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ORIGINAL RESEARCH

Cardiovascular Health Trajectories and Elevated C-Reactive Protein: The CARDIA Study

Jonathan J. Ruiz-Ramie, PhD; Jacob L. Barber, MS; Donald M. Lloyd-Jones, MD; Myron D. Gross, PhD; Jamal S. Rana, MD, PhD; Stephen Sidney, MD, MPH; David R. Jacobs, Jr, PhD; Abbi D. Lane-Cordova, PhD; Mark A. Sarzynski, PhD

BACKGROUND: The relationship between long-term cardiovascular health (CVH) patterns and elevated CRP (C-reactive protein) in late middle age has yet to be investigated. We aimed to assess this relationship.

METHODS AND RESULTS: Individual CVH components were measured in 4405 Black and White men and women (aged 18–30 years at baseline) in the CARDIA (Coronary Artery Risk Development in Young Adults) study at 8 examinations over 25 years. CRP was measured at 4 examinations (years 7, 15, 20, and 25). Latent class modeling was used to identify individuals with similar trajectories in CVH from young adulthood to middle age. Multivariable Poisson regression models were used to assess the association between race-specific CVH trajectories and prevalence of elevated CRP levels (>3.0 mg/L) after 25 years of follow-up. Five distinct CVH trajectories were identified for each race. Lower and decreasing trajectories had higher prevalence of elevated CRP relative to the highest trajectory. Prevalence ratios for elevated CRP in lowest trajectory groups at year 25 were 2.58 (95% CI, 1.89–3.51) and 7.20 (95% CI, 5.09–10.18) among Black and White people, respectively. Prevalence ratios for chronically elevated CRP (elevated CRP at 3 or more of the examinations) in the lowest trajectory groups were 8.37 (95% CI, 4.37–16.00) and 15.89 (95% CI, 9.01–28.02) among Black and White people, respectively.

CONCLUSIONS: Lower and decreasing CVH trajectories are associated with higher prevalence of elevated CRP during the transition from young adulthood to middle age.

Key Words: high sensitivity C-reactive protein ■ ideal cardiovascular health ■ lifestyle

Cardiovascular disease (CVD) is the leading cause of death in the United States.[1] In 2010, the American Heart Association established "Life's Simple 7," a conglomeration of metrics aimed at defining cardiovascular health (CVH).[2] Seven health factors (blood cholesterol, blood pressure [BP], and fasting plasma glucose) and behaviors (diet quality, physical activity [PA], smoking, and body mass index [BMI]) are emphasized within the construct, each being scored either into ideal, intermediate, or poor categories. The sum of the scores for each factor provides an individual's CVH score. Artero et al. found that the achievement of each additional ideal CVH metric was associated with a graded reduction in risk of cardiovascular disease (CVD) mortality.[3] Furthermore, multiple studies have found inverse associations of CVH score and future CVD outcomes.[4–9]

Cardiovascular disease has been classified as a chronic inflammatory disease.[10] CRP (C-reactive protein) is a systemic inflammatory marker, secreted primarily by hepatocytes in response to interleukin-6 and tumor necrosis factor-alpha.[11] CRP activates multiple atherogenic processes including, but not limited to, monocyte cytokine expression, expression

Correspondence to: Mark A. Sarzynski, PhD, Department of Exercise Science, University of South Carolina, 921 Assembly St, Room 301B, Columbia, SC 29201, USA. E-mail: sarz@mailbox.sc.edu

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CLINICAL PERSPECTIVE

What Is New?

- Latent class modeling was used to identify race-specific trajectories of ideal cardiovascular health scores over 25 years of follow-up.
- Relative risks of elevated C-reactive protein, either at 1 or multiple examinations, were higher for lower cardiovascular health trajectories and trajectories that declined over time.

What Are the Clinical Implications?

- The study findings suggest that achieving and maintaining a favorable ideal cardiovascular health score may be beneficial for the chronic inflammatory burden associated with cardiovascular disease.

Abbreviations

CARDIA	coronary artery risk development in young adults
CVH	cardiovascular health
PA	physical activity
TC	total cholesterol

of adhesion molecules, and platelet aggregation.[11] Multiple studies support CRP as an independent risk factor for CVD, with its individual predictive utility comparable to that of total and high-density lipoprotein cholesterol or BP.[12–15] The American Heart Association and Centers for Disease Control and Prevention classify an elevated CRP concentration of >3.0 mg/L as high risk.[16] Although CRP is a significant, independent predictor of CVD outcomes, a recent review found that when added to traditional risk factor models, the performance of CRP in improving CVD risk classification was inconsistent across 25 studies,[17] with minimal effect on prediction shown in the largest study (increased C-index by 0.0039 and net reclassification improvement of 1.52%).[18] Nevertheless, the American Heart Association and American College of Cardiology recommend the additional measurement of newer risk markers, such as CRP, to inform treatment decisions if quantitative risk assessment via traditional risk factors results in an uncertain treatment decision.[19] While we recognize these previous studies and their findings on the associations between CRP and CVD, we propose to explore a different relationship where traditional CVD risk factors, compiled into the CVH score, are associated with the risk of elevated CRP levels.

Although individual components of CVH have been associated with inflammatory markers,[20–27] earlier work suggests that the predictive value of the CVH score exceeds that of any of its individual parts.[28] Cross-sectional studies have found an inverse relationship between CVH and CRP,[29–31] but no studies have examined whether different long-term patterns in CVH are associated with elevated CRP in late middle age. Therefore, the aims of our study were to (1) determine whether CVH trajectory throughout adulthood was associated with prevalent elevated CRP in late-middle age, and (2) determine whether CVH trajectory throughout adulthood was associated with chronically elevated CRP in Black and White adults.

METHODS

The data used in this analysis are available through the CARDIA (Coronary Artery Risk Development in Young Adults) study (https://www.cardia.dopm.uab.edu/) upon request.

The CARDIA study is a multicenter prospective cohort of 5115 Black and White men and women examining the determinants of clinical and subclinical CVD and its risk factors. Participants, aged 18 to 30 years at baseline (year 0), were recruited from 4 regions within the United States: Birmingham, AL; Chicago, IL; Minneapolis, MN, and Oakland, CA. Enrollment in the study was balanced at each site by sex, age (18–24 vs. 25–30 years), race, and education. Follow-up of participants was performed at years 2, 5, 7, 10, 15, 20, and 25 with retention rates of 90%, 86%, 81%, 77%, 74%, 72%, and 72%, respectively. Further details on design and recruitment for the study have been published.[32] Institutional review board approval was obtained annually by each field center, and all participants provided written informed consent at each examination. Standardized protocols were used at each center across all examinations. Participants were asked to fast for at least 12 hours before each examination and avoid smoking or heavy PA at least 2 hours prior.

