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PREVALENCE AND PROGRESSION OF SUBCLINICAL ATHEROSCLEROSIS IN YOUNGER ADULTS WITH LOW SHORT-TERM BUT HIGH LIFETIME ESTIMATED RISK FOR CARDIOVASCULAR DISEASE: THE CARDIA AND MESA STUDIES

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Abstract

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Clinical Perspective: Although the Framingham Risk Score represents a significant advance in the primary prevention of cardiovascular disease, it has well-established limitations. For example, it classifies virtually all younger adults as low risk regardless of risk factor burden. One proposed solution is to extend the time horizon to include the remaining lifespan where differences in risk factor burden translate into substantial differences in risk for cardiovascular disease across the remaining lifespan. Thus, we hypothesized that among individuals < 50 years with low 10-year risk there are two distinct groups: those we would predict to have a high lifetime risk and those we would predict to have a low lifetime risk. In two unique cohorts, the CARDIA and MESA studies, we found that those with low short term but high lifetime risk had a greater burden and progression of subclinical atherosclerosis as measured by coronary artery calcium and carotid intima-media thickness when compared to the low short-term and low lifetime risk—even at these younger ages of less than 50 years. Thus, prior data would suggest that individuals with these differences in risk factor burden would have marked differences in event rates across the lifespan. But what about now? The present findings would suggest that these risk factor differences translate into significant differences in the prevalence and progression of subclinical atherosclerosis even at younger ages. We believe these findings suggest a potential benefit of more aggressive prevention efforts for individuals less than 50 years with low short-term but high lifetime risk.

Background—We hypothesized that individuals with low 10-year but high lifetime cardiovascular disease (CVD) risk would have a greater burden of subclinical atherosclerosis than those with low 10-year but low lifetime risk.

Methods and Results—We included 2988 individuals age ≤50 at exam year 15 from the Coronary Artery Risk Development in Young Adults (CARDIA) study and 1076 individuals age ≤50 at study entry from the Multi-Ethnic Study of Atherosclerosis (MESA). The 10-year risk and lifetime risk for CVD were estimated for each participant, permitting stratification into three groups: low 10-year (<10%)/low lifetime (<39%) risk, low 10-year (<10%)/high lifetime risk (≥39%), and high 10-year risk (≥10%) or diagnosed diabetes. Baseline levels and change in levels of subclinical atherosclerosis (coronary artery calcium [CAC] or carotid intima-media thickness [IMT]) were compared across risk strata. Among participants with low 10-year risk (91% of all participants) in CARDIA, those with a high lifetime risk compared to low lifetime risk had significantly greater common (0.83 vs 0.80 mm in men; 0.79 vs 0.75 mm in women) and internal (0.85 vs 0.80 mm; 0.80 vs 0.76 mm) carotid IMT, higher CAC prevalence (16.6 vs 9.8%; 7.1 vs 2.3%), and significantly greater incidence of CAC progression (22.3 vs 15.4%; 8.7 vs 5.3%). Similar results were observed in MESA.

Conclusions—Individuals with low 10-year but high lifetime risk have a greater subclinical disease burden and greater incidence of atherosclerotic progression compared to individuals with low 10-year and low lifetime risk, even at younger ages.

Keywords

epidemiology; risk estimation; prevention

Although the Framingham Risk Score (FRS) represents an important advance in the primary prevention of cardiovascular disease (CVD)[1, 2], it has well-recognized limitations. For example, the FRS classifies most younger individuals[3] and virtually all women[4, 5] as low-risk in spite of significant differences in risk factor burden, reflecting the importance of age in the 10-year risk equation. Recently, we have found that adults age 50 years with 1 or more elevated traditional risk factor(s) have observed lifetime risks for CVD of 39% to 70% despite 10-year predicted risks <10%[6]. In response to these and other data, practice guidelines 7–9 suggest physicians consider current risk factor burden within the context of long-term or lifetime risk for CVD.

