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25-Year Physical Activity Trajectories and Development of Subclinical Coronary Artery Disease as Measured by Coronary Artery Calcium: The Coronary Artery Risk Development in Young Adults (CARDIA) Study

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Abstract

Objective: To evaluate 25-year physical activity (PA) trajectories from young to middle age and assess associations with the prevalence of coronary artery calcification (CAC).

Patients and Methods: This study includes 3175 participants in the Coronary Artery Risk Development in Young Adults (CARDIA) study who self-reported PA by questionnaire at 8 follow-up examinations over 25 years (from March 1985-June 1986 through June 2010-May 2011). The presence of CAC (CAC>0) at year 25 was measured using computed tomography. Group-based trajectory modeling was used to identify PA trajectories with increasing age.

Results: We identified 3 distinct PA trajectories: trajectory 1, below PA guidelines (n=1813; 57.1%); trajectory 2, meeting PA guidelines (n=1094; 34.5%); and trajectory 3, 3 times PA guidelines (n=268; 8.4%). Trajectory 3 participants had higher adjusted odds of CAC>0 (adjusted odds ratio [OR], 1.27; 95% CI, 0.95-1.70) vs those in trajectory 1. Stratification by race showed that white participants who engaged in PA 3 times the guidelines had higher odds of developing CAC>0 (OR, 1.80; 95% CI, 1.21-2.67). Further stratification by sex showed higher odds for white males (OR, 1.86; 95% CI, 1.16-2.98), and similar but nonsignificant trends were noted for white females (OR, 1.71; 95% CI, 0.79-3.71). However, no such higher odds of CAC>0 for trajectory 3 were observed for black participants.

Conclusion: White individuals who participated in 3 times the recommended PA guidelines over 25 years had higher odds of developing coronary subclinical atherosclerosis by middle age. These findings warrant further exploration, especially by race, into possible biological mechanisms for CAC risk at very high levels of PA.

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Coronary artery calcification (CAC) has emerged as a strong predictor of incident coronary heart disease (CHD) and provides predictive information beyond standard risk factors,[1] allowing for substantially improved risk stratification for future cardiovascular disease (CVD) events.[2] Physical activity (PA) has been shown to be associated with a reduction in CVD morbidity and mortality.[2,3] Given the importance of primary prevention of CHD, there remains a need to better understand risk factors and lifestyle behaviors that can have an impact from an earlier age.

National guidelines, including the 2008 Physical Activity Guidelines for Americans, advocate the benefits of PA, specifically,

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prolonged bouts of moderate- to vigorous-intensity PA or exercise.[4] There is agreement from large epidemiologic studies suggesting that there are relative cardiovascular (CV) benefits and reduced risk of CVD incidence and CV mortality of a physically active lifestyle in study populations of mid- to late-life men and women.[2,5,6] However, in healthy individuals, the "optimum" dose of PA necessary to derive the upper threshold of CV benefit, and potential harms associated with very high levels of activity, remains undefined[4] and equally controversial.[5,6] Recent studies of frequency and dose of PA have shown a U-shaped association with vascular disease risk and mortality,[6-8] suggesting an attenuation of health benefits at higher PA doses above the recommended PA levels (150 minutes of moderate- vigorous-intensity PA per week).[2,5]

There is a paucity of data regarding the association of PA and the development of subclinical atherosclerosis. Cross-sectional data have shown that asymptomatic patients with 2 or more metabolic risk factors who regularly engage in PA (≥30 minutes, 1 to 2 times per week) have a lower prevalence of CAC than do those who are sedentary.[9] On the other hand, no association between PA and the presence of CAC has been observed in middle-aged adults.[10-12] Likewise, evidence in older postmenopausal women showed that higher levels of PA were associated with no detectable CAC[13] or lower CAC.[14] In the Coronary Artery Risk Development in Young Adults (CARDIA) study population, high levels of cardiorespiratory fitness, evaluated at baseline, were associated with a lower risk of having CAC 15 years later.[15] However, a common limitation of these studies is that the evaluation of PA or fitness was limited to a single baseline assessment. Physical activity can vary greatly during the life course[15]; therefore, longitudinal data are needed to describe age-related changes in PA and how they may relate to CAC.