Determination of CVH Score

CVH status was determined at each examination between years 0 through 25 according to American Heart Association criteria (Table S1).[2] A 14-point CVH score was determined by summing points for each CVH metric at ideal (2 points), intermediate (1 point), and poor (0 points) levels, with a final score of 0 corresponding to meeting poor criteria for all 7 components and 14 corresponding to meeting ideal criteria for all components (ie, a higher CVH score is more desirable).

Smoking Status

Smoking status was attained via self-report. Thresholds for CVH smoking score are the following: 0, Poor=current smoker; 1, Intermediate=former smoker, quit within last 12 months; and 2, Ideal=Never smoker or quit >1 year ago.

Body Mass Index

Height and weight were measured at each examination while participants wore light examination clothing and no shoes. Height was measured to the nearest 0.5 cm via vertical ruler and weight to the nearest 0.2 kg with a calibrated balance beam scale. BMI was then calculated as weight in kg divided by height in meters squared. Thresholds for CVH BMI score are as follows: 0, Poor=≥30 kg/m^2; 1, Intermediate=≥25 and ≤30 kg/m^2; and 2, Ideal=<25 kg/m^2.

Physical Activity

PA was measured using the CARDIA Physical Activity History questionnaire, which inquires about time spent per week among 13 categories of PA over the past 12 months.[33] Physical activity level was expressed as exercise units (EU) of total activity involving moderate to vigorous intensity PA. Thresholds for CVH PA score were as follows: 0, Poor=<100 exercise units; 1, Intermediate=≥100; and <300 exercise units; and 2, Ideal=≥300 exercise units.

Diet

A trained interviewer administered a diet history questionnaire, developed specifically for the CARDIA study, at years 0, 7, and 20.[34,35] The CVH diet score is based upon 5 recommended measures, which include (1) ≥4.5 cups/d of fruits/vegetables, (2) ≥2 servings (3.5 oz.) of fish per week (3.5-oz servings), (3) <1500 mg/d of sodium, (4) <450 kcal (36 oz.)/wk of sweets/sugar-sweetened beverages, and (5) ≥3 servings/d of whole grains. Thresholds for the CVH diet score are 0, Poor=achievement of 0-1 diet recommendation; 1, Intermediate=achievement of 2-3 diet recommendations; and 2, Ideal=achievement of 4-5 diet recommendations. Diet data from year 0 was carried forward to determine diet status for years 2 and 5, while year 7 diet data carried forward for years 10 and 15. Year 20 diet data were also carried forward to determine diet status for year 25.

Total Cholesterol

Fasted blood draws were taken according to standard protocol.[32] Total cholesterol (TC) was measured via enzymatic assay. Threshold for CVH TC score were 0, Poor=TC ≥240 mg/dL; 1, Intermediate=TC ≥200 mg/dL and <240 or being treated for hypercholesterolemia; and 2, Ideal=TC <200 mg/dL.

Blood Pressure

BP was measured after 5 minutes of rest on the right arm by trained technicians using a random zero sphygmomanometer in the first 6 examinations (years 0 through 15). Years 20 and 25 BP was measured using an Omron digital BP monitor. All pressures were measured in triplicate with the average of the final 2 measurements used for analysis. Thresholds for CVH BP score are 0, Poor=systolic blood pressure ≥140 or diastolic blood pressure ≥90 mm Hg; 1, Intermediate=systolic blood pressure ≥120 and <140 mm Hg or diastolic blood pressure ≥80 and <90 mm Hg or use of hypertensive medications; and 2, Ideal=untreated systolic blood pressure <120 and diastolic blood pressure <80.

Blood Glucose

Fasting blood glucose was measured using the hexokinase method in years 0, 2, and 5, and via hexokinase coupled to glucose-6-phosphate dehydrogenase in years 7, 10, 15, 20, and 25. Thresholds for CVH blood glucose score are 0, Poor=fasting blood glucose ≥126 mg/dL; 1, Intermediate=fasting blood glucose ≥100 and <126 mg/dL or use of diabetic medications; and 2, Ideal=fasting blood glucose <100 mg/dL.

High-Sensitivity CRP

Fasting plasma samples from years 7, 15, 20, and 25 were used to measure CRP via a Roche latex-particle enhanced immunoturbidimetric assay kit. Assays were read on the Roche Modular P Chemistry analyzer. The assay range for CRP was 0.175 to 1100 µg/mL.[36] Elevated CRP was classified as a concentration >3.0 mg/L. Chronically elevated CRP was classified as elevated CRP levels on 3 or more of the 4 available examinations (years 7, 15, 20, and 25).

Statistical Analysis

Latent class modeling was used to identify groups that share a similar underlying trajectory in CVH score over the first 8 examinations. Of the 5115 participants, 710 did not have CVH measured on at least 3 examinations and thus were excluded from the analyses. Race-specific trajectories were modeled among all 4405 CARDIA participants with CVH measured at 3 or more examinations. Race stratification of trajectories was used to consider disparities in CRP levels and the risk factors that make up the CVH score. This model was fit using SAS Proc Traj using the censored normal model.[37] Bayesian information criterion as well as the number of participants in each trajectory (>5% of total race-specific population) were used to assess model fit. Trajectory group characteristics were compared via ANOVA, Kruskal–Wallis, or χ^2 tests as appropriate.

Multivariable Poisson regression was used to model the predictive value of CVH trajectory group on both the probability of having elevated CRP at year 25, and the probability of chronically elevated CRP from years 7 to 25. All models were adjusted for sex, center, current age, and current education level.

Sensitivity analysis was performed using CVH score from only years 0, 7, and 20 to test for the effect of diet data carry-forward. Race-specific trajectory groups were modeled among the same 4405 participants included in the original analysis via SAS Proc Traj.[37] Identical Poisson regression models were also used to model the predictive value of 3-examination CVH trajectory group on both the probability of having elevated CRP at year 25 and the probability of chronically elevated CRP from years 7 to 25. Further sensitivity analysis was done utilizing the original trajectories while removing individuals with measured CRP ≥10 mg/L at any examination from the regression models. All analyses were performed using SAS 9.4 (Cary, NC).