Long-term risk estimates provide novel information regarding risk prediction that is not obtained through modifications of the 10-year risk window. For example, adjusting the threshold of “low risk” to < 5% will do little to improve stratification of risk across the remaining lifespan[10]. Because of the intuitive nature and distinct features of lifetime risk estimates[11, 12], we sought to combine the 10-year and the lifetime risk window into a single, clinically relevant method of risk stratification[13].

We hypothesized that among individuals ≤ 50 years with “low predicted 10-year risk” there would be two distinct groups: one with low predicted lifetime risk and one with high predicted lifetime risk. We further hypothesized that individuals with low-10 year but *high* lifetime predicted risk would have a greater burden and progression of established measures of subclinical atherosclerosis such as CAC (coronary artery calcium)[14] and carotid intima-media thickness (IMT)[15] compared to those with low 10-year and *low* predicted lifetime risk.

Differences in subclinical atherosclerotic burden between these two groups would provide a mechanistic explanation for differences in observed event rates seen in prior studies of

lifetime risk in younger adults, and potentially identify novel groups of individuals for more intensive lifestyle or pharmacologic preventive interventions.

METHODS

Study Populations

The Coronary Artery Risk Development in Young Adults (CARDIA) study is a National Heart, Lung and Blood Institute (NHLBI)-sponsored longitudinal study of the development of cardiovascular risk in young adults. Details of the study have been reported previously [16]. Of the 3652 CARDIA participants age 32–47 at year 15, the exclusion criteria were: missing CAC score data (n=615), missing total cholesterol data (n=36), and missing other critical covariates (n=13), leaving a total of 2988 individuals for analyses. Carotid (IMT) was measured in 3164 participants ages 38–50 at the Year 20 CARDIA examination. For these analyses, we excluded those with missing total cholesterol data (n=34), and missing other critical covariates (n=33), leaving a total of 3097 individuals for analyses.

The Multi-Ethnic Study of Atherosclerosis (MESA) Study is a NHLBI-sponsored community-based study of 6814 men and women aged 45 to 84 years who were free of clinical CVD at study entry. Participants from four ethnic backgrounds were recruited from 6 US communities. Details of the study have been reported previously17. Carotid IMT and CAC were measured at study entry; CAC was then repeated once in each participant at exam 2 or exam 3. Of the 1085 MESA participants age 44–50, we excluded individuals with missing risk factor data (n=9), leaving a total of 1076 for analyses. Both CARDIA and MESA studies have been approved by the Institutional Review Board at each contributing institution, and all participants have given informed consent for their participation at each examination. For both CARDIA and MESA, baseline characteristics were obtained in accordance with standard protocols17, 16. For CARDIA participants, risk factors measured at Year 15 when participants were aged 33 to 45 were included for CAC analyses (year 20 risk factors for carotid IMT analyses).

Risk Classification Definitions

Low predicted short-term risk was defined as an estimated 10-year risk <10% using the ATP-III risk assessment tool, which incorporates age, gender, total and HDL-cholesterol levels, smoking, blood pressure, and treatment for hypertension into a multivariable equation to estimate 10-year risk for hard CHD (coronary death or non-fatal myocardial infarction)[7]. For the present study, high 10-year (short-term) risk was defined as 10-year risk ≥10% or presence of diabetes. Individuals with diabetes were treated as having a high 10-year risk as suggested by current ATP-III guidelines. Lifetime risk estimation was performed for 5 mutually exclusive strata of risk factor burden using our previously published algorithm6 where risk factors were classified as all optimal risk factors, ≥1 not-optimal risk factors, ≥1 elevated risk factors, 1 major risk factor or ≥ 2 major risk factors (Table 1).

Differences in baseline risk factors result in marked differences in remaining lifetime risk for CVD[6]. For example, a 50-year old man with “all optimal risk factors” has a lifetime risk for CVD of 5%. In contrast, a different 50-year old man with two major risk factors (i.e. untreated SBP 160 mmHg and total cholesterol of 250 mg/dL) has a lifetime risk for CVD of 69% despite a low 10-year risk. Based on these findings, we observed an apparent natural separation in lifetime risks based on these differences in risk factors and defined *a priori* “high predicted lifetime risk” as ≥ 39% and “low predicted lifetime risk” as < 39%. This threshold was also chosen a priori because of clinical relevance: individuals with a calculated lifetime risk ≥ 39% have at least one elevated risk factor that could be treated.

