeated visits from mid- to late-life (visits 1-5). Lower average total cholesterol, especially <160 mg/dL, was strongly associated with a higher probability of CAC 0 (Figure 1A). For those with an average total cholesterol of 220 mg/dL, adjusted probability of CAC 0 was 6%, while for those with total cholesterol of 140 mg/dL, the corresponding probability of CAC 0 was 20%. Higher average HDL-C was linearly associated with higher probability of CAC 0, with a slightly sharper gradient at <40-45 mg/dL (Figure 1B). For example, the adjusted probability of CAC 0 at an HDL-C concentration of 40 mg/dL was 8%, while that of an HDL-C level of 80 mg/dL was 15%. Similarly, a linear association was seen for SBP, with slightly sharper gradient at <125 mm Hg (Figure 1C). The adjusted probability of CAC 0 at an SBP of 125 mm Hg was 8%, while the probability at 105 mm Hg was 15%. The association appeared least evident for averaged fasting glucose (Figure 1D), with no increase in the probability of CAC 0 at <95 mg/dL. We observed largely similar

FIGURE 1 Adjusted Probability of CAC 0 by Mid- to Late-Life Average Risk Factor Profile



Total cholesterol (A), HDL-C (B), SBP (C), and fasting glucose (D). Adjusted to median (for continuous variables) or most prevalent (for categorical variables) age, race, sex, body mass index, smoking, use of diabetes, hypertension, cholesterol-lowering medication, and all other variables listed. CAC = coronary artery calcium; HDL-C = high-density lipoprotein cholesterol; SBP = systolic blood pressure.

associations when we modeled probabilities of CAC <10 rather than CAC 0 (Supplemental Figure 3). Results were consistent when modeling traditional risk factors linearly (**Table 2**), with the strongest CAC 0 association with averaged lower total cholesterol, followed by lower SBP and higher HDL-C. CAC 1-10 was associated only with lower averaged total cholesterol.

Not smoking in mid- to late-life was associated with a higher probability of CAC 0 (Supplemental Figure 4). Never smoking from mid- to late-life was associated with 5.7 times greater odds of CAC 0 and 4.3 times greater odds of CAC 1-10 compared with continuous smoking (**Table 3**). According to our model, smoking only 26% of the time, the median intermittent smoking duration in this sample, yielded 1.6 times higher odds of CAC 0 and 1.5 times higher odds of CAC 1-10, compared with continuous smoking. Focusing on mid- and late-life time points, never and former smoking were both associated with higher odds of CAC 0, relative to current smokers.

TABLE 2 ORs (95% CIs) of CAC by Midlife to Late-Life Average Healthy Risk Factor Profiles

	CAC >10	CAC 1-10	CAC 0
Total cholesterol (per 10 mg/dL decrement)	Ref.	1.04 (0.97-1.12)	**1.15 (1.08-1.23)**
HDL-C (per 5 mg/dL increment)	Ref.	1.03 (0.96-1.11)	**1.11 (1.04-1.19)**
SBP (per 10 mm Hg decrement)	Ref.	**1.18 (1.00-1.40)**	**1.32 (1.13-1.54)**
Fasting glucose (per 10 mg/dL decrement)	Ref.	0.99 (0.84-1.17)	1.12 (0.95-1.33)

An OR >1 represents higher odds of having either CAC 1-10 or CAC 0 (as labeled) by risk factor profile, averaged across repeated measures from mid- to late-life. The reference is CAC >10. **Bold** indicates significant ORs. Adjusted for all other variables listed along with age; race; sex; average body mass index; proportion of time smoking; and using antidiabetic, antihypertensive, or cholesterol-lowering medications.

Ref. = Reference; other abbreviations as in Table 1.