RESULTS

Participants

CVH trajectories were modeled among 4405 (2136 Black participants, 2269 White participants) CARDIA participants with CVH measurements at 3 or more examinations. Of these, 3336 (1523 Black participants, 1813 White participants) had CRP measurements at year 25 and 2549 (1050 Black participants, 1499 White participants) had CRP measurements at all 4 examinations used to classify chronically elevated CRP.

CVH Trajectory Groups

Five distinct trajectories in CVH from young adulthood to middle age were identified for each race (Figure 1): 10.3% (n=220) of Black participants and 6.8% (n=155) of White participants started at a low CVH and progressively decreased (low decreasing group); 18.3% (n=391) of Black participants and 10.0% (n=227) of White participants maintained a low-moderate CVH level throughout follow-up (low-moderate stable group); 31.8% (n=680) of Black participants and 18.7% (n=424) of White participants started at a low-moderate CVH level and decreased (low-moderate decreasing group); 24.2% (n=517) of Black participants and 32.8% (n=744) of White participants started at a high-moderate CVH level and decreased (high-moderate decreasing); and 15.4% (n=328) of Black participants and 31.7% of White participants (n=719) maintained high CVH levels throughout (high stable group).

In general, each trajectory group displayed steady decreases in CVH score over time; however, the high stable group remained relatively the same and the low-moderate stable group showed an initial decline and then maintenance of CVH for the remainder of the examinations (Tables S2 and S3). In Black participants, the high-moderate decreasing group experienced the largest decline in CVH (3.1, SE 0.1) while in White participants, the low-moderate decreasing group declined the most (3.1, SE 0.1).

The high-stable group for both races completed more years of education than the other trajectory groups. Graded worsening of individual CVH components was generally seen when moving from higher to lower trajectory groups as well (Tables 1 and 2).

Year 25 Elevated CRP

The overall prevalence of elevated CRP at year 25 was 38.9% in Black participants and 19.5% in White participants, which significantly differed between trajectory groups (P<0.0001 for trend in both Black and White participants). The prevalence of elevated CRP was higher in Black participants for all trajectory groups relative to White participants , varying from 14.3% in the high-stable group to 34.1% in the low decreasing group for Black participants and 7.1% to 32.3%, respectively, in White participants (Table 3). Between the 2 groups that started at a similar CVH level (low-moderate stable and low-moderate decreasing), the low-moderate decreasing group had a higher prevalence of elevated CRP at year 25 for both races (23.3% vs. 37.4%, respectively, for Black participants, 16.3% vs. 24.5% for White participants).

Among both Black and White participants, all lower CVH trajectories were at an increased risk relative to the high stable group. Among Black participants, adjusted relative risks for elevated CRP at year 25 ranged from 1.6 (95% CI, 1.2–2.2) for low-moderate stable, to 2.7 (95% CI, 2.0–3.5) for the low-moderate decreasing group as compared with high stable. Adjusted relative risks for elevated CRP at Year 25 for White participants ranged from 2.5 (95% CI, 1.8–3.4) for high-moderate decreasing, to 7.2 (95% CI, 5.1–10.2) for the low decreasing group compared with high stable (Table 3).

Chronically Elevated CRP

The prevalence of chronically elevated CRP across years 7 to 25 was 27.3% in Black participants and 11.3% in White participants in the total sample. This prevalence ranged from 3.0% in the high stable group to 20.0% in the low-decreasing group among Black participants and 2.2% to 22.6%, respectively, in White participants (P<0.0001 for trend in both Black and White participants, Table 4). Among both low-moderate groups (low-moderate stable and low-moderate decreasing), the low-moderate decreasing group had higher prevalence of chronically elevated CRP for both