In the present study, we examined the effects of long-term PA patterns and their association with subclinical atherosclerosis during a 25-year transition from young adulthood to middle age in the CARDIA study. We hypothesized that higher PA levels from young adulthood to midlife will be associated with lower year 25 CAC prevalence.

METHODS

Study Population

The CARDIA study is a multicenter, community-based, longitudinal cohort study designed to investigate the development of CHD risk factors in young adults. The baseline cohort consisted of 5115 black and white men and women aged 18 to 30 years (at baseline) who were recruited from March 1, 1985, through June 30, 1986, from 4 cities in the United States (Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; and Oakland, California), with population-based samples approximately balanced within center by sex, age (18-24 years and 25-30 years), race (white or black), and educational level (high school or less or higher than high school). Participant data have been collected across 8 examination cycles, including baseline and at years 2, 5, 7, 10, 15, 20, and 25, with retention of the cohort of 91%, 86%, 81%, 79%, 74%, 72%, and 72%, respectively. Details about the study design, sampling strategy, eligibility criteria, and baseline demographic characteristics have been previously published.[16]

For this analysis, we excluded 1616 participants (32%) who did not have CAC assessment at the year 25 examination (June 1, 2010, through May 31, 2011) and, furthermore, if they did not have at least 3 measures of PA during the 25 years of follow-up (examinations 1-8) (n=324). The remaining 3175 participants were included in the analytic sample, representing 62.1% of the initial CARDIA cohort at baseline. The study was approved by the institutional review board at each center, and written informed consent was obtained from all the participants.

PA Measurement

At each of the 8 examinations, self-reported leisure-time PA was ascertained by the interviewer-administered CARDIA Physical Activity History Questionnaire.[17] Participants were asked about the frequency of participation in 13 specific categories (8 vigorous intensity and 5 moderate intensity) of recreational sports, exercise, home maintenance, and occupational activities during the previous 12 months. Intensity for each activity was expressed as metabolic equivalents (METs), in which 1 MET is defined

as the energy expended at rest, which is approximately equivalent to an oxygen consumption of 3.5 mL per 1 kg of body weight per minute.[18] Vigorous activities (≥6 METs) included running or jogging; racquet sports; biking; swimming; exercise or dance class; job lifting, carrying, or digging; shoveling or lifting during leisure; and strenuous sports. Moderate-intensity activities (3-5 METs) included non-strenuous sports, walking and hiking, golfing and bowling, home exercises or calisthenics, and home maintenance or gardening.[19] Each activity was scored according to whether it was performed for 1 hour or longer during any 1 month during the past year, the number of months it was performed at that level, and the number of months the activity was performed frequently. Each activity was then assigned an intensity score, ranging from 3 to 8 METs, and a duration threshold (ranging from 2-5 hours per week), above which participation was considered to be frequent.[20]

A total PA score was computed using a computer-based algorithm by multiplying the frequency (number of months) by the intensity score of the activity with a weighting factor to represent duration of participation.[20] The total activity score was the sum of scores for all activities expressed in exercise units (EUs), and a threshold of 300 EU was used as the criterion to create distinct PA trajectory groups. For reference, a total activity score of 300 EU approximates Health and Human Services recommendations of approximately 150 minutes of moderate-intensity activity per week.[21] Previously in the CARDIA study, the 300-EU threshold has been shown to provide a more conservative estimate of meeting PA guidelines (sensitivity and specificity of 64.5% and 97.1%, respectively).[22,23] The CARDIA PA questionnaire shows test-retest reliability in the range of 0.77 to 0.84,[20] which is comparable with that of other activity questionnaires.[17]