TABLE 3 ORs (95% CIs) of Low CAC by Smoking Status

	CAC 0	CAC <10
Mid- to late-life exposure[a]		
Continuous smoking from mid- to late-life	Ref.	Ref.
Intermittent smoking between mid- to late-life[a]	**1.57 (1.24-2.08)**	**1.46 (1.22-1.79)**
Never smoked between mid- to late-life	**5.67 (2.26-16.70)**	**4.30 (2.14-9.36)**
Visit 1 (midlife)		
Smoking at midlife	Ref.	Ref.
Smoked before midlife	**2.84 (1.61-5.24)**	**2.23 (1.43-3.54)**
Never smoked before midlife	**2.88 (1.70-5.16)**	**2.53 (1.69-3.89)**
Visit 5 (late-life)		
Smoking in late-life	Ref.	Ref.
Smoked before late-life	**2.48 (1.05-7.30)**	1.67 (0.89-3.46)
Never smoked before late-life	**2.69 (1.15-7.91)**	**2.10 (1.11-4.32)**

An OR >1 represents higher odds of having CAC 0 or <10 by smoking status relative to the reference indicated. **Bold** indicates significant ORs. Adjusted for age; race; sex; average or respective study visit body mass index; total cholesterol; high-density lipoprotein cholesterol; body mass index; systolic blood pressure; fasting glucose; and use of antidiabetic, antihypertensive, and cholesterol-lowering medications. [a]Mid- to late-life smoking status was categorized as: 1) continuous smoking (smoked throughout mid- to late-life); 2) intermittent smoking (smoked intermittently from mid- to late-life, modeled on a median of smoking 26% of the elapsed time); and 3) never smoked.

CAC = coronary artery calcium; other abbreviation as in Table 2.

PREDICTION OF CAC 0 ACCORDING TO MID- TO LATE-LIFE AVERAGE EXPOSURES OF TRADITIONAL MODIFIABLE RISK FACTORS. Probabilities of CAC 0 at 75 years of age by demographics and average risk factor profiles are presented in **Figure 2**. Women and Black individuals tended to have a higher overall probability of having CAC 0 compared with their counterparts. With lower average SBP and non-HDL-C levels, the likelihood of CAC 0 at 75 years of age increased. Continuous smoking made it very unlikely, especially among White men (<3%), to have CAC 0 at 75 years of age, even with an optimal profile of other risk factors. Within the same sex and race group, the average exposures of the modifiable risk factors, SBP, non-HDL-C, and smoking, contributed to substantial differences in the probability of CAC 0. For example, in Black women, the predicted CAC 0 probability was 53% for a low risk factor profile (SBP 100-119 mm Hg, non-HDL-C 100-119 mg/dL, and never smoking) vs 0.4% for a high risk factor profile (SBP 160-179 mm Hg, non-HDL-C 200-219 mg/dL, and continuous smoking from mid- to late-life) (**Central Illustration**).

ASSOCIATIONS OF MIDLIFE AND LATE-LIFE TRADITIONAL MODIFIABLE RISK FACTORS WITH LOW CAC. As a whole, midlife risk factors were more strongly associated with CAC 0 and 1-10 than late-life factors (Supplemental Table 3). Lower total cholesterol at both midlife and late-life were associated with CAC 0, while higher HDL-C was linearly and strongly associated with higher probability of CAC 0 at both mid- and late-life (**Figure 3**). Lower SBP (especially <125 mm Hg at midlife and <140 mm Hg in late-life) and less so fasting glucose (up to about 100 mg/dL) were generally associated with a modestly increasing probability of CAC 0. Results were comparable when modeling probability of CAC <10 (Supplemental Figure 5). Of note, when modeled as a linear term, fasting glucose was not independently associated with CAC 0 or CAC 1-10 at either mid- or late-life (Supplemental Table 3). Associations were similar when we conducted a sensitivity analysis stratifying individuals by diabetes status (Supplemental Table 4) and also when we modeled HbA_{1c} measures instead of fasting glucose, where HbA_{1c} was not significantly associated with CAC 0 or CAC 1-10 (Supplemental Table 5).

CAC 0 PREDICTION WITH MIDLIFE, LATE-LIFE, AND AVERAGE EXPOSURES. Midlife risk factors were more strongly predictive of CAC 0 in older age than late-life risk factors (C-statistic = 0.782 and 0.765, respectively) (**Table 4**). Including both midlife and late-life risk factors improved the C-statistic over that of each time point alone ($P = 0.02$ when adding late-life to midlife factors, and $P < 0.001$ when adding midlife to late-life factors); however, average exposures model achieved the highest C-statistic for CAC 0 (C-statistic = 0.794).