Using the above definitions, the study samples were first stratified into two groups: those with low predicted short-term risk (10-year risk < 10%) and those with high predicted short-term risk (10-year risk ≥ 10% *or* diabetes). The low predicted short-term risk group was then further stratified into two groups: low predicted lifetime risk and high predicted lifetime risk. This method of classification resulted in the formation of three mutually exclusive risk groups: low short-term/low lifetime predicted risk; low short-term/high lifetime predicted risk; and high predicted short-term risk.

Subclinical disease measures

In both CARDIA and MESA, CAC was measured using an electron-beam CT scanner18 or a multidetector CT system19 in accordance with standard protocols. Details of these techniques have been reported previously[20]. In CARDIA, CAC was measured both at Year 15 and at Year 20, with an average of 60 months between examinations. The prevalence of coronary calcium was treated as a categorical variable (CAC = 0 or CAC > 0) and as a continuous variable using the Agatston score for participants with CAC > 0[21]. Prior analyses in the CARDIA and MESA studies have demonstrated the presence or absence of CAC to be a reliable measure, with observed agreement of 96% in both studies20. Because of the challenges posed by the large number of zeros and skewed distribution for CAC change data, and because there is no consensus in the literature, we defined "CAC progression" *a priori* as follows. For those with CAC = 0 at baseline, progression was defined as CAC score > 0 at follow-up. For participants with 0 < CAC ≤ 100 at baseline, progression was defined as annualized change of ≥ 10 Agatston units at follow-up. For participants with CAC > 100 at baseline, progression was defined as annualized percent change (annualized change in CAC score divided by the baseline CAC score) greater than or equal to 10% at follow-up. This method allowed a categorical definition of CAC progression (progression vs. no progression). In MESA, CAC was measured at study entry. Follow-up examinations were performed in 50% of individuals at exam 2 and the remaining 50% at exam 3 with an average of 22 and 40 months between examinations, respectively. Similar methods were used to define CAC prevalence and progression. For both CARDIA and MESA, "annualized" refers to the difference between CAC score at baseline and follow-up divided by the number of years between examinations. Carotid IMT was measured at the Year 20 examination in CARDIA and at the baseline examination in MESA using high-resolution B-mode ultrasound in accordance with standard procedures[22]. Although the techniques were similar in CARDIA and MESA, there were minor differences in technique as reported previously23, 24.

Statistical Methods

In all analyses, the risk group functioned as the independent variable and the measure of atherosclerosis (i.e. CAC or IMT) as the dependent, or outcome variable. Due to potentially large differences in associations of CAC and carotid IMT with the risk groups by gender, all analyses were conducted separately for women and men. Baseline characteristics were computed for the 3 risk groups using general linear models for continuous variables and cross-tabulations (proportions) for categorical variables. The age-adjusted prevalence (percentage) rates of CAC>0 (or CAC progression) across the 3 risk groups were computed using general linear models with the binary variable of CAC>0 (or CAC progression) as the outcome, in which least square means of the binary outcome provided the percentages of CAC>0 (or CAC progression) for each risk group, adjusting for the age distribution within each risk group. Logistic regression was used to calculate age-adjusted odds ratios and 95% confidence intervals for each binary outcome across risk groups. Age-adjusted logistic regression was also used to test differences between the reference group (low short-term and low lifetime risk) and other risk groups (represented by the coefficient for the dummy variable of that group). Means for common and internal carotid IMT were computed using

general linear models with adjustment for age. Linear regression was used to test associations between each IMT outcome variable and the 3 risk groups (2 dummy variables, with low short-term and low lifetime risk category as the omitted reference group) with adjustment for age. All analyses were conducted using SAS statistical software (Version 9.1). The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