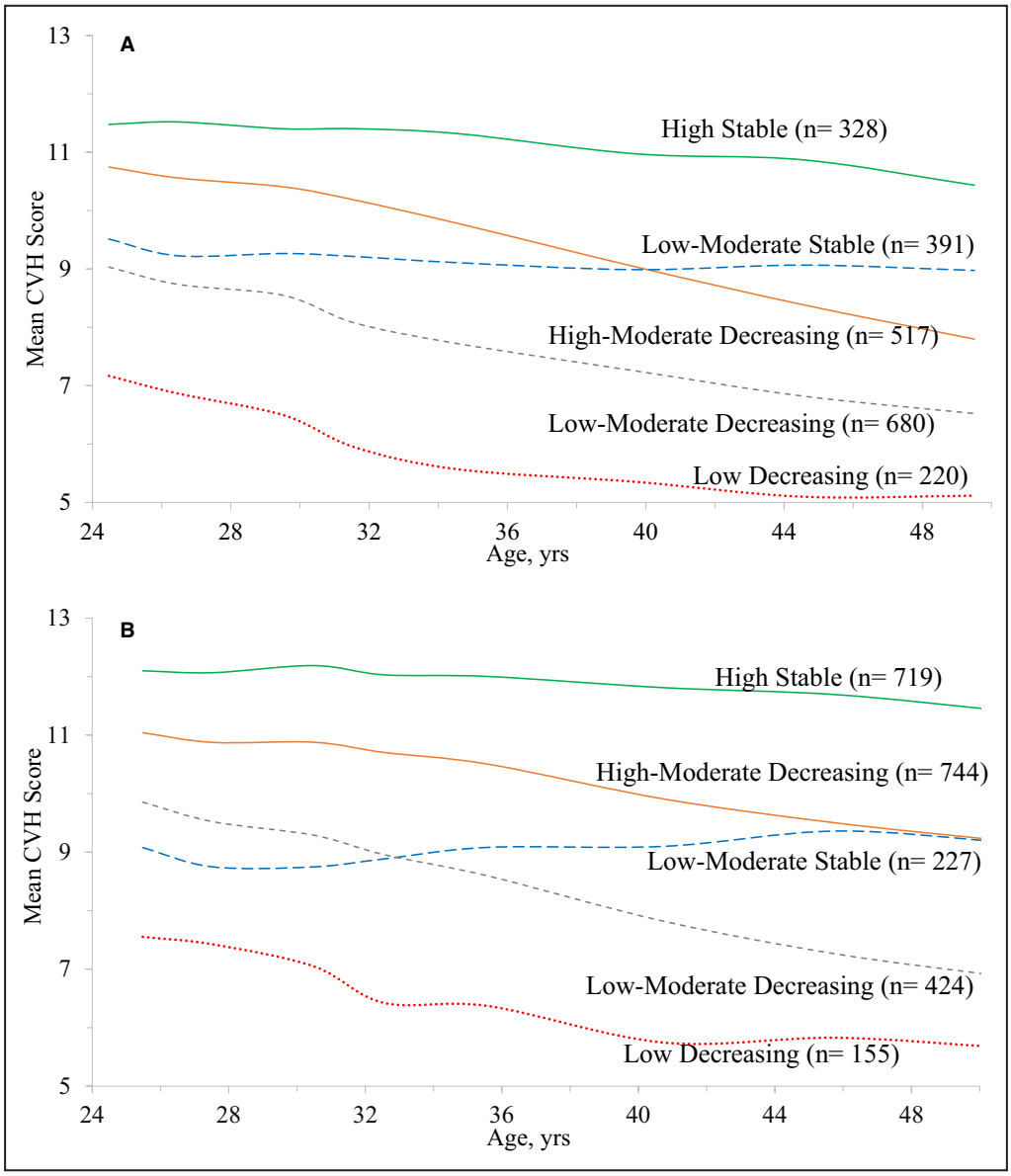

Figure 1. Trajectories in CVH score among Black (A) and White (B) participants in the CARDIA (Coronary Artery Risk Development in Young Adults) Study.
CVH indicates cardiovascular health.

races (11.0% vs. 18.7%, respectively, for Black participants, 5.7% vs. 14.2% for White participants).

Among Black participants, adjusted relative risks for chronically elevated CRP ranged from 3.9 (95% CI, 2.0–7.4) for low-moderate stable, to 8.4 (95% CI, 4.4–16.0) for the low decreasing group compared with high stable. Among White participants, adjusted relative risks for chronically elevated CRP ranged from 3.5 (95% CI, 2.0–6.1) for high-moderate decreasing, to 15.9 (95% CI, 9.0–28.0) for the low decreasing group compared with high stable (Table 4).

Sensitivity analysis with CVH score taken at only 3 examinations resulted in similar trajectory patterns (Figure S1) and trends in prevalence ratios, with less favorable CVH trajectories associated with greater prevalence of elevated and chronically elevated CRP (Tables S4 and S5). Further analysis utilizing the original trajectories but removing individuals with CRP ≥10 mg/L at any examination also revealed similar results (Tables S6 and S7).

DISCUSSION

We found 5 unique race-specific trajectories in CVH score from young adulthood to late middle age. Lower and decreasing trajectories in CVH score were independently associated with elevated CRP in late middle

Table 1. Demographic Characteristics of Black Participants by CVH Score Trajectory Group at Baseline

	Low-Decreasing	Low-Moderate Decreasing	Low-Moderate Stable	High-Moderate Decreasing	High Stable	
	n=220	n=680	n=391	n=517	n=328	*P* Value
Demographic characteristics						
Age, mean (SE), y	24.0 (0.3)	24.5 (0.1)	24.7 (0.2)	24.3 (0.2)	24.4 (0.2)	0.19
Study center, n (%)						
Birmingham, AL	62 (28.2)	191 (28.1)	93 (23.8)	138 (26.7)	64 (19.5)	0.01
Chicago, IL	49 (22.3)	134 (19.7)	96 (24.6)	99 (19.1)	72 (22.0)	
Minneapolis, MN	57 (25.9)	143 (21.0)	87 (22.3)	109 (21.1)	62 (18.9)	
Oakland, CA	52 (23.6)	212 (31.2)	115 (29.4)	171 (33.1)	130 (39.6)	
Sex, n (%)						
Male	86 (39.1)	259 (38.1)	178 (45.5)	225 (43.5)	154 (47.0)	0.03
Female	134 (60.9)	421 (61.9)	213 (54.5)	292 (56.5)	174 (53.0)	
Education, n (%)						
Less than high school	58 (26.4)	103 (15.1)	47 (12.0)	40 (7.7)	12 (3.7)	<0.0001
High school	85 (38.6)	271 (39.9)	132 (33.8)	191 (36.9)	95 (29.0)	
Postsecondary	67 (29.1)	236 (34.7)	159 (40.7)	203 (39.3)	140 (427)	
Bachelor's degree	9 (4.1)	56 (8.2)	38 (9.7)	63 (12.2)	66 (20.1)	
Graduate or professional	4 (1.8)	14 (2.1)	15 (3.8)	20 (3.9)	15 (4.6)	
CVH score, mean (SE)	7.2 (0.1)	9.0 (0.1)	9.4 (0.1)	10.8 (0.0)	11.5 (0.1)	<0.0001
CVH components, mean (SE) unless labeled otherwise						
Smoking status, n (%)*						
Never smoker	58 (26.4)	327 (48.1)	208 (53.2)	401 (77.6)	266 (81.1)	<0.0001
Former smoker	13 (5.9)	61 (9.0)	29 (7.4)	45(8.7)	41 (12.5)	
Current smoker	145 (65.9)	286 (42.1)	153 (39.1)	70 (13.5)	20 (6.1)	
Body mass index, kg/m^2	30.6 (0.5)	26.9 (0.2)	25.2 (0.3)	23.5 (0.2)	22.0 (0.1)	<0.0001
Physical activity, exercise units	271.2 (16.4)	347.2 (11.3)	360.1 (15.1)	413.3 (12.9)	495.2 (18.0)	<0.0001
Healthy diet score, number of components	0.8 (0.05)	0.9 (0.0)	0.8 (0.0)	1.1 (0.0)	1.4 (0.1)	<0.0001
Total cholesterol, mg/dL	198.5 (2.6)	180.1 (1.4)	178.3 (1.8)	172.8 (1.3)	170.0 (1.6)	<0.0001
Systolic blood pressure, mm Hg	117.4 (0.8)	113.0 (0.4)	110.7 (0.5)	109.5 (0.4)	108.5 (0.6)	<0.0001
Diastolic blood pressure, mm Hg	72.3 (0.8)	69.7 (0.4)	68.0 (0.5)	67.8 (0.4)	67.3 (0.5)	<0.0001
Fasting serum glucose, mg/dL	91.2 (3.1)	82.5 (0.5)	80.6 (0.4)	79.8 (0.4)	78.9 (0.4)	<0.0001

CVH indicates cardiovascular health.
*Some data missing for smoking status.

age, as well as chronically elevated CRP from years 7 to 25 of the CARDIA study. Associations persisted after adjustment for baseline or year 25 CVH score. In support of the importance of achieving and/or maintaining favorable CVH throughout adulthood, we found the low-moderate stable group had a greater prevalence of chronically elevated CRP versus the high-moderate decreasing group, although both groups had a similar CVH score at year 25. When comparing the 2 outcomes of interest (elevated CRP at year 25 and chronically elevated CRP), we found that the prevalence ratios for chronically elevated CRP were considerably larger than those for elevated CRP at year 25, regardless of trajectory group.