SENSITIVITY ANALYSIS. Healthy risk factor profile associations were also consistent in secondary analyses when separately evaluating associations with CAC 0 and CAC <10 outcomes (Supplemental Table 6), when including participants at old age with clinical histories of CHD in the non-CAC 0 unhealthy arterial aging category (Supplemental Table 7), after excluding participants with histories of stroke at CAC scanning (Supplemental Table 8), and after implementing inverse probability of attrition weighting, on the basis of the population at ARIC visit 1 (Supplemental Table 9). Subgroup analyses by sex and race also yielded no effect measure modification (Supplemental Table 10). In additional secondary analyses on low-density lipoprotein cholesterol (LDL-C), effect sizes for LDL-C associations were similar to that of total cholesterol (Supplemental Table 11, Supplemental Figure 6). Midlife LDL-C was more strongly associated with CAC 0 than late-life LDL-C, which did not reach statistical significance.

DISCUSSION

In this prospective cohort study of community-dwelling adults in the ARIC study, we observed that favorable 30-year mid- to late-life average risk factor profiles—lower total cholesterol, lower SBP, and higher HDL-C—were associated with CAC 0 among those who reached old age. Never smoking was also

FIGURE 2 **Mid- to Late-Life Average Risk Factor Profile and Probability of a Coronary Artery Calcium Score of 0 at 75 Years of Age**

Female								Male							
		Non-HDL-C (mg/dL)								Non-HDL-C (mg/dL)					
	Systolic Blood Pressure (mm Hg)	100-119	120-139	140-159	160-179	180-199	200-219	Smoking Status	Systolic Blood Pressure (mm Hg)	100-119	120-139	140-159	160-179	180-199	200-219
Black	100-119	53	45	37	29	23	17	Never Smoked	100-119	25	19	15	11	8	6
	120-139	36	29	22	17	13	9		120-139	14	11	8	6	4	3
	140-159	22	17	12	9	7	5		140-159	8	6	4	3	2	2
	160-179	12	9	7	5	3	2		160-179	4	3	2	1	1	0.7
	100-119	42	34	27	21	16	12	Intermittent Smoking*	100-119	18	13	10	7	5	4
	120-139	26	20	15	12	8	6		120-139	10	7	5	4	3	2
	140-159	15	11	8	6	4	3		140-159	5	4	3	2	1	0.9
	160-179	8	6	4	3	2	2		160-179	2	2	1	0.9	0.7	0.5
	100-119	17	13	9	7	5	4	Continuous Smoking	100-119	6	4	3	2	2	1
	120-139	9	7	5	4	2	2		120-139	3	2	2	1	0.8	0.5
	140-159	5	3	2	2	1	0.9		140-159	1	1	0.7	0.5	0.4	0.3
	160-179	2	2	1	0.9	0.6	0.4		160-179	0.7	0.5	0.4	0.3	0.2	0.1
White	100-119	40	32	25	19	15	11	Never Smoked	100-119	16	12	9	7	5	3
	120-139	25	19	14	11	8	6		120-139	9	6	5	3	2	2
	140-159	14	10	8	6	4	3		140-159	4	3	2	2	1	0.9
	160-179	7	5	4	3	2	1		160-179	2	2	1	0.8	0.6	0.4
	100-119	30	23	18	13	10	7	Intermittent Smoking*	100-119	11	8	6	4	3	2
	120-139	17	13	10	7	5	4		120-139	6	4	3	2	2	1
	140-159	9	7	5	4	3	2		140-159	3	2	2	1	0.8	0.5
	160-179	5	4	2	2	1	0.9		160-179	2	1	0.7	0.5	0.4	0.3
	100-119	10	8	6	4	3	2	Continuous Smoking	100-119	3	2	2	1	0.9	0.6
	120-139	6	4	3	2	2	1		120-139	2	1	0.9	0.6	0.4	0.3
	140-159	3	2	1	1	0.7	0.5		140-159	0.8	0.6	0.4	0.3	0.2	0.2
	160-179	1	1	0.7	0.5	0.4	0.3		160-179	0.4	0.3	0.2	0.1	0.1	0.1

Red denotes <5%, orange denotes 5% to 9%, yellow denotes 10% to 19%, and green denotes ≥20%. *Smoked intermittently from mid- to late-life, modeled on a median of smoking 26% of the elapsed time. HDL-C = high-density lipoprotein cholesterol.