RESULTS

Baseline Characteristics

Baseline characteristics are shown for the three strata of classification for CARDIA (Table 2a) and MESA (Table 2b) participants, separately for men and women. The low predicted short-term risk group comprised a substantial proportion of the study sample (91% of the CARDIA cohort; 75% of the MESA cohort). Lifetime risk stratification further divided the low predicted short-term risk group into two approximately equal-sized groups: one with low and one with high predicted lifetime risk. For CARDIA, the low short-term/low lifetime predicted risk represented 48% of the total low predicted short-term risk group, and a similar pattern was observed in MESA. There were some racial differences noted in both the CARDIA and MESA cohorts across the classification scheme. Overall, the pattern of risk factor differences across the three groups was similar between the two cohorts with higher risk factor burden in individuals with low predicted short-term but high predicted lifetime risk. Although the mean 10-year risk was significantly higher ($p < 0.001$) for individuals classified as low short-term/high lifetime predicted risk compared to individuals classified as low short-term/low-lifetime predicted risk, the levels were far below treatment thresholds of 10% or 20% 10-year risk[7].

Baseline Subclinical Disease: Carotid IMT and Coronary Artery Calcium

For CARDIA participants with low short-term/high lifetime predicted risk, both the common carotid and the internal carotid IMT were greater when compared to the low short-term/low lifetime predicted risk group. The point estimates for MESA participants were similar though non-significant, with wider confidence intervals (Table 3). Similarly, in both CARDIA and MESA, CAC prevalence was higher in the low short-term/high lifetime predicted risk group compared to the low short-term/low lifetime predicted risk group (Table 4). When CAC was analyzed as a continuous variable (Agatston score in those with CAC>0), the findings were less consistent, particularly in women (see Table 4).

Progression of Coronary Artery Calcium

We noted a similar pattern of results for CAC progression. In CARDIA, CAC progression was higher in the low short-term/high lifetime predicted risk group when compared to the low short-term/low lifetime predicted risk group. The point estimates for MESA participants were similar though non-significant, with wider confidence intervals (Table 5). Of interest, we also observed a similar pattern of results for CAC progression using a variety of different measures, including CAC incidence and annualized CAC change scores (data not shown). When we compared the regression coefficients in both studies for baseline subclinical atherosclerosis (carotid-IMT and CAC prevalence) and progression of atherosclerosis (CAC change), we noted a similar effect size across the risk strata (Table 6).

Secondary Analyses

Because we classified all individuals with at least one major risk factor (current smoking, stage 2 or treated hypertension, or total cholesterol ≥ 240 mg/dL or treated) as having “high predicted lifetime risk”, we performed secondary analyses to determine whether our findings

were largely due to any single major risk factor. For example, we excluded all smokers from the analysis and compared atherosclerotic burden and progression between the 3 risk strata. Similar analyses were performed after excluding those with stage 2 hypertension or total cholesterol ≥ 240 mg/dL. In all cases, the pattern of results was nearly identical in both CARDIA and MESA men and women, suggesting that no individual risk factor alone determined our findings. In secondary analyses designed to examine whether our findings were consistent across race/ethnic groups, we performed the regressions in white and non-white participants in both the CARDIA and MESA samples separately. Likewise, we also examined the association of the present risk stratification method with CAC >100 as an outcome. Although our power was limited for these analyses, we observed an overall similar pattern of results for whites and non-whites, and for the endpoint of CAC>100 (data not shown).

DISCUSSION

There were several important findings in our study. First, among the relatively large group with low short-term risk (10-year risk ≤10%), two distinct, similarly-sized groups could be identified using our previously published algorithm[6] for lifetime risk stratification: one with high lifetime risk and one with low lifetime risk. Second, the low short-term/high lifetime risk group had a baseline burden of subclinical atherosclerosis that was significantly greater than the low short-term/low lifetime risk group. Third, the low short-term/high lifetime risk group had a rate of CAC progression that was also significantly higher than the low short-term/low lifetime risk group. Finally, in two distinct cohorts with different racial characteristics, we found a very similar pattern of results.