Computed Tomography

Subclinical coronary atherosclerosis was assessed as the presence of any CAC at year 25 (2010-2011) using computed tomography (CT) of the chest. At all the centers, calcified coronary artery plaque measurement was performed with an electrocardiographically gated multidetector CT scanner, using a standardized protocol[24] with published accuracy and reproducibility.[25] Images were transmitted electronically to the CARDIA Reading Center, and image analysts blinded to participant characteristics calculated a total CAC score using a modified Agatston method,[26] with select overreading by a physician expert in CV imaging. Briefly, total calcium scores were obtained by summing all lesions in a given artery and across all arteries (left main, left anterior descending, left circumflex, and right coronary artery). Similar to a previous CARDIA analysis, the outcome of this study was the presence of CAC, defined as a total calcification score greater than 0 Agatston units measured at year 25.[27] A minimal CAC score >0 has been identified as a significant predictor of incident CHD[28] and a marker of mortality risk in young and middle-aged adults.[29] In addition, CAC>20 and CAC>100 were examined in sensitivity analyses.[27,30]

Other Measurements

Standardized protocols for data collection were used across study centers and examinations. Before each examination, participants were asked to fast for at least 12 hours and to avoid smoking or engaging in heavy PA for at least 2 hours. At each examination, height, weight, and waist circumference were measured as described previously.[15] Blood pressure was measured at every examination as described previously.[27] Plasma concentrations of total cholesterol and triglycerides were measured at all the examinations using enzymatic methods.[16] High-density lipoprotein cholesterol (HDL-C) levels were measured after dextran-magnesium precipitation,[31] and serum low-density lipoprotein cholesterol levels were calculated using the Friedewald equation.[32] Hyperlipidemia was defined as a total cholesterol level of 240 mg/dL or greater (to convert to mmol/L, multiply by 0.0259).[33] Fasting glucose levels were measured according to standardized CARDIA procedures, and diabetes mellitus was defined as a self-reported physician diagnosis of diabetes, a fasting glucose level of at least 126 mg/dL (to convert to mmol/L, multiply by 0.0555), or use of hypoglycemic agents.[31,32]

Information regarding age, race/ethnicity, cigarette use, medications, and medical history

was reported through questionnaire. The use of antihypertensive and lipid-lowering medications was assessed by self-report at each examination.

Statistical Analyses

Group-based trajectory class modeling was used to identify and categorize CARDIA participants based on patterns of longitudinal change in PA during the 25 years of follow-up.[27] These models were fit using SAS Proc Traj.[34] Group-based trajectory analysis, an application of finite mixture modeling, is designed to identify clusters of individuals with similar patterns of change over time. Relative to standard growth trajectory analyses focusing on population mean trajectories (with individual-level random effects for time-associated regression coefficients), this approach allowed us to identify groups of individuals who experience similar levels and patterns of change from young adulthood to midlife. Model fit was assessed using the Bayesian information criterion. In the final model, we had 3 classes with cubic order terms, from which we calculated the posterior predicted class membership probability for each individual. As in other studies, mean posterior probabilities were calculated to account for uncertainty in the PA trajectory group assignment and to ensure internal reliability of the model. In all the models, participants were assigned to the trajectory group for which they had the greatest posterior predictive probability (ie, has a high probability of belonging to the assigned trajectory group and a low probability of belonging to another group) over the 25-year follow-up. Trajectory groups were qualitatively examined and named to describe the visual pattern of change. A similar group-based trajectory method in the CARDIA study has been previously described.[27]

Distributions of covariates at baseline and at year 25 were described for each PA trajectory group using means, medians, and proportions as appropriate. Differences and trends were tested using linear regression models and χ^2 analyses for continuous and categorical characteristics, respectively.