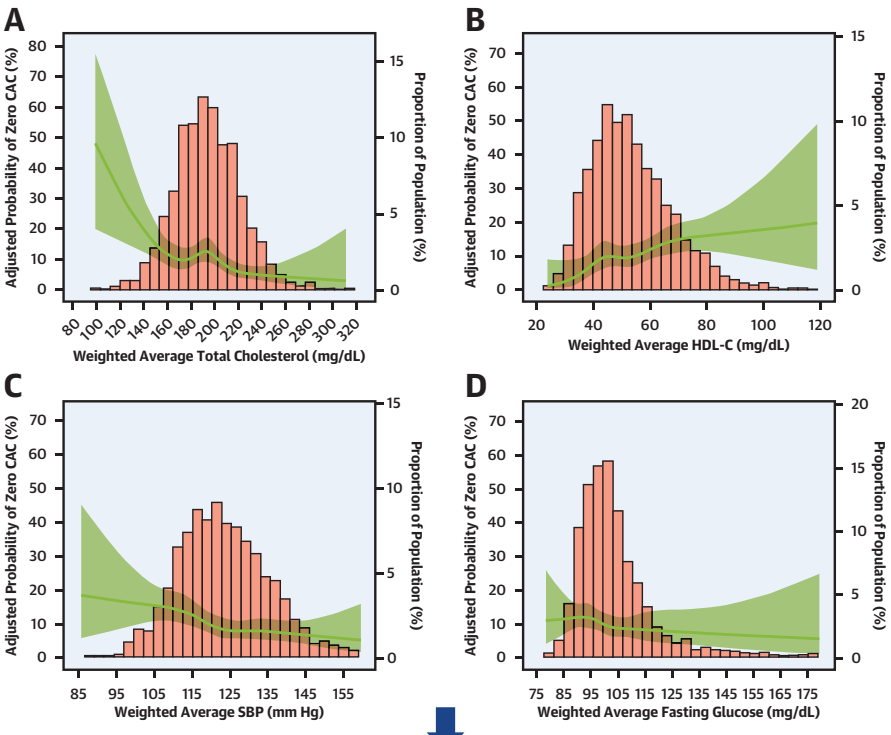
strongly associated with a greater odds of having CAC 0, compared with sustained smoking. Cumulative average exposures to these modifiable risk factors resulted in substantial differences in the probability of CAC 0 at 75 years of age for the most extreme tails of the risk distribution. Healthy 30-year average risk factor profiles were most strongly associated with CAC 0, followed by profiles at midlife and then in late-life. These results highlight the importance of maintaining healthy risk factor profiles throughout the life course for healthy arterial aging.

Prior studies have suggested that the process of maintaining healthy arterial aging can be complex, and unlike general adverse disease prevention, the maintenance of a comprehensive healthy cardiovascular risk factor profile may be more important for healthy arterial aging rather than optimal conditions of a specific individual risk factors.[25,26] Indeed, one of the few prior studies on cardiovascular risk factor associations with CAC 0 in the general population also suggested that risk factor burden in those with persistent CAC 0 is lower than for those who develop CAC.[25] Our study uniquely observed that better 30-year profiles of cardiovascular risk factors—total cholesterol, HDL-C, SBP, and smoking—were independently associated with higher CAC 0 probability.

Our study showed that low total cholesterol is one of the strongest predictors of CAC 0. Indeed, we observed that total cholesterol <160 mg/dL, with no lower limit in the range explored, demonstrated a sharp positive association with healthy arterial aging. Our observation seems consistent with prior studies showing that the lower cholesterol levels, the better the outcomes.[27] For example, the CARDIA (Coronary Artery Risk Development in Young Adults) study demonstrated that even from a young age (18-30 years), low cholesterol is associated with 15-year CAC 0.[28] The potential causal contribution of low cholesterol to CAC 0 has also been further supported by Mendelian randomization analyses.[29] Along with prior studies, our findings highlight the importance of maintaining low cholesterol, whether through