Clinical Implications

Even though more than 90% of individuals < 50 years have a low 10-year risk[4], prior data suggest that differences in risk factor burden translate into marked differences in CVD events across the remaining lifespan. Clinical practice guidelines [7–9] recognize the discordance between short-term and long-term risk, encouraging long-term risk estimation as a supplement to the 10-year risk window.

Consider a hypothetical case of a 50-year old woman with the following risk factors: total cholesterol 220 mg/dL, systolic blood pressure 130 mmHg, non-smoker, non-diabetic. Prior data suggest that in spite of a 10-year risk of 1%, her expected lifetime risk for CVD is 39%[25]. But what about now? Without any additional testing, we would predict she would have a greater burden and progression of subclinical atherosclerosis compared to a woman with an optimal cholesterol and blood pressure. These results suggest a potential benefit of aggressive prevention efforts for individuals < 50 years with low short-term but *high* lifetime predicted risk.

Throughout the lifespan, exposure to high risk factor levels promotes the accumulation of subclinical atherosclerosis[26]. In older adults, this accumulated atherosclerotic burden confers an increased risk for clinical CVD events[14, 15]. In younger adults, these risk factors will translate into CVD events, but typically only until much later in life [27, 28]. Thus, multiple risk factors in young adulthood (< 40 years) appear to promote greater subclinical atherosclerotic burden in middle-age (40–50 years), but the majority of clinical CVD events do not occur until older ages (> 65 years).

The converse is also true. Clinical CVD in individuals with low risk factor burden is rare[29, 6]. We have shown previously that an optimal risk factor profile at age 50 years is associated with a remaining lifetime risk for atherosclerotic CVD of approximately 5%[6], even in the face of a dramatically longer median survival The lower prevalence and progression of

subclinical disease we found in the present study is consistent with the virtual absence of clinical CVD events in these low-risk individuals.

Clinical Significance of Subclinical Atherosclerosis

The significant differences in subclinical atherosclerosis noted in the present study may provide a mechanistic explanation for the substantial differences in lifetime risk for CVD among individuals with differences in baseline risk factor burden[6, 30]. For example, among individuals age ≥65 years in the Cardiovascular Health Study, a difference of 0.20 mm for common carotid IMT was associated with approximately a 40% increase in risk for incident myocardial infarction and stroke[15]. In the present study of adults < 50 years, individuals with a low short-term/high lifetime predicted risk had a common carotid IMT that was approximately 0.05 mm greater than individuals with a low short-term/low lifetime predicted risk. Such a difference in baseline subclinical atherosclerosis in younger adults would likely translate into substantial differences in cumulative risk across the lifespan.

Limitations

Several limitations should be acknowledged. We applied a risk prediction algorithm derived from the Framingham Heart Study (exclusively Caucasian) to two separate, multi-ethnic samples. Although this might have influenced our results, prior literature suggests risk factors in isolation[31] and in aggregate32 provide reliable estimates of CVD burden across ethnicities. For example, we recently demonstrated the similarity of lifetime risk estimates for CVD in blacks and whites33, providing further justification for using a similar stratification method for whites and non-whites.

Second, the group with low short-term but high lifetime predicted risk had slightly higher risk factor burden and 10-year risk. Nevertheless, these levels are *far* below current treatment thresholds, underscoring the importance of long-term risk estimation emphasized by current clinical guidelines[7–9]. Finally, there were mild differences in techniques used to measure IMT in the two cohorts[23, 24]. In spite of these differences in technique, we observed a pattern of results that was remarkably similar.

Conclusions

In summary, in the present study we found that individuals with low short-term but high lifetime predicted risk had a subclinical disease burden that was intermediate between individuals with low short-term/low lifetime predicted risk and those individuals with high short-term predicted risk. In addition, we also found that the rate of progression of subclinical disease was greater in this group, although the clinical significance of this measure of CAC progression remains unknown. Nevertheless, these findings taken together provide a mechanistic explanation for the marked differences in lifetime risk across different strata of risk factors and may have potential clinical and public health implications.