Multivariable logistic regression models were used to estimate the association of each 25-year PA trajectory class with year 25 CAC>0. Regression analyses were sequentially adjusted for age (model 1), with further adjustment for race and sex and additionally for covariates reported at the year 25 follow-up examination: education and CVD risk factors and behaviors (eg, smoking status, diabetes, hyperlipidemia, body mass index, and hypertension status) (model 2). Potential effect modification by sex and race was explored by testing the statistical significance of appropriate cross-product terms and by comparing risk estimates in the sex × race−stratified analyses.

Two sensitivity analyses were performed using alternative thresholds to define the prevalence of CAC. First, we defined the prevalence of CAC as greater than 20 Agatston units. Second, the prevalence of CAC was defined as CAC>100 Agatston units. Multivariable logistic regression models were used to estimate the association of each 25-year PA trajectory class with CAC>20 and CAC>100, respectively.

Tests of statistical significance were 2-tailed, with an α level of .05. SAS version 9.3 (SAS Institute Inc) was used to perform all the statistical analyses.

RESULTS

A total of 3175 men and women who participated in the CARDIA study from January 1, 1985, through December 31, 2011, who had CAC data available at year 25 were included in the analyses. Of the 3175 eligible participants, 47.4% were black and 56.6% were women (Table 1).

Three distinct PA trajectories were identified (Figure), and the mean ± SD posterior probability for individuals in each group is presented: trajectory 1, below PA guidelines (n=1813; 57.1%; 0.95±0.11); trajectory 2, meeting PA guidelines (n=1094; 34.5%; 0.91±0.13); and trajectory 3, 3 times PA guidelines (n=268; 8.4%; 0.93±0.12). In general, all 3 PA trajectories showed a general age-related decline from young adulthood to midlife (Figure). The PA levels declined more during early adulthood than during midlife. A consistent rate of decline in PA levels was observed in participants who engaged in 3 times the PA guidelines (trajectory 3), whereas PA engagement plateaued with increasing age in trajectories 1 and 2.

TABLE 1. Participant Characteristics by PA Trajectory Group at Baseline and Examination Year 25[a,b]

Characteristic	Below PA guidelines (n=1813)	Meeting PA guidelines (n=1094)	3 times PA guidelines (n=268)	*P* value[c]
Age, baseline (*y*), mean ± SD	25.4±0.5	25.4±0.5	25.4±0.5	.75
Male sex (No. [%])	557 (30.7)	614 (56.1)	207 (77.2)	<.001
Sex and race (No. [%])				<.001
Black male; n=597	251 (13.8)	247 (22.6)	99 (36.9)	
White male; n=781	306 (16.9)	367 (33.6)	108 (40.3)	
Black female; n=908	744 (41.0)	150 (13.7)	14 (5.2)	
White female; n=889	512 (28.2)	330 (30.2)	47 (17.6)	
Education ≥16 y (No. [%])	484 (26.7)	408 (37.3)	88 (32.8)	<.001
Smoking (No. [%])				.01
Current	502 (27.8)	284 (26.2)	65 (24.3)	
Past	216 (12.0)	177 (16.3)	34 (12.7)	
BMI, mean ± SD	24.9±5.4	24.0±4.1	23.7±3.2	<.001
HDL-C, mean ± SD	49.8±12.9	50.2±12.8	49.9±11.1	.89
Hyperlipidemia (No. [%])	88 (4.9)	41 (3.8)	10 (3.7)	.32
Hypertension (No. [%])	70 (3.9)	35 (3.2)	4 (1.5)	.12
Diabetes (No. [%])	21 (1.2)	6 (0.6)	3 (1.1)	.24
Year 25				
Education ≥16 y (No. [%])	798 (44.0)	601 (54.9)	134 (50.0)	<.001
Smoking (No. [%])				.08
Current	316 (17.8)	177 (16.4)	41 (15.4)	
Past	371 (20.9)	265 (24.5)	50 (18.8)	
BMI, mean ± SD	31.4±7.7	29.0±6.3	28.0±5.1	<.001
HDL-C, mean ± SD	54.1±17.9	52.9±16.7	53.9±17.0	.70
Hyperlipidemia (No. [%])	180 (9.9)	110 (10.1)	27 (10.1)	.99
Hypertension (No. [%])	704 (38.8)	318 (29.1)	67 (25.0)	<.001
Diabetes (No. [%])	282 (15.6)	120 (11.0)	30 (11.2)	.001
CAC>0 (No. [%])	525 (29.0)	363 (33.2)	112 (41.8)	<.001
CAC>20 (No. [%])	301 (16.6)	234 (21.4)	67 (25.0)	<.001
CAC>100 (No. [%])	156 (8.6)	115 (10.5)	32 (11.9)	.09