CENTRAL ILLUSTRATION Favorable 30-Year Mid- to Late-Life Average Risk Factor Profiles Associated With Healthy Vascular Aging

Average Risk Factor Associations With CAC 0



Predicted CAC 0 Probability at Age 75 by Average Risk Factor Profile

		Female							Male						
		Non-HDL-C (mg/dL)							Non-HDL-C (mg/dL)						
	Systolic Blood Pressure (mm Hg)	100-119	120-139	140-159	160-179	180-199	200-219	Smoking Status	Systolic Blood Pressure (mm Hg)	100-119	120-139	140-159	160-179	180-199	200-219
Black	100-119	53	45	37	29	23	17	Never Smoked	100-119	25	19	15	11	8	6
	120-139	36	29	22	17	13	9		120-139	14	11	8	6	4	3
	140-159	22	17	12	9	7	5		140-159	8	6	4	3	2	2
	160-179	12	9	7	5	3	2		160-179	4	3	2	1	1	0.7
	100-119	42	34	27	21	16	12	Intermittent Smoking*	100-119	18	13	10	7	5	4
	120-139	26	20	15	12	8	6		120-139	10	7	5	4	3	2
	140-159	15	11	8	6	4	3		140-159	5	4	3	2	1	0.9
	160-179	8	6	4	3	2	2		160-179	2	2	1	0.9	0.7	0.5
	100-119	17	13	9	7	5	4	Continuous Smoking	100-119	6	4	3	2	2	1
	120-139	9	7	5	4	2	2		120-139	3	2	2	1	0.8	0.5
	140-159	5	3	2	2	1	0.9		140-159	1	1	0.7	0.5	0.4	0.3
	160-179	2	2	1	0.9	0.6	0.4		160-179	0.7	0.5	0.4	0.3	0.2	0.1
White	100-119	40	32	25	19	15	11	Never Smoked	100-119	16	12	9	7	5	3
	120-139	25	19	14	11	8	6		120-139	9	6	5	3	2	2
	140-159	14	10	8	6	4	3		140-159	4	3	2	2	1	0.9
	160-179	7	5	4	3	2	1		160-179	2	2	1	0.8	0.6	0.4
	100-119	30	23	18	13	10	7	Intermittent Smoking*	100-119	11	8	6	4	3	2
	120-139	17	13	10	7	5	4		120-139	6	4	3	2	2	1
	140-159	9	7	5	4	3	2		140-159	3	2	2	1	0.8	0.5
	160-179	5	4	2	2	1	0.9		160-179	2	1	0.7	0.5	0.4	0.3
	100-119	10	8	6	4	3	2	Continuous Smoking	100-119	3	2	2	1	0.9	0.6
	120-139	6	4	3	2	2	1		120-139	2	1	0.9	0.6	0.4	0.3
	140-159	3	2	1	1	0.7	0.5		140-159	0.8	0.6	0.4	0.3	0.2	0.2
	160-179	1	1	0.7	0.5	0.4	0.3		160-179	0.4	0.3	0.2	0.1	0.1	0.1

