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Relationship of Change in Traditional Cardiometabolic Risk Factors to Change in Coronary Artery Calcification Among Individuals with Detectable Subclinical Atherosclerosis: The Multi-Ethnic Study of Atherosclerosis

William Arguelles, Ph.D.¹, Maria M. Llabre, Ph.D.¹, Frank J. Penedo, Ph.D.¹, Martha L. Daviglus, M.D., Ph.D.^{3,4}, Ralph L. Sacco, M.D.², Kiang Liu, Ph.D.³, Moyses Szklo, M.D., M.P.H., Dr.Ph⁵, Joseph F. Polak, M.D., M.P.H.⁶, John Eng, M.D.⁷, Gregory L. Burke, M.D., M.Sc.⁸, and Neil Schneiderman, Ph.D.¹

¹Department of Psychology, University of Miami; This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

²Department of Neurology, University of Miami Miller School of Medicine; This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

³Department of Preventive Medicine, Northwestern University Feinberg School of Medicine; This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

⁴Department of Medicine, University of Illinois at Chicago; This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

⁵Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health; This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

⁶Radiology, Tufts University School of Medicine; This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

⁷Department of Radiology and Radiological Science, Johns Hopkins University School of Medicine; This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

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Address for correspondence: William Arguelles, PhD, Department of Psychology, University of Miami, Clinical Research Building, 1120 NW 14th Street, 15th Floor (Room 1515), Miami, FL 33136, Phone: (305) 284-2519, Fax: (305) 243-2055, warguelles@psy.miami.edu.

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⁸Division of Public Health Sciences, Wake Forest School of Medicine; This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

Abstract

Background/Objectives—Data describing relationships between change in risk factors and coronary artery calcification (CAC) are lacking and could inform optimal cardiovascular disease prevention and treatment strategies. This study aimed to examine how change in traditional cardiometabolic risk factors related to change in CAC among individuals with detectable subclinical atherosclerosis.

Methods—Latent growth modeling was used to examine change in cardiometabolic risk factors (waist circumference, body mass index, systolic and diastolic blood pressure, high- and low-density lipoprotein cholesterol, triglycerides, and glucose) related to change in CAC up to an average 4.9-year follow-up in a multi-ethnic cohort of 3,398 asymptomatic individuals (57.8% men) who had detectable CAC (score > 0) at baseline, adjusting for baseline risk factor levels and CAC values, age, gender, race/ethnicity, smoking, family history of CVD, income, and use of antihypertensive, lipid-lowering, and glucose-lowering medications.

Results—Greater declines in blood pressure (systolic and diastolic) and low-density lipoprotein cholesterol at follow-up were each associated with greater CAC progression. The observed inverse associations were attributable to greater CAC progression in participants taking antihypertensive and lipid-lowering drugs who, as expected, had declines in blood pressure and lipid levels, respectively. These inverse associations did not emerge in participants not taking these medications.

Conclusions—Among individuals with subclinical atherosclerosis, the unexpected inverse associations observed between change in blood pressure and lipid levels with CAC progression emphasize the importance of considering medication use, and, when feasible, the severity and duration of disease, in exploring associations between risk factors and CAC change.

Keywords

risk factors; coronary artery calcification; atherosclerosis

Introduction

An emerging body of research aims to elucidate how risk factors influence the progression of subclinical cardiovascular disease (CVD) markers such as coronary artery calcification (CAC). Although some studies have found no association between change in cholesterol following lipid-lowering therapy and CAC progression, what is usually reported is the relationship of baseline risk factor levels to CAC change(1–3). Thus, it remains unclear how changes in other risk factors impact CAC.

Using data from the Multi-Ethnic Study of Atherosclerosis (MESA), we examined how change in various traditional cardiometabolic risk factors (waist circumference, body mass index, systolic and diastolic blood pressure, high-density and low-density lipoprotein

cholesterol, triglycerides, and glucose) related to change in CAC up to an average 4.9-year follow-up among individuals with detectable CAC at baseline. We hypothesized that increases in risk factor levels (decreases in high-density lipoprotein cholesterol) would be associated with greater CAC progression.