The results of our study provide novel insights into long-term patterns of CVH, with the identification of heterogeneous subgroups of individuals with similar CVH scores at each examination. Our findings highlight that long-term trajectories in CVH may be associated with CRP levels in late middle age. Our findings also emphasize the importance of achieving and maintaining high CVH throughout adulthood in order to reduce the odds of having elevated CRP. In a meta-analysis of 54 prospective studies encompassing 1.3-million-person years at risk, CRP concentrations were positively correlated with systolic BP as well as non-high-density lipoprotein cholesterol and BMI.[14] We observed the same general trend in our investigation: all groups experienced a decrease in CVH components and total CVH score over the 25-year period, which was correlated with increased CRP levels.

Table 2. Demographic Characteristics of White Participants by CVH Score Trajectory Group at Baseline

	Low-Decreasing	Low-Moderate Decreasing	Low-Moderate Stable	High-Moderate Decreasing	High Stable	
	n=155	n=424	n=227	n=744	n=719	*P* Value
Demographic characteristics						
Age, mean (SE), y	25.1 (0.3)	25.4 (0.2)	24.5 (0.2)	25.7 (0.1)	25.7 (0.1)	<0.0001
Study center, n (%)						
Birmingham, AL	48 (31.0)	112 (26.4)	66 (29.1)	160 (21.5)	89 (12.4)	<0.0001
Chicago, IL	26 (16.8)	74 (17.5)	40 (17.6)	175 (23.5)	193 (26.8)	
Minneapolis, MN	57 (36.8)	151 (35.6)	85 (37.4)	236 (31.7)	208 (28.9)	
Oakland, CA	24 (15.5)	87 (20.5)	36 (15.9)	173 (23.3)	229 (31.9)	
Sex, n (%)						
Male	81 (52.3)	253 (59.7)	114 (50.2)	383 (51.5)	242 (33.7)	<0.0001
Female	74 (47.7)	171 (40.3)	113 (49.8)	361 (48.5)	477 (66.3)	
Education, n (%)						
Less than high school	27 (17.4)	37 (8.7)	23 (10.1)	30 (4.0)	7 (1.0)	<0.0001
High school	57 (36.8)	111 (26.2)	73 (32.2)	150 (20.2)	76 (10.6)	
Postsecondary	47 (30.3)	155 (36.6)	71 (31.3)	236 (31.7)	170 (23.6)	
Bachelor's degree	16 (10.3)	75 (17.7)	40 (17.6)	198 (26.6)	292 (40.6)	
Graduate or professional	8 (5.2)	46 (10.8)	20 (8.8)	130 (17.5)	174 (24.2)	
CVH score, mean (SE)	7.5 (0.1)	9.8 (0.1)	9.0 (0.1)	11.0 (0.0)	12.1 (0.0)	<0.0001
CVH components, mean (SE) unless labeled otherwise						
Smoking status, n (%)*						
Never smoker	38 (24.5)	190 (44.8)	55 (24.2)	464 (62.4)	526 (73.2)	<0.0001
Former smoker	10 (6.5)	68 (16.0)	33 (14.5)	142 (19.1)	152 (21.1)	
Current smoker	104 (67.1)	163 (38.4)	136 (59.9)	137 (18.4)	37 (5.1)	
Body mass index, kg/m^2	29.3 (0.5)	25.3 (0.2)	25.0 (0.3)	23.1 (0.1)	21.6 (0.1)	<0.0001
Physical activity, exercise units	294.7 (18.7)	422.0 (13.2)	383.3 (16.2)	45.9 (10.4)	525.6 (10.6)	<0.0001
Healthy diet score, number of components	0.9 (0.1)	1.2 (0.1)	0.9 (0.1)	1.6 (0.0)	2.1 (0.0)	<0.0001
Total cholesterol, mg/dL	195.8 (3.1)	182.0 (1.6)	185.2 (2.5)	175.3 (1.2)	167.0 (1.0)	<0.0001
Systolic blood pressure, mm Hg	116.1 (1.0)	111.9 (0.1)	110.4 (0.7)	109.6 (0.4)	105.6 (0.3)	<0.0001
Diastolic blood pressure, mm Hg	73.1 (0.9)	69.3 (0.5)	67.9 (0.7)	68.8 (0.3)	66.6 (0.3)	<0.0001
Fasting serum glucose, mg/dL	89.9 (2.3)	83.7 (0.4)	83.1 (0.7)	82.5 (0.4)	81.6 (0.3)	<0.0001

CVH indicates cardiovascular health.
*Some data missing for smoking status.

Ishii et al. found that in the CARDIA cohort, increased BMI and female sex were associated with increased odds of 1-time and repeated elevations in CRP (>10 mg/L).[38] Notably, 69.9% of repeated CRP elevations were in obese women. This relationship may have influenced our results because there were significant sex and BMI differences between trajectories; however, the joint effect of PA and diet on BMI also should not be ignored in considering influential CVH factors when it comes to elevated CRP levels. Having PA, diet, and BMI, among the other CVH factors in our analysis, may offer a more comprehensive look at how these factors interact with CRP levels. Furthermore, CVH score was found to be an independent predictor of elevated CRP levels when adjusting for sex in our models.