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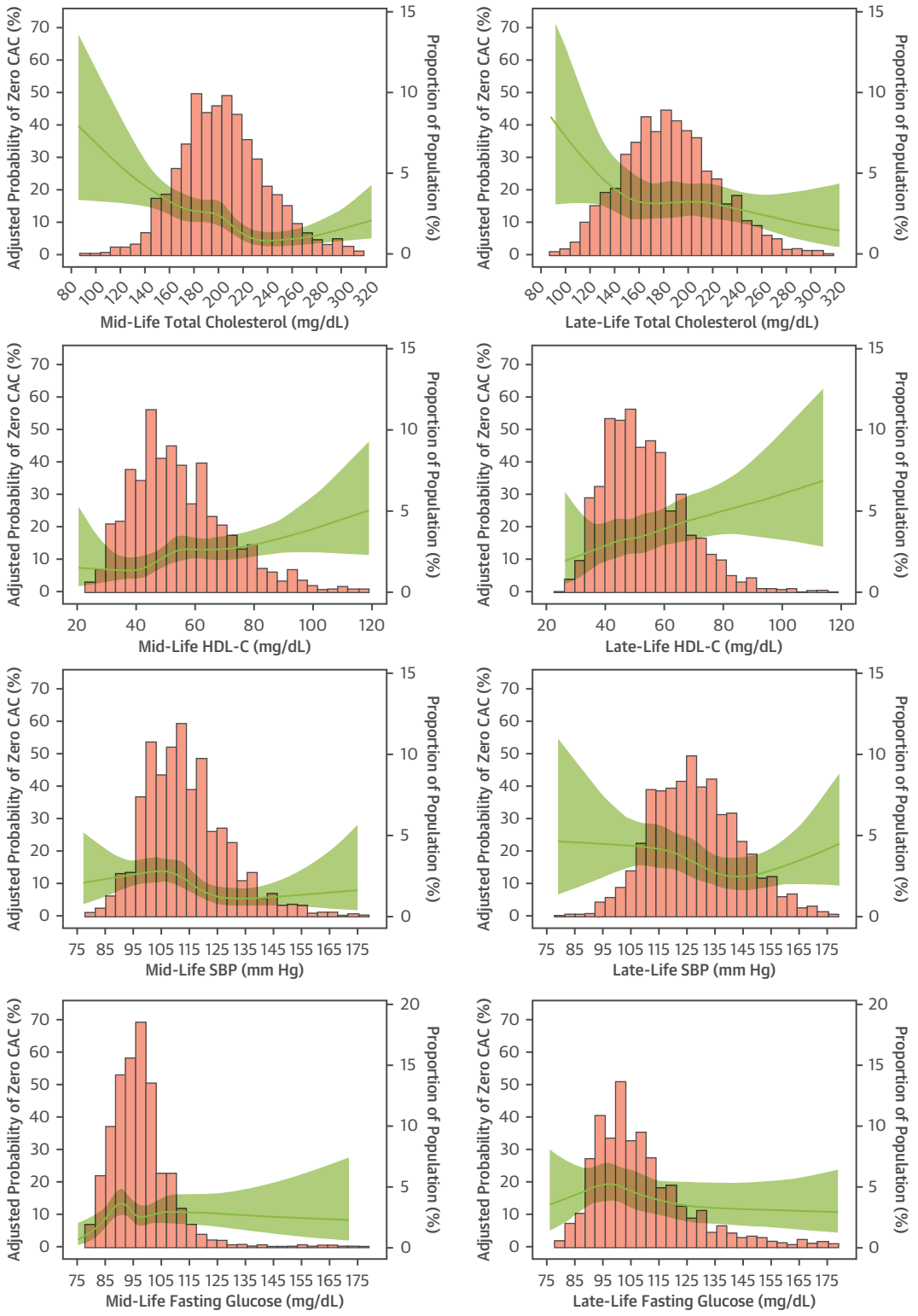
Total cholesterol (A), high-density lipoprotein cholesterol (HDL-C) (B), systolic blood pressure (SBP) (C), and fasting glucose (D). CAC = coronary artery calcium.

FIGURE 3 **Adjusted Probability of CAC 0 by Mid- and Late-Life Risk Factor Profile**



Adjusted to median (for continuous variables) or most prevalent (for categorical variables) age, race, sex, body mass index, smoking, use of diabetes, hypertension, cholesterol-lowering medication, and all other variables listed. Abbreviations as in Figure 1.

TABLE 4 Predictive Value of Midlife, Late-Life, and Average Risk Factor Exposures for a Coronary Artery Calcium Score of 0

Model	C-Statistic (95% CI)
Midlife	0.782 (0.750-0.814)
Late-life	0.765 (0.731-0.798)
Midlife and late-life	0.793 (0.761-0.824)
Mid- to late-life average	0.794 (0.761-0.826)

lifestyle modifications or medications, throughout the life course for optimizing vascular health.