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Table 1

Risk Factor Stratification* and Predicted Lifetime Risks for the 5 Strata

	"Low Predicted Lifetime Risk"		"High Predicted Lifetime Risk"		
	All Optimal RF	**≥1 Not Optimal RF**	**≥1 Elevated RF**	**1 Major RF**	**≥2 Major RF**
Systolic/Diastolic (mmHg)	< 120/80	120–139/80–89	140–159/90–99	≥160 ≥100 (or treated)	≥160 ≥100 (or treated)
Total Cholesterol (mg/dL)	< 180	180–199	200–239	≥240 (or treated)	≥240 (or treated)
Diabetes†	--	--	--	--	--
Smoking	No	No	No	Yes	Yes
Predicted Lifetime Risk (Men)	5%	36%	46%	50%	69%
Predicted Lifetime Risk (Women)	8%	27%	39%	39%	50%

*Risk factor stratification derived from Lloyd-Jones, et al.[6]

†Diabetes was included in the original published stratification. Because all diabetics were considered to have "high short-term risk", this risk factor was not included in the present paper (see Methods section).

Table 2

Table 2a. Baseline (Year 15) Characteristics among Participants Age 32–47 at Year 15 in the CARDIA Study According to Gender and Risk Group Strata

	Men (N=1367)			Women (N=1621)		
	Low short-term and Low lifetime risk	Low short-term and High lifetime risk	High short-term risk	Low short-term and Low lifetime risk	Low short-term and High lifetime risk	High short-term risk
	N=543	N=704	N=120	N=808	N=770	N=43
Age, y	40.0 (3.6)	40.2 (3.5)	41.6 (3.4)	40.1 (3.6)	40.6 (3.6)	41.3 (2.9)
African American, %	36.8	45.2	40.8	40.6	54.2	74.4
SBP, mmHg	111.3 (9.7)	117.2 (15.1)	122.1 (15.8)	106.7 (10.6)	115.4 (17.2)	123.9 (19.5)
Total cholesterol, mg/dL	168.8 (21.0)	198.7 (38.2)	223.5 (49.2)	166.0 (19.8)	197.7 (33.7)	196.4 (43.3)
HDL cholesterol, mg/dL	45.2 (12.6)	45.8 (12.8)	39.6 (10.9)	55.6 (12.9)	55.0 (15.4)	48.0 (14.6)
Body mass index, kg/m^2	27.4 (4.4)	28.2 (5.0)	30.2 (5.7)	27.6 (6.7)	30.1 (7.4)	33.1 (5.6)
Current smokers, %	0.0	30.4	71.7	0.0	38.8	41.9
Diabetes, %	0.0	0.0	26.7	0.0	0.0	88.4
Lipid-lowering therapy, %	0.0	3.1	6.7	0.0	1.2	13.9
Antihypertensive therapy, %	0.0	11.1	17.5	0.0	13.9	39.5
Framingham 10-year risk, %	1.1	2.7	10.9	<1.0	1.0	2.2

Table 2b. Baseline Characteristics among Participants Age 44–50 in the MESA Study According to Gender and Risk Group Strata

	Men (N=508)			Women (N=568)		
	Low short-term and Low lifetime risk	Low short-term and High lifetime risk	High short-term risk	Low short-term and Low lifetime risk	Low short-term and High lifetime risk	High short-term risk
	N=168	N=220	N=120	N=242	N=289	N=37
Age, y	47.6 (1.8)	47.4 (1.7)	47.7 (1.6)	47.3 (1.7)	47.5 (1.8)	47.5 (1.7)
Race, %						
White	32.7	37.3	32.5	36.8	38.1	16.2
Chinese	16.7	8.6	4.2	18.6	7.6	8.1
African American	25.6	25.9	27.5	20.7	29.8	40.5
Hispanic	25.0	28.2	35.8	24.0	24.5	35.2
SBP, mmHg	112.6 (10.0)	119.8 (15.4)	119.2 (17.0)	106.2 (12.4)	115.6 (17.5)	124.3 (19.2)
Total cholesterol, mg/dL	172.1 (20.0)	203.0 (35.4)	200.9 (33.6)	171.1 (20.6)	203.6 (37.1)	195.0 (40.1)