[a]BMI = body mass index; CAC = coronary artery calcification; HDL-C = high-density lipoprotein cholesterol; PA = physical activity.

[b]The total number of observations was 3175 except for the following variables: at baseline—smoking, n=3155; BMI, n=3164; and diabetes, n=3118; and at year 25—smoking, n=3126; BMI, n=3169; and diabetes, n=3166.

[c]Values are significantly different among PA trajectories ($P<.05$).

Baseline characteristics of the CARDIA subsample (n=3175) across the 3 PA trajectory groups are presented in Table 1. In the total analytic sample, the mean ± SD age of participants was 25.4±0.5 years, and the cohort consisted of 18.9% black men, 24.6% white men, 28.6% black women, and 28.0% white women. At baseline, individuals in trajectory 3 (ie, 3 times PA guidelines) were more likely to be male ($P<.001$), whereas individuals in trajectory 1, which was below PA guidelines, were more likely to be women (69.3%) and black (54.9%) (all $P<.001$). The CV risk factors also differed across the 3 PA groups at baseline and at year 25. Whereas there was no difference at baseline, at year 25, hypertension ($P<.001$) and type 2 diabetes ($P=.001$) were highest in participants who engaged below the PA guidelines. Current smoking status, although lower in participants who engaged in 3 times the PA guidelines at year 25, did not significantly differ across the 3 PA groups. Although HDL-C levels did not significantly differ across overall PA groups at baseline or year 25 (both $P<.05$), further analyses revealed that white males consistently had the lowest HDL-C levels across nearly all 3 PA groups and compared with black males and black and white females (data not shown). Finally, at year 25, the prevalence of CAC>0 (41.8%; $P<.001$) and, similarly, CAC>20 (25.0%; $P<.001$) was highest in participants who engaged in 3 times the PA guidelines.

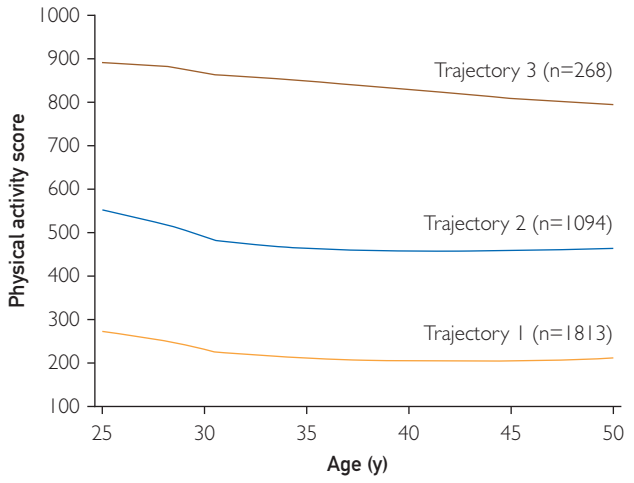

FIGURE. Trajectories of physical activity (PA) in the Coronary Artery Risk Development in Young Adults (CARDIA) study. Plotted lines represent the trajectory class identified for the estimated pattern of PA scores by age and number of CARDIA participants in each class. Trajectory 1 is defined as below PA guidelines (n=1813; 57.1%); trajectory 2, meeting PA guidelines (n=1094; 34.5%); and trajectory 3, 3 times PA guidelines (n=268; 8.4%).