The absence of association between fasting glucose and healthy arterial aging in our study also deserves discussion. This observation may sound counterintuitive, as diabetes is recognized as one of the most potent risk factors for atherosclerotic disease.[30] One explanation for this finding may be that the number of participants with diabetes at baseline was low in our cohort. However, a few prior studies, such as the Framingham Heart Study and PESA (Progression of Early Subclinical Atherosclerosis), have likewise demonstrated a lack of independent association between fasting glucose and CAC.[31-33] Also, unlike total cholesterol, HDL-C, and SBP, for which the probability of CAC 0 continuously increased by "better" profiles, in our study, the highest probability of CAC 0 was observed in average fasting glucose levels between about 90 to 100 mg/dL. Of note, low CAC was found to be associated with HbA_{1c} in the PESA study, perhaps because it better represents glycemic status compared with fasting blood glucose. Nonetheless, further studies are necessary to develop our understanding of the connection between glycemic status and healthy arterial aging.

Although both midlife and late-life risk factor exposures are associated with cardiovascular outcomes, previous published reports have suggested that earlier exposure to cardiovascular risk factors more strongly contribute to the development of cardiovascular disease than at older age.[34,35] Our results for CAC 0 were in line with those previous studies. This supports growing efforts to optimize cardiovascular health by promoting primordial prevention (eg, the AHA statement on the value of primordial prevention[36]). Although both early- and late-life risk factor exposures are biologically important in healthy aging, on a human behavior perspective, early risk factor prevention is further supported by the concept that those with healthy lifestyle behaviors in midlife tend to maintain these healthy profiles into late-life.[37,38] Indeed, our analysis demonstrated a moderate to high correlation between midlife risk factor profiles and late-life risk factor profiles.

Although 30-year cumulative average profiles of traditional atherosclerotic risk factors may not seem relevant in current clinical practice or public health, with increasing availability of electronic health records, questions of how to parameterize longitudinal exposures of these risk factors and how they can be used to understand patient health and need for health intervention are becoming increasingly relevant. Cumulative risk factor measures, such as mid- to late-life averages in our study, may be a practical and valuable way to summarize longitudinal exposures. Indeed, as risk factors vary within person in both the short and long term, averaging multiple measures provides a better measure of conditions the arteries are exposed to during adulthood. Although the optimal way to parameterize longitudinal exposures is yet to be determined, integrating cumulative measures in addition to a common approach of relying on single-time point risk factors is likely to improve the understanding and management of cardiovascular risk.

STUDY LIMITATIONS. First, in average risk factor analyses, there was a 15-year gap between ARIC visits 4 and 5, during which risk factor exposures were not measured. Despite this, the ARIC study was well positioned for studying longitudinal cardiovascular risk factor exposures as the longest, most expansive, and well-characterized contemporary cohort to date with CAC measures in old age (mostly ≥75 years of age). Even with the gap in risk factor assessment, the association between average risk factors and CAC 0 remained strong, highlighting the value of measuring cumulative risk factors. Also, potential survival bias from mid- to late-life would likely lead to our observed estimates being conservative because individuals with worse risk factor profiles and unhealthy arterial aging were more likely to differentially drop out of the study (eg, because of mortality). Last, because of the ARIC study design, this analysis was limited to individuals who were Black and White, which may limit the generalizability of these findings to people of other races or ethnicities.

CONCLUSIONS

Favorable mid- to late-life average risk factor profiles (lower total cholesterol, higher HDL-C, lower SBP) are associated with CAC 0 in older adulthood. These cumulative average risk factors were more strongly associated with CAC 0 than either midlife or late-life single time points. Within sex and race strata, differences in these modifiable cumulative average risk factors were associated with substantial differences in the probability of CAC 0 at older adulthood.

These results strongly support the importance of maintaining a healthy risk factor profile from the entire mid- to late-life period to optimize healthy arterial aging.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Favorable mid- to late-life average risk factor profiles (eg, lower total cholesterol, lower blood pressure, and not smoking) are associated with CAC 0 in older adulthood. These cumulative average risk factors are more strongly associated with CAC 0 than either midlife or late-life single time points.

TRANSLATIONAL OUTLOOK: Maintaining long-term healthy cardiovascular risk factor profiles starting from midlife, and likely earlier, is critical for healthy vascular aging.

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KEY WORDS coronary artery calcification, healthy aging, life-course prevention, subclinical atherosclerosis

APPENDIX For an expanded Methods section as well as supplemental figures and tables, please see the online version of this paper.