Table 2b. Baseline Characteristics among Participants Age 44–50 in the MESA Study According to Gender and Risk Group Strata

	Men (N=508)			Women (N=568)		
	Low short-term and Low lifetime risk	Low short-term and High lifetime risk	High short-term risk	Low short-term and Low lifetime risk	Low short-term and High lifetime risk	High short-term risk
	N=168	N=220	N=120	N=242	N=289	N=37
HDL cholesterol, mg/dL	44.4 (10.0)	45.1 (10.8)	39.4 (10.1)	53.7 (13.2)	54.3 (14.0)	46.4 (11.1)
Body mass index, kg/m^2	27.2 (4.1)	28.4 (4.5)	29.3 (4.6)	27.5 (6.2)	29.4 (7.0)	34.0 (7.5)
Current smokers, %	0.0	13.6	69.2	0.0	30.4	18.9
Diabetes, %	0.0	0.0	28.3	0.0	0.0	86.5
Lipid-lowering therapy, %	0.0	11.4	5.8	0.0	5.2	13.5
Antihypertensive therapy, %	0.0	20.9	16.7	0.0	21.8	45.9
Framingham 10-year risk, %	3.1	5.3	12.3	<1.0	1.5	2.8

For continuous variables, values are mean (SD).

SBP: systolic blood pressure; HDL: high density lipoprotein

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Table 3

Age-adjusted Carotid Intima-Media Thickness (IMT) among Year 20 CARDIA (age 37–50) and Baseline MESA (age 44–50) Participants According to Gender and Risk Group Strata

	Men			Women		
	Low short-term risk/ Low lifetime risk	Low short-term risk/High lifetime risk	High short-term risk	Low short-term risk/ Low lifetime risk	Low short-term risk/High lifetime risk	High short-term risk
CARDIA						
Common Carotid IMT, N	476	673	191	746	903	105
Adjusted Mean, mm (SE)	0.80 (0.01)	0.83 (0.01)*	0.86 (0.01) *	0.75 (0.01)	0.79 (0.01) *	0.86 (0.01) *
Internal Carotid IMT, N	456	636	178	716	839	91
Adjusted Mean, mm (SE)	0.80 (0.01)	0.85 (0.01) *	0.88 (0.02) *	0.76 (0.01)	0.80 (0.01) *	0.82 (0.02) †
MESA						
Common Carotid IMT, N	165	218	120	242	283	37
Adjusted Mean, mm (SE)	0.75 (0.01)	0.78 (0.01)	0.82 (0.01) *	0.71 (0.01)	0.73 (0.01)	0.81 (0.02) *
Internal Carotid IMT, N	164	214	119	236	278	36
Adjusted Mean, mm (SE)	0.83 (0.03)	0.88 (0.02)	0.94 (0.03) †	0.73 (0.02)	0.76 (0.02)	0.90 (0.05) *

*P<0.001,

†P<0.01 compared with the referent group (Low short-term risk and Low lifetime risk).

Table 4

Age-adjusted Coronary Artery Calcified Plaque (CAC) Score and Prevalence of CAC Score >0 among Year 15 CARDIA (age 32–47) and Baseline MESA (age 44–50) Participants According to Gender and Risk Group Strata