Methods

Study Sample

MESA is a cohort study of the prevalence, correlates, and progression of subclinical CVD. At baseline, participants of both genders were ages 45 through 84 years, free of clinical CVD, and self-reported being either white, black, Hispanic, or Chinese. Participants were recruited across 6 US communities. A detailed description of the study design and methods has been previously published(4). The institutional review board at each site approved the study protocol and all participants gave informed consent.

Measurement of Cardiometabolic Risk Factors

Height and weight were measured to the nearest 0.1 cm and 0.5 kg, respectively. Body mass index (BMI) was calculated as kg/m². Waist circumference (WC) was measured at the umbilicus to the nearest 0.1 cm. After 5 minutes in the seated position, systolic (SBP) and diastolic blood pressure (DBP) were measured 3 times in the right arm using an automated oscillometric method (Dinamap); the average of the second and third readings was used in analyses. Blood samples were collected and analyzed for high-density (HDL-C) and low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), and glucose. All participants received a baseline and 3 follow-up clinic examinations, with mean intervals of 1.6, 3.2, and 4.8 years following their baseline examination.

Measurement of CAC

CAC was measured with an electron-beam computed tomography (EBCT) scanner (Imatron C-150, Imatron) at 3 study sites and with a multidetector row helical computed tomography (MDCT) scanner (Lightspeed, General Electric or Siemens, Volume Zoom) at 3 study sites. A detailed description of the methods used to acquire and interpret scans has been previously published(5). Participants received two consecutive scans performed over radiographic phantoms containing identical and known calcium concentrations used to calibrate CAC measurements. Scans were read blindly with respect to scan pairs and other participant data by a cardiologist at a centralized reading center (Harbor-UCLA Research and Education Institute) using a computer interactive scoring system similar to that previously described by Yaghoubi et al(6). Calcium was quantified using the Agatston scoring method(7). Scores from both scans were averaged. CAC presence was defined as an average score > 0. Interobserver and intraobserver κ -statistics were, respectively, 0.90 and 0.93 for CAC presence. The intraclass correlation coefficient for between-reader Agatston score was 0.99.

All participants received a baseline and one follow-up CAC examination. A randomly selected half of the cohort (n = 2,953) received their follow-up exam a mean of 1.6 years after the baseline exam (during the first follow-up clinic exam), and the other half (n =

2,805) received their follow-up exam a mean of 3.2 years after the baseline exam (during the second follow-up clinic exam). In addition, a randomly selected one-fourth of the cohort (n = 1,406) received a second follow-up exam a mean of 4.9 years after the baseline exam (during the third follow-up clinic exam).

Measurement of Covariates

Information on age, gender, race/ethnicity, smoking, family history of CVD, socioeconomic status, and medication use was collected using standardized questionnaires. Participants were asked to bring medication containers used during the 2 weeks prior to their baseline clinic visit; interviewers recorded each medication name. Age was treated as a continuous variable. Race/ethnicity was categorized as white, black, Hispanic, or Chinese. Smoking at baseline was classified as former, current, or never. History of myocardial infarction in parents, siblings, or children was examined as a dichotomous variable. Total gross family income was used as an indicator of socioeconomic status, with the following 13 categories: < \$5,000; \$5,000 to \$7,999; \$8,000 to \$11,999; \$12,000 to \$15,999; \$16,000 to \$19,999; \$20,000 to \$24,999; \$25,000 to \$29,999; \$30,000 to \$34,999; \$35,000 to \$39,999; \$40,000 to \$49,999; \$50,000 to \$74,999; \$75,000 to \$99,999; and \$100,000. Use of antihypertensive, lipid-lowering, and glucose-lowering medications was examined as a dichotomous variable at each exam time point.

Statistical Analyses

Change in each risk factor and in CAC was examined using latent growth modeling. Detailed descriptions of this longitudinal analytic method have been previously published(8,9). A random effects approach that incorporated time as a variable to reflect individually varying times of observations across repeated measurements was utilized. Raw variable scores were analyzed since conventional log transformations are inappropriate for modeling change. Residual variances of corresponding variables were assumed to be equal across all time points. Change in each variable was described in terms of mean baseline level (intercept) and mean annual rate of change (slope), as well as variability across participants.

Change in each risk factor was then related to change in CAC in separate models by regressing the CAC slope on the risk factor slope, controlling for the baseline risk factor level. Three models were examined. Model 1 examined the univariate association. Model 2 adjusted for age, gender, race/ethnicity, smoking, family history of CVD, income, and the time-varying use of antihypertensive, lipid-lowering, and glucose-lowering medications.¹ Model 3 further adjusted for baseline CAC level.