Previous studies have also examined CVH trajectories and their associations with CVD-related outcomes.[39–41] Of note, each of these studies also identified 5 distinct trajectories for CVH. In a pooled cohort analysis of >9000 individuals, the highest (ie, most favorable) CVH trajectory group had significantly lower carotid intima-media thickness versus other groups.[40] Analyses from the Kailuan study also found that when comparing with the lowest trajectory groups, higher level trajectory groups displayed lower arterial stiffness (as measured by brachial–ankle pulse wave velocity) as well as a lower incidence of CVD.[39,41] Thus, these findings, along with our current study, corroborate the relationship of CVH trajectories with clinical and subclinical CVD outcomes as well as other biomarkers of CVD risk. This collective

Table 3. Adjusted Relative Risks of Elevated CRP at Year 25 in Black and White Participants by CVH Score Trajectory Group

	No. (%) of Participants With CRP >3.0 mg/L at Y25	Relative Risk (95% CI)*	No. (%) of Participants With CRP >3.0 mg/L at Y25	Relative Risk (95% CI)*
CVH Trajectory Group	Black Participants		White Participants	
High stable	47 (14.3)	1 (reference)	51 (7.1)	1 (reference)
High-moderate decreasing	126 (24.3)	1.8 (1.4, 2.5)	111 (14.9)	2.5 (1.8, 3.4)
Low-moderate stable	91 (23.3)	1.6 (1.2, 2.2)	37 (16.3)	3.0 (2.0, 4.4)
Low-moderate decreasing	254 (37.4)	2.7 (2.0, 3.5)	104 (24.5)	5.0 (3.6, 6.8)
Low decreasing	75 (34.1)	2.6 (1.9, 3.5)	50 (32.3)	7.2 (5.1, 10.2)

CRP indicates C-reactive protein; and CVH, cardiovascular health.
*Model adjusted for sex, age, center, and highest level of education.

Table 4. Adjusted Relative Risks of Chronically Elevated CRP from Year 7 to Year 25 in Black and White Participants by CVH Score Trajectory Group

	No. (%) of Participants With Chronically Elevated CRP	Relative Risk (95% CI)*	No. (%) of Participants With Chronically Elevated CRP	Relative Risk (95% CI)*
CVH Trajectory Group	Black Participants		White Participants	
High stable	10 (3.0)	1 (reference)	16 (2.2)	1 (reference)
High-moderate decreasing	63 (12.2)	4.5 (2.4–8.5)	45 (6.0)	3.5 (2.0–6.1)
Low-moderate stable	43 (11.0)	3.9 (2.0–7.4)	13 (5.7)	3.8 (1.8–7.8)
Low-moderate decreasing	127 (18.7)	7.0 (3.8–13.0)	60 (14.2)	10.3 (6.1–17.6)
Low decreasing	44 (20.0)	8.4 (4.4–16.0)	35 (22.6)	15.9 (9.0, 28.0)

CRP indicates C-reactive protein; and CVH, cardiovascular health.
*Model adjusted for sex, age, center, and highest level of education.

literature on CVH trajectories throughout the lifespan further highlights the importance of promoting, achieving, and maintaining optimal CVH.

Some strengths and limitations of our study should be noted. The calculated CVH scores took into account medication use for BP, cholesterol levels, and glucose, increasing the real-world applicability of the results. Our study population was a large, well-characterized cohort of Black and White Americans followed up over 25 years. The results of our study may not be generalizable to other race/ethnic groups. Although race-specific CVH trajectories were created, we did not also separate trajectories by sex. We categorized participants as having elevated CRP based on a single measurement at each examination. Although CRP is an acute-phase protein and circulating levels of CRP are subject to variability, a meta-analysis of 54 studies found that the year-to-year stability of circulating CRP concentration among the same individuals was generally similar to that for systolic BP and TC.[14] CRP measurements were available at 4 time points—years 7, 15, 20, and 25—but we do not have information on CRP levels before these time points. The diet score component of CVH was measured at years 0, 7, and 20, with the score from previous years being factored into overall CVH score until the next true measurement (ie, diet score from year 0 was carried over into years 2 and 5). However, our sensitivity analysis with only truly measured diet score (3 examinations) produced similar trajectories and associations with elevated CRP levels.

CONCLUSIONS

Our study found that adulthood trajectories of CVH are independently associated with elevated levels of CRP. Our results emphasize the importance of achieving and maintaining favorable CVH from young adulthood to middle age.

ARTICLE INFORMATION

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Affiliations

Department of Kinesiology, Augusta University, Augusta, GA (J.J.R.); Department of Exercise Science, Arnold School of Public Health, University of South Carolina, Columbia, SC (J.J.R., J.L.B., A.D.L., M.A.S.); Department of Preventive Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL (D.M.L.); Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN (M.D.G.); Division of Cardiology (J.S.R.); and Division of Research (J.S.R., S.S.), Kaiser Permanente of Northern California, Oakland, CA; and Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, MN (D.R.J.).

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Drs Ruiz-Ramie and Sarzynski had full access to the data in this study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Ruiz-Ramie and Sarzynski are responsible for the conception and study design. Drs Ruiz-Ramie, Lane-Cordova, and Sarzynski conducted statistical analysis. Drs Lane-Cordova and Sarzynski supervised the analysis. Dr Ruiz-Ramie drafted the manuscript. All authors were responsible for critical revision of the manuscript.

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DISCLOSURES

None.

Supplementary Material

Tables S1-S7
Figure S1

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Supplemental Material

Table S1. Scoring Criteria for CVH scores.

Measure	Poor (0 points)	Intermediate (1 point)	Ideal (2 points)
Smoking	Current	Former	Never
Body mass Index, kg/m^2	≥30	≥25 and <30	<25
Physical activity, exercise units	<100	≥100 and <300	≥300
Healthy diet score, No. of components	0-1	2-3	4-5
Total cholesterol, mg/dL	≥240	≥200 and <240	<200[a]
Blood pressure, mm Hg	SBP ≥140 or DBP ≥90	140> SBP ≥120 or 90>DBP ≥80	SBP <120 and DBP <80[b]
Fasting blood glucose, mg/dL	≥126	100-125	<100[c]

SBP = systolic blood pressure; DBP = diastolic blood pressure;

[a]Plus no previous physician diagnosis of hypercholesterolemia

[b]Plus no previous physician diagnosis of hypertension

[c]Plus no previous physician diagnosis of diabetes or use of insulin

Table S2. Mean CVH Score and hsCRP levels of Black Trajectory Groups at Each Study Examination.