The adjusted odds ratio (AOR) for the presence of CAC>0 according to PA trajectories at the year 25 follow-up are shown in Table 2, with trajectory 1 (below PA guidelines) as the reference group. Minimal adjustment for age (model 1) had a significantly higher odds of CAC prevalence in participants who were meeting PA guidelines (OR, 1.22; 95% CI 1.04-1.43) and engaged in 3 times the PA guidelines (OR, 1.76; 95% CI, 1.35-2.29) compared with participants with activity levels below PA guidelines. In the fully adjusted model (model 2), findings of a higher odds of CAC>0 were attenuated and no longer significant (AOR=1.00; 95% CI, 0.80-1.15 for meeting PA guidelines; and AOR=1.27; 95% CI, 0.95-1.70 for 3 times the PA guidelines).

Interactions between PA trajectory class and CAC>0 across race (P=.11) and race/sex categories (P=.48) were tested but were not statistically significant. However, to evaluate the clinical significance of findings reported in Table 2, we further assessed potential sex and race differences in the association between PA trajectory group and CAC (Table 2). Fully adjusted models stratified by race revealed that white but not black participants who were exceeding PA guidelines had a significantly increased odds of CAC (AOR=1.80; 95% CI, 1.21-2.67); further stratification by sex/race groups (eg, white men, black men, white women, and black women) showed that white men who exceeded PA guidelines had significantly higher odds of CAC (AOR=1.86; 95% CI, 1.16-2.98). However, the AOR estimating the association between the PA trajectory classes and CAC prevalence were not statistically significant for black men, black women, or white women, likely due to the low number of participants with detected CAC>0 in these respective groups.

In sensitivity analyses, findings of higher odds of CAC prevalence among white participants exceeding PA guidelines were similar but attenuated in models using the alternative threshold of CAC>20 as the outcome; however, associations between 25-year PA trajectories and the presence of CAC>100 were not significant among all CARDIA study participants (Supplemental Tables 1 and 2, available online at http://www.mayoclinicproceedings.org). Finally, all the analyses were repeated with additional adjustment for year 25 HDL-C levels; however, the results remained similar to those reported in Table 2.

DISCUSSION

In this prospective observational study, we identified 3 distinct PA trajectories over 25 years from young adulthood to middle age: participants who engaged in PA below national guidelines (trajectory 1), who met PA guidelines (trajectory 2), and who exceeded PA guidelines (trajectory 3). We found 27% higher odds of CAC>0 in participants who exceeded PA guidelines vs those below PA guidelines. Further stratification by sex and race showed that white men who reported PA that exceeded guidelines had greater odds of CAC prevalence by middle age; similar nonsignificant trends were noted for white women. Few data are available regarding the association of PA patterns from young adulthood to middle age on subclinical coronary atherosclerosis.

The present findings align with those of other large epidemiologic studies that focused on the cumulative doses of exercise and reported a U- or reverse J—shaped relationship between high doses of leisure-time PA and

TABLE 2. Odds Ratios for CAC>0 at 25 Years Associated With PA Trajectory Groups, Overall and Stratified by Race and Sex[a]

Model	Odds ratio (95% CI) [%CAC>0]		
	Below PA guidelines [29.0%]	Meeting PA guidelines [33.2%]	3 times PA guidelines [41.8%]
Model 1 (adjusted for age)	Reference	1.22 (1.04-1.43)	1.76 (1.35-2.29)
Model 2 (fully adjusted)[b,c]	Reference	1.00 (0.80-1.15)	1.27 (0.95-1.70)
Model 2[b] stratified by race (includes model 2 covariates except race)			
All black participants	Reference [28.3]	0.83 (0.62-1.12) [31.2]	0.89 (0.56-1.41) [34.5]
All white participants	Reference [29.7]	1.11 (0.87-1.42) [34.3]	1.80 (1.21-2.67) [47.1]
Model 2[b] stratified by race and sex (includes model 2 covariates except race and sex)[d]			
Black male	Reference [42.2]	0.87 (0.60-1.26) [38.5]	0.94 (0.57-1.54) [38.4]
Black female	Reference [23.7]	0.79 (0.50-1.26) [19.3]	0.46 (0.06-3.67) [7.1]
White male	Reference [49.0]	1.10 (0.79-1.51) [48.5]	1.86 (1.16-2.98) [58.3]
White female	Reference [18.2]	1.17 (0.79-1.73) [18.5]	1.71 (0.79-3.71) [21.3]