Analyses were conducted using Mplus software (version 5)(10). Missing data were handled using full information maximum likelihood (FIML) estimation(11). By study design, one-fourth of the entire MESA cohort received three CAC examinations. Given that this subgroup was randomly selected, missing data on the third CAC examination for the

¹This was done by simultaneously regressing each of the 3 follow-up CAC exam scores on corresponding medication use data at those times. Medication associations with CAC were assumed equal across all time points.

remainder of the cohort are considered missing completely at random. Using FIML under this assumption has been shown to provide unbiased parameter estimates(11,12).

Results

In MESA, 3,398 participants had detectable CAC at baseline and were included in analyses. Table 1 presents the sample's baseline demographic, risk factor, and CAC information. Given our aim was to examine individuals who already had detectable subclinical disease at baseline (given their at-risk status as well as allowing for the modeling of progression as opposed to incidence), those with undetectable CAC at baseline ($n = 3,416$) were excluded from these analyses. Among these excluded individuals, change in risk factors was not associated with incident CAC (data not shown).

Table 2 presents the intercept (mean baseline level and standard deviation) and slope (mean annual rate of change and standard deviation) estimates for each risk factor and CAC. Significant variability in both baseline level and rate of change was observed for all variables. On average, WC (0.08 cm per year), HDL-C (0.33 mg/dL per year), glucose (0.54 mg/dL per year), and CAC (53.92 units per year) increased over time, whereas BMI (-0.02 units per year), SBP (-0.77 mm Hg per year), DBP (-0.61 mm Hg per year), LDL-C (-2.44 mg/dL per year), and TG (-1.89 mg/dL per year) decreased over time. Significant inverse correlations between baseline level and rate of change were observed for SBP, DBP, LDL-C, and glucose, suggesting that higher initial level was associated with greater decline or lower rate of increase in these risk factors. Baseline CAC level was significantly and positively correlated with CAC change, indicating that CAC progressed more rapidly among individuals with higher initial levels.

Table 3 presents the associations between change in each risk factor and change in CAC. In univariate models, changes in SBP, DBP, LDL-C, and TG were significantly and inversely associated with CAC progression. Changes in SBP, DBP, and LDL-C – but not TG – remained significantly associated with change in CAC after multiple adjustment, including baseline CAC level. No significant associations between changes in WC, BMI, HDL-C, or glucose and CAC progression were observed².

Post-hoc Analyses

Post-hoc analyses were conducted to explore whether the observed inverse association between changes in SBP, DBP, and LDL-C and CAC progression were moderated by medication use. Individuals never taking either antihypertensive ($n = 868$) or lipid-lowering medication ($n = 1,305$), depending on the risk factor being examined, were studied separately from individuals on medications at all exam time-points ($n = 987$ for antihypertensive medication use and $n = 411$ for lipid-lowering medication use). The specific medications used by analyzed individuals taking antihypertensive medication included: ACE inhibitors (36.5%), Thiazide diuretics (30.7%), beta blockers (26.4%), angiotensin type 2 antagonists (15.7%), amlodipine (15.5%), nifedipine (5.9%),

²Similar patterns were observed in men and women when analyzed separately. However, due to the complexity of the models, formal tests of gender interactions were not performed.

dihydropyridines other than nifedipine or amlodipine (2.5%), vasodilators (13.6%), diltiazem (4.6%), potassium-sparing agents alone (1.2%), and loop diuretics (5.3%). The specific medications used by analyzed individuals taking lipid-lowering medication included: statins (92.0%), fibrates (7.5%), niacin and nicotinic acid (3.9%), and bile-acid sequestrants (2.7%).

Table 4 presents the risk factor and CAC change estimates for these groups. Compared to individuals not taking medication, individuals taking antihypertensive or lipid-lowering medication 1) had higher mean baseline levels of SBP and DBP, and lower mean baseline levels of LDL-C, respectively, 2) showed significant decline over time in SBP, DBP, and LDL-C (as opposed to the average increase or non-significant change in the risk factors observed among individuals not taking medication), 3) showed significant inverse correlations between baseline level and change in these risk factors (as opposed to non-significant correlations among individuals not taking medication), 4) had higher mean baseline CAC levels, and 5) had higher mean rate of CAC progression.