	Low-Decreasing n=220		Low-Moderate Decreasing n=680		Low-Moderate Stable n=391		High-Moderate Decreasing n=517		High stable n=328	
Exam Year	CVH Score	hsCRP mg/L	CVH Score	hsCRP mg/L	CVH Score	hsCRP mg/L	CVH Score	hsCRP mg/L	CVH Score	hsCRP mg/L
Year 0	7.2 (0.1)		9.0 (0.1)		9.4 (0.1)		10.8 (0.1)		11.5 (0.1)	
Year 2	6.8 (0.1)		8.8 (0.1)		9.1 (0.1)		10.6 (0.1)		11.6 (0.1)	
Year 5	6.5 (0.1)		8.5 (0.1)		9.2 (0.1)		10.5 (0.1)		11.5 (0.1)	
Year 7	5.9 (0.1)	5.7 (0.6)	8.0 (0.1)	4.4 (0.3)	9.2 (0.1)	3.2 (0.3)	10.2 (0.1)	2.8 (0.2)	11.4 (0.1)	2.8 (1.2)
Year 10	5.5 (0.1)		7.7 (0.1)		9.1 (0.1)		9.8 (0.1)		11.4 (0.1)	
Year 15	5.3 (0.1)	6.4 (0.6)	7.2 (0.1)	5.4 (0.3)	9.1 (0.1)	3.7 (0.3)	9.0 (0.1)	3.3 (0.2)	11.0 (0.1)	2.3 (0.4)
Year 20	5.0 (0.2)	5.5 (0.5)	6.8 (0.1)	4.9 (0.3)	9.2 (0.1)	2.6 (0.2)	8.3 (0.1)	3.4 (0.3)	10.9 (0.1)	1.9 (0.3)
Year 25	5.1 (0.2)	7.0 (0.7)	6.5 (0.1)	5.9 (0.5)	9.1 (0.1)	3.1 (0.2)	7.7 (0.1)	3.9 (0.3)	10.5 (0.1)	2.3 (0.3)

Values reported as mean (SE). CVH score measured at each examination. hsCRP measured only in years 7, 15, 20, and 25

Table S3. Mean CVH Score and hsCRPlevels of White Trajectory Groups at Each Study Examination.

	Low-Decreasing n=155		Low-Moderate Decreasing n=424		Low-Moderate Stable n=227		High-Moderate Decreasing n=744		High stable n=719	
Exam Year	CVH Score	hsCRP mg/L	CVH Score	hsCRP mg/L	CVH Score	hsCRP mg/L	CVH Score	hsCRP mg/L	CVH Score	hsCRP mg/L
Year 0	7.5 (0.2)		9.8 (0.1)		9.0 (0.1)		11.0 (0.0)		12.1 (0.0)	
Year 2	7.4 (0.1)		9.5 (0.1)		8.6 (0.1)		10.8 (0.0)		12.1 (0.0)	
Year 5	7.0 (0.1)		9.3 (0.1)		8.6 (0.1)		10.9 (0.0)		12.2 (0.0)	
Year 7	6.4 (0.1)	4.3 (0.4)	8.9 (0.1)	2.8 (0.4)	8.8 (0.2)	2.6 (0.2)	10.7 (0.0)	2.2 (0.2)	12.0 (0.0)	1.4 (0.1)
Year 10	6.3 (0.2)		8.5 (0.1)		9.1 (0.1)		10.5 (0.1)		12.0 (0.0)	
Year 15	5.8 (0.2)	5.6 (0.5)	7.8 (0.1)	3.0 (0.3)	9.1 (0.1)	3.3 (0.2)	9.9 (0.1)	2.3 (0.2)	11.8 (0.0)	1.4 (0.1)
Year 20	5.8 (0.2)	3.9 (0.4)	7.2 (0.1)	2.2 (0.3)	9.5 (0.1)	3.1 (0.3)	9.5 (0.1)	2.0 (0.2)	11.7 (0.0)	1.2 (0.1)
Year 25	5.7 (0.2)	5.1 (0.7)	6.8 (0.1)	2.2 (0.2)	9.3 (0.1)	3.5 (0.3)	9.2 (0.1)	2.1 (0.1)	11.4 (0.0)	1.2 (0.1)

Measures reported as mean (SE). CVH score measured at each examination. hsCRP measured only in years 7, 15, 20, and 25

Table S4. Sensitivity Analysis. Adjusted Relative Risks of the Association of Black (A) and White (B) CVH Score Trajectory Groups with Elevated CRP at Year 25. Trajectories utilized CVH data from exam years 0, 7, and 20 only.

A. Black Trajectories (n=2136)

	No. (%) of Participants with CRP > 3.0 mg/L at Y25	Relative Risk (95% CI) *
CVH Trajectory Group		
High stable	43 (14.0)	1 (reference)
High-Moderate Decreasing	260 (25.3)	2.0 (1.5, 2.7)
Low-Moderate Stable	186 (35.5)	2.7 (2.0, 3.6)
Low-Moderate Decreasing	59 (41.0)	2.6 (1.9, 3.6)
Low Decreasing	45 (34.4)	2.9 (2.1, 4.1)

*Model adjusted for sex, age, center, highest level of education

B. White Trajectories (n=2269)

	No. (%) of Participants with CRP > 3.0 mg/L at Y25	Relative Risk (95% CI) *
CVH Trajectory Group		
High stable	85 (8.6)	1 (reference)
High-Moderate Decreasing	108 (18.7)	2.6 (2.0, 3.4)
Low-Moderate Stable	53 (20.4)	2.6 (1.9, 3.6)
Low-Moderate Decreasing	91 (23.2)	3.9 (3.0, 5.1)
Low Decreasing	16 (34.8)	6.6 (4.2, 10.4)

*Model adjusted for sex, age, center, highest level of education

Table S5. Sensitivity Analysis. Adjusted Relative Risks of the Association of Black (A) and White (B) CVH Score Trajectory Groups with Chronically Elevated CRP from Year 7 to Year 25. Trajectories utilized CVH data from exam years 0, 7, and 20 only.