[a]CAC = coronary artery calcification; %CAC>0 = percentage of participants with CAC prevalent (CAC>0) at year 25 examination with respect to the PA trajectory group; PA = physical activity.

[b]Model 2 covariates: age, race, sex + year 25 follow-up hypertension, diabetes, smoking status, body mass index, education, and hyperlipidemia. Interaction between PA trajectory class and race, *P*=.11. Interaction between PA trajectory class and race/sex categories, *P*=.48.

[c]Sixty-three observations were excluded from all the multivariate analyses due to missing values for the response or explanatory variable.

[d]Black males: trajectory 1, n=106; trajectory 2, n=95; trajectory 3, n=38; black females: trajectory 1, n=176; trajectory 2, n= 29; trajectory 3, n=1; white males: trajectory 1, n=150; trajectory 2, n=178; trajectory 3, n=63; and white females: trajectory 1, n=93; trajectory 2, n=61; trajectory 3, n=10.

CV and all-cause mortality.[6-8] Specifically, the Million Women Study showed that women who engaged in any form of exercise at least once a week had a lower incidence of CHD compared with inactive women, but engagement in PA beyond once a week was associated with smaller benefits up to a certain point, beyond which there was no additional risk reduction.[7] Similarly, in the Copenhagen City Heart Study, compared with light joggers, moderate and strenuous joggers had significantly higher mortality risk (hazard ratio=3.06 [95% CI, 1.11-8.45] and 9.08 [95% CI, 1.87-44.01], respectively).[8]

Other studies have reported potentially adverse CV effects of long-term, vigorous, extreme endurance exercise. For example, some athletes demonstrate exercise-induced elevations in cardiac troponin levels,[35] an increased incidence of atrial fibrillation,[36] myocardial late gadolinium enhancement, which is predictive of subclinical myocardial damage,[37] and even evidence of myocardial fibrosis[38] and biventricular systolic and diastolic dysfunction.[39,40] Finally, Möhlenkamp et al[37] showed that compared with age-matched Framingham risk score controls, healthy male marathon runners (50-72 years) had higher CAC scores; and those with CAC≥100 were also noted to have myocardial late gadolinium enhancement, a predictor of subclinical myocardial damage. It was suggested that the higher CAC scores in the marathoners can be explained by higher values of unmeasured risk factors[37]; alternatively, the sheer stress of faster heart rate and systolic blood pressure during exercise training could have accelerated the atherosclerotic process in the runners.[5]

The results of the present study showing a relationship between higher doses of PA (ie, exceeding PA guidelines) and CAC development suggest yet another possible mechanistic explanation for the existence of an upper limit for CV benefit. However, we cannot exclude the possibility of a chance finding given the low prevalence of metabolic risk factors in the highest-activity trajectory group. Nonetheless, further evidence examining the cardiac benefits vs risk of prodigious amounts of exercise to the level of excessive is warranted. However, it may also be possible that higher PA engagement confers atherosclerotic benefit by promoting plaque stabilization and preventing its rupture, leading to thrombosis. Along these lines, recent studies in healthy, middle-aged, highly active adults have reported that higher doses of exercise were associated with higher levels of CAC and that the atherosclerotic plaques were, in fact, likely to be more calcified plaques, suggesting that the stable nature of coronary plaques in highly

active individuals may mitigate plaque rupture.[41,42] Additional research investigating whether higher PA levels, including