Table 5 presents the associations between change in the risk factors and change in CAC for these groups, adjusting for covariates and baseline CAC. Among individuals not taking respective medications, changes in SBP, DBP, or LDL-C were not significantly associated with change in CAC. However, among individuals taking antihypertensive medication, change in SBP remained significantly and inversely associated with CAC progression. The association between change in DBP or LDL-C and CAC progression among individuals taking respective medications was no longer statistically significant. It should be noted that the consequent decrease in sample size for these post-hoc analyses might have decreased power to detect significant associations.

Discussion

In MESA participants who had detectable CAC at baseline, WC, HDL-C, and glucose increased over a mean follow-up of up to 4.9 years, whereas BMI, SBP, DBP, LDL-C, and TG decreased³. Observed decreases in some of these risk factors was seemingly due to antihypertensive and lipid-lowering treatment. The WC increase and the BMI decrease may possibly be due to muscle mass loss in this sample of older persons. CAC increased on average by approximately 54 Agatston units per year. Consistent with prior studies, higher CAC at baseline was associated with greater progression(13).

Contrary to hypotheses, greater declines in SBP, DBP, and LDL-C were associated with greater CAC progression controlling for covariates and baseline CAC. These initially counterintuitive findings became more comprehensible after stratification by medication use.

Individuals taking medication targeting SBP, DBP, or LDL-C showed significant decreases in these risk factors, with greater declines occurring in those with higher initial level, whereas individuals not taking medication showed average increases or no change in the risk

³Insulin was not included in this study because it was collected only at baseline, and was not reassessed in follow-up examinations.

factors over the study period. Individuals on medication also had higher baseline CAC and greater CAC progression than those not taking medication. Moreover, the observed inverse associations between changes in SBP, DBP, or LDL-C and CAC progression were stronger in participants on medication.

Results suggest that individuals on medication, and thus likely to have a greater and longer history of underlying pathology, may continue to exhibit increased CAC progression despite showing decline in risk factor level(14). Of note, our analyses only examined persons who were either on or off medication throughout the entire study period, and excluded those who may have been prescribed or taken off medication during this time. Our findings are consistent with a recently published study showing no association between longitudinal change in cholesterol level and CAC progression over a median of 5.6 years among individuals receiving and not receiving statin/fibrate treatment, as well as two clinical trials reporting no association of statin treatment with CAC progression amidst decline or stabilization of cholesterol level(1–3). Prospective studies examining how pharmacological treatment of other cardiometabolic risk factors impact CAC progression are lacking. Additionally, we did not further stratify individuals by specific types of medication (e.g., ACE inhibitors vs. beta blockers) or by combinations of medications (e.g., individuals taking both antihypertensive and lipid-lowering drugs) to assess potential differences in changes in risk factors and CAC, or their relationship. Given previous reports of interactive effects between combinations of specific medications on CHD events, this area warrants further investigation in future studies(15).

In our study, risk factor changes related to CAC progression were controlled for baseline risk factor levels. It is possible that previous change in risk factors already manifested at baseline were also controlled. However, post-hoc analyses conducted on a select number of variables (data not shown) showed that change associations were not substantially influenced upon the removal of baseline risk factor level from the model.

Several hypotheses may be postulated to further explain our results. For example, change in risk factors may influence CAC in a time-lagged, as opposed to directly parallel fashion, and a 4.9-year period may not have been sufficient to detect these effects. It is also premature to assume that changes in different risk factors influence CAC in a similar temporal manner, given that these variables may affect the calcification process via diverse mechanisms. Additionally, risk factors may progress/regress differently across different stages of their pathology, and their influence on CAC progression may be obscured when simultaneously examining heterogeneous samples of individuals (i.e., in terms of age, risk profiles, medication use, etc.). Moreover, risk factor level may be restricted by physiological ceiling or treatment, and may thus not change or even regress over time despite being otherwise elevated and possibly associated with CAC increase. Lastly, the supposition that changes in risk factors do not greatly influence CAC should not be discounted. Although previous studies have shown associations between baseline risk factor levels and CAC progression, multivariate models have explained very little of the variability in progression(14). Another hypothesis is that risk factors primarily influence the initiation of plaque development rather than its progression. The fact that CAC has been shown to add incremental value in

predicting CVD events above and beyond traditional risk factors suggest that these processes are somewhat independent(16–18).