A. Black Trajectories (n=2136)

	No. (%) of Participants with Chronically Elevated CRP	Relative Risk (95% CI) *
CVH Trajectory Group		
High stable	9 (2.9)	1 (reference)
High-Moderate Decreasing	119 (11.6)	4.8 (2.5, 9.3)
Low-Moderate Stable	92 (17.6)	7.7 (4.0, 14.8)
Low-Moderate Decreasing	37 (25.7)	7.8 (3.9, 15.5)
Low Decreasing	30 (22.9)	10.8 (5.4, 21.8)

*Model adjusted for sex, age, center, highest level of education

B. White Trajectories (n=2269)

	No. (%) of Participants with Chronically Elevated CRP	Relative Risk (95% CI) *
CVH Trajectory Group		
High stable	29 (2.9)	1 (reference)
High-Moderate Decreasing	59 (10.2)	4.5 (3.0, 6.9)
Low-Moderate Stable	19 (7.3)	2.9 (1.6, 5.0)
Low-Moderate Decreasing	51 (13.0)	7.2 (4.7, 11.1)
Low Decreasing	11 (23.9)	15.4 (8.2, 29.0)

*Model adjusted for sex, age, center, highest level of education

Table S6. Adjusted Relative Risks of the Association of Black (A) and White (B) CVH Score Trajectory Groups with Elevated CRP at Year 25. Individuals with CRP levels at or above 10 mg/L measured at any exam were removed from analyses.*

A. Black Trajectories (n=1751)

	No. (%) of Participants with CRP > 3.0 mg/L at Y25	Relative Risk (95% CI) *
CVH Trajectory Group		
High stable	36 (11.7)	1 (reference)
High-Moderate Decreasing	74 (16.6)	1.6 (1.1, 2.3)
Low-Moderate Stable	61 (18.0)	1.6 (1.1, 2.3)
Low-Moderate Decreasing	130 (25.6)	2.5 (1.8, 3.5)
Low Decreasing	29 (19.1)	2.0 (1.3, 3.0)

*Model adjusted for sex, age, center, highest level of education

B. White Trajectories (n=2071)

	No. (%) of Participants with CRP > 3.0 mg/L at Y25	Relative Risk (95% CI) *
CVH Trajectory Group		
High stable	39 (5.7)	1 (reference)
High-Moderate Decreasing	83 (12.1)	2.5 (1.7, 3.6)
Low-Moderate Stable	24 (12.1)	2.7 (1.6, 4.3)
Low-Moderate Decreasing	74 (19.3)	5.0 (3.4, 7.2)
Low Decreasing	26 (20.8)	6.2 (3.9, 10.0)

*Model adjusted for sex, age, center, highest level of education

Table S7. Adjusted Relative Risks of the Association of Black (A) and White (B) CVH Score Trajectory Groups with Chronically Elevated CRP from Year 7 to Year 25. Individuals with CRP levels at or above 10 mg/L measured at any exam were removed from analyses.*

A. Black Trajectories (n=1751)

	No. (%) of Participants with Chronically Elevated CRP	Relative Risk (95% CI) [a]
CVH Trajectory Group		
High stable	6 (2.0)	1 (reference)
High-Moderate Decreasing	29 (6.5)	4.2 (1.8, 9.8)
Low-Moderate Stable	22 (6.5)	3.9 (1.6, 9.4)
Low-Moderate Decreasing	48 (9.5)	6.9 (3.0, 15.6)
Low Decreasing	13 (8.6)	7.7 (3.0, 19.6)

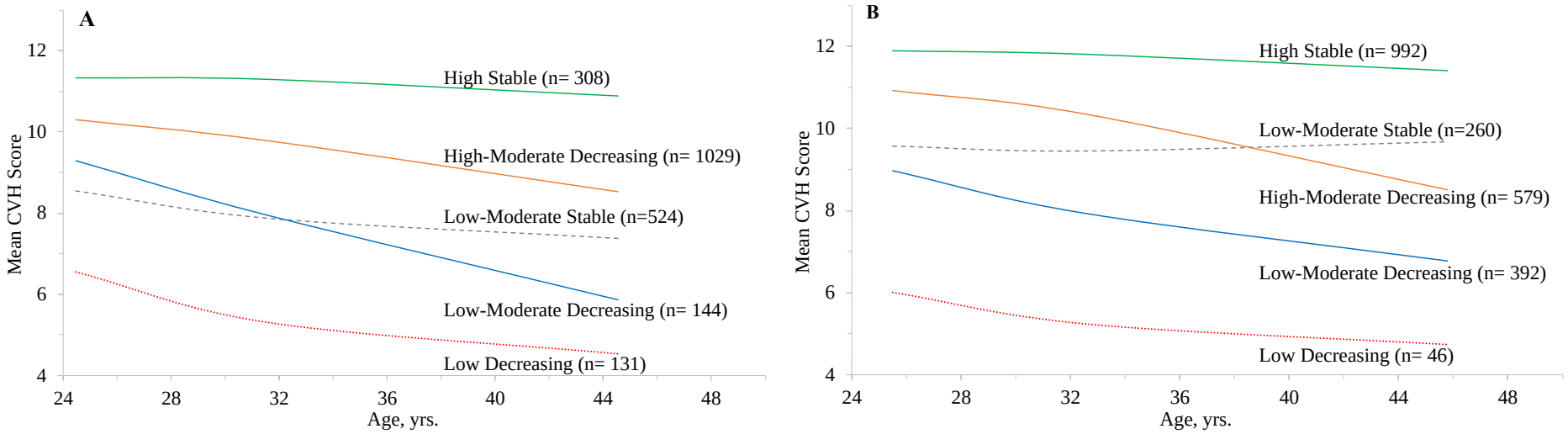
*Model adjusted for sex, age, center, highest level of education

B. White Trajectories (n=2071)

	No. (%) of Participants with Chronically Elevated CRP	Relative Risk (95% CI) [a]
CVH Trajectory Group		
High stable	8 (1.2)	1 (reference)
High-Moderate Decreasing	24 (3.5)	3.7 (1.7, 8.3)
Low-Moderate Stable	3 (1.5)	1.8 (0.5, 6.7)
Low-Moderate Decreasing	37 (9.9)	13.1 (6.1, 28.3)
Low Decreasing	13 (10.4)	15.8 (6.5, 38.6)

*Model adjusted for sex, age, center, highest level of education

Figure S1. Sensitivity Analysis. Trajectories in Cardiovascular Health (CVH) Score among Black (A) and White (B) Participants in the Coronary Artery Risk Development in Young Adults (CARDIA) Study.



Trajectories utilized CVH data from exam years 0, 7, and 20 only.

When excluding participants in this manner, the dataset was decreased from 4405 to 3822 individuals (583 individuals excluded). Of these 583 individuals, 399 (68.4%) had only one measure of CRP ≥ 10 mg/L, however, 212 (53.1% of the 399) of these individuals were classified as having chronically elevated CRP based on our criteria of ≥ 3.0 mg/L at 3 or more exams. Overall, 253 of the 583 individuals excluded in this analysis were classified as having chronically elevated CRP.