	Men			Women		
	Low short-term risk/ Low lifetime risk	**Low short-term risk/ High lifetime risk**	**High short-term risk**	**Low short-term risk/ Low lifetime risk**	**Low short-term risk/ High lifetime risk**	**High short-term risk**
			CARDIA			
Age-adjusted baseline CAC Prevalence, % (CAC positive/Total)	9.8 (50/543)	16.7* (117/704)	26.9* (36/120)	2.3 (18/808)	7.1 * (55/770)	20.6 * (9/43)
Baseline CAC (Agatston) Score Adjusted Mean (SE)	6.8 (5.2)	12.9 (4.6)	50.7* (11.2)	1.7 (0.9)	3.3 (0.9)	19.5 * (3.7)
			MESA			
Age-adjusted baseline CAC Prevalence, % (CAC positive/Total)	21.3 (36/168)	30.4‡ (66/220)	45.3* (55/120)	5.8 (14/242)	13.5† (39/289)	24.3* (9/37)
Baseline CAC (Agatston) Score Adjusted Mean (SE)	13.5 (12.1)	31.4 (10.6)	86.6* (14.4)	2.80 (1.85)	5.09 (1.69)	7.44(4.72)

*P<0.001,

†P<0.01,

‡P<0.05 compared with the referent group (Low short-term risk and Low lifetime risk).

Table 5

Age-adjusted Annualized Coronary Artery Calcified Plaque (CAC) Progression among CARDIA (age 32–47) and MESA (age 44–50) Participants According to Gender and Risk Group Strata

	Men			Women		
	Low short-term risk/Low lifetime risk	**Low short-term risk/High lifetime risk**	**High short-term risk**	**Low short-term risk/ Low lifetime risk**	**Low short-term risk/High lifetime risk**	**High short-term risk**
			CARDIA			
CAC Progression (%) (N/Total)	15.4 (67/446)	22.3† (121/545)	36.6* (35/90)	5.3 (36/683)	8.7† (56/641)	23.7* (8/33)
			MESA			
CAC Progression (%) (N/Total)	13.4 (19/142)	21.6‡ (42/195)	37.1* (39/105)	6.9 (15/217)	10.1 (25/249)	22.6* (7/31)

*P<0.001,

†P<0.01,

‡P<0.05 compared with the referent group (Low short-term risk and Low lifetime risk).

Table 6

Age-adjusted Linear Regression Coefficients (Carotid IMT) and Age-adjusted Odds Ratios (CAC Prevalence and CAC Progression) for MESA and CARDIA Participants

	Men			Women		
	Low short-term risk/Low lifetime risk	**Low short-term risk/High lifetime risk**	**High short-term risk**	**Low short-term risk/Low lifetime risk**	**Low short-term risk/High lifetime risk**	**High short-term risk**
			CARDIA			
Common Carotid IMT β (SE)	Referent	0.033 * (0.01)	0.063 * (0.01)	Referent	0.046 * (0.01)	0.111 * (0.01)
Internal Carotid IMT β (SE)	Referent	0.058 * (0.01)	0.083 * (0.02)	Referent	0.041 * (0.01)	0.060 † (0.02)
CAC Prevalence OR (95% CI)	Referent	1.94 (1.35 to 2.78) *	3.30 (1.99 to 5.46) *	Referent	3.25 (1.89 to 5.59) *	10.7 (4.47 to 25.7) *
CAC Progression OR (95% CI)	Referent	1.60 (1.15 to 2.24) †	3.13 (1.88 to 5.19) *	Referent	1.68 (1.09 to 2.59) †	5. 35 (2.23 to 1278) *
			MESA			
Common Carotid IMT β (SE)	Referent	0.028 (0.02)	0.070 * (0.02)	Referent	0.022 ‡ (0.01)	0.099 * (0.02)
Internal Carotid IMT β (SE)	Referent	0.049 (0.03)	0.113† (0.04)	Referent	0.037 (0.02)	0.169 * (0.05)
CAC Prevalence OR (95% CI)	Referent	1.62 (1.01 to 2.60) ‡	3.10 (1.85 to 5.20) *	Referent	2.53 (1.34 to 4.79) †	5.22 (2.07 to 13.2) *
CAC Progression OR (95% CI)	Referent	1.78 (0.99 to 3.22)	3.81 (2.04 to 7.11) *	Referent	1.52 (0.78 to 2.97)	3.98 (1.47 to 10.7) *

*P<0.001,

†P<0.01,

‡P<0.05 compared with the referent group (Low short-term risk and Low lifetime risk).