Limitations of our study include potential variability in CAC measures due to technical and non-physiological factors. Persons with clinical CVD were excluded from MESA and individuals who had undetectable CAC at baseline were not analyzed, thus limiting generalizability. Lastly, multiple statistical models were tested in this study, and the overall error rate was not controlled. While the examination of change in risk factors and CAC related to clinical events was beyond the scope of this paper, the positive association between CAC progression and incident coronary heart disease events in the MESA cohort has been previously published(19). Future investigations examining how change in risk factors relate to clinical events, in addition to subclinical processes, may help us better understand the pathophysiology of CVD.

Strengths of MESA include a large sample size, a community-based recruitment approach, prospective data collection using standardized procedures, and representation of both genders as well as different racial/ethnic groups. Additionally, latent growth modeling in the current study allowed controlling for measurement error and medication use across time. Although racial/ethnic groups were not examined separately in our study, race/ethnicity was included as a covariate and no race/ethnic differences (relative to whites) in CAC progression rate were observed after covariate adjustment. However, whether different racial/ethnic groups exhibit differential associations between change in risk factors and CAC progression was not addressed.

To our knowledge, this study is the first to systematically report on rate of change in multiple cardiometabolic risk factors related to CAC progression. Medication use that lowered initially high blood pressure and lipid levels but not higher rates of CAC progression likely explained the inverse relationships observed between risk factor change and CAC change. To date, little is known regarding CAC pathogenesis and associated risk factors. Given the significant and continued burden posed by atherosclerotic disease in our society, continued research aimed at further elucidating how risk factor changes over time relate to subclinical disease progression – which precedes irreversible clinical events – may help identify important targets for therapies.

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Table 1

Baseline Demographic, Cardiometabolic Risk Factor, and Coronary Artery Calcification Information for Individuals who had Detectable CAC at Baseline.

Variable	N = 3,398	
	Mean or Percentage	Standard Deviation
Age	66.4	9.5
Gender		
Male	57.8%	----
Female	42.2%	----
Race/ethnicity		
White	44.0%	----
Black	24.2%	----
Hispanic	20.0%	----
Chinese	11.9%	----
Family history of CVD	45.1%	----
Income		
< \$20K	26.9%	----
\$20K to < \$40K	26.5%	----
\$40K to < \$75K	25.2%	----
\$75K	21.3%	----
Smoking		
Never	44.6%	----
Former	42.5%	----
Current	12.9%	----
Antihypertensive medications	45.7%	----
Lipid-lowering medications	21.8%	----
Glucose-lowering medications	11.0%	----
Body mass index (kg/m ²)	28.4	5.3
Waist circumference (cm)	99.7	13.9
Systolic blood pressure (mm Hg)	130.8	21.7
Diastolic blood pressure (mm Hg)	72.6	10.2
HDL cholesterol (mg/dL)	49.4	14.5
LDL cholesterol (mg/dL)	118.4	32.2
Triglycerides (mg/dL)	136.4	92.3
Glucose (mg/dL)	100.6	33.1
CAC score (Agatston units)	292.9	553.2

Abbreviations: CAC, coronary artery calcification; CVD, cardiovascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 2Cardiometabolic Risk Factor and Coronary Artery Calcification Rate of Change Estimates.^{**}

Risk Factor	N = 3,398		
	Baseline Mean (Standard Deviation)	Change Mean (Standard Deviation)	Standardized Baseline and Change Correlation
WC (cm)	99.53 (13.36)	0.08* (0.85*)	−0.01
BMI (kg/m ²)	28.36 (5.22)	−0.02* (0.33*)	−0.03
SBP (mm Hg)	130.31 (17.58)	−0.77* (2.36*)	−0.37*
DBP (mm Hg)	72.27 (8.55)	−0.61* (1.09*)	−0.33*
HDL-C (mg/dL)	49.50 (13.41)	0.33* (1.01*)	0.01
LDL-C (mg/dL)	117.41 (26.43)	−2.44* (4.51*)	−0.29*
TG (mg/dL)	136.85 (73.31)	−1.89* (11.62*)	−0.35
Glucose (mg/dL)	100.92 (28.50)	0.54* (3.40*)	−0.52*
CAC (Agatston units)	290.48 (553.24)	53.92* (83.29*)	0.74*

Abbreviations: CAC, coronary artery calcification; WC, waist circumference; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.

*
p < .05

**
Analyses not stratified by antihypertensive, lipid-lowering, or glucose-lowering medication use.

Unstandardized Path Estimates Associating Rate of Change in Each Cardiometabolic Risk Factor and Rate of Change in Coronary Artery Calcification.^{††}

Table 3

N = 3,398						
Risk Factor	Model 1		Model 2		Model 3	
	Path Estimate (Beta)	p	Path Estimate (Beta)	p	Path Estimate (Beta)	p
WC	1.06	0.673	5.93	0.181	5.93	0.181
BMI	-1.11	0.864	3.26	0.658	3.26	0.658
SBP	-3.09	0.018	-4.25	0.009	-4.25	0.009
DBP	-10.01	<0.001	-14.65	<0.001	-14.65	<0.001
HDL-C	-3.11	0.243	-9.65	0.326	-9.63	0.325
LDL-C	-2.18	<0.001	-2.31	<0.001	-2.31	<0.001
TG	-0.42	0.012	-0.58	0.057	-0.58	0.057
Glucose	-0.54	0.632	-0.35	0.798	-0.35	0.798

Abbreviations: CAC, coronary artery calcification; WC, waist circumference; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.

^{††} Analyses not stratified by antihypertensive, lipid-lowering, or glucose-lowering medication use.

Systolic Blood Pressure, Diastolic Blood Pressure, Low-Density Lipoprotein Cholesterol, and Coronary Artery Calcification Rate of Change Estimates Stratified by Antihypertensive and Lipid-Lowering Medication Use.^{††}

Table 4

Variable	Taking Antihypertensive Medication				Taking Lipid-Lowering Medication			
	Yes (n = 987)		No (n = 868)		Yes (n = 411)		No (n = 1305)	
	Baseline Mean (Standard Deviation)	Change Mean (Standard Deviation)	Standardized Baseline and Change Correlation	Baseline Mean (Standard Deviation)	Change Mean (Standard Deviation)	Standardized Baseline and Change Correlation	Baseline Mean (Standard Deviation)	Change Mean (Standard Deviation)
SBP	134.91 (15.97)	-0.99* (2.37*)	-0.23*	118.57 (13.10)	0.59* (1.64*)	0.08		
DBP	72.52 (8.53)	-0.74* (1.09*)	-0.33*	70.05 (7.80)	-0.06 (0.78*)	-0.09		
LDL-C	---	---	---	---	---	---	116.31 (25.71)	-0.17 (2.47*)
CAC	327.00 (564.92)	64.50* (93.57*)	0.76*	187.57 (388.33)	30.58* (39.76*)	0.71*	207.03 (25.71)	38.55* (2.47*)

Abbreviations: CAC, coronary artery calcification; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol.

* $p < .05$

^{††} The sample sizes reported in this table represent individuals who had available data on medication use at all exam time-points and who were either consistently taking or consistently not taking respective medications throughout the entire study exam period, and thus do not sum up to the total sample of individuals who had detectable CAC at baseline (i.e., individuals that either had missing data on medication use or who may have been prescribed or taken off respective medications during the study period were not included).

Table 5

Unstandardized Path Estimates Associating Rates of Change in Systolic Blood Pressure, Diastolic Blood Pressure, and Low-Density Lipoprotein Cholesterol and Rate of Change in Coronary Artery Calcification Stratified by Antihypertensive and Lipid-Lowering Medication Use (Controlling for Covariates and Baseline CAC, Model 3).

Variable	Taking Antihypertensive Medication			Taking Lipid-Lowering Medication		
	Yes (n = 987)			Yes (n = 411)		
	Path Estimate (Beta)	p	No (n = 868)	Path Estimate (Beta)	p	No (n = 1305)
SBP	-52.47	0.026	-2.12	0.522		
DBP	-20.97	0.712	-2.22	0.721		
LDL-C						
				-8.01	0.204	-0.79
						0.741

Abbreviations: CAC, coronary artery calcification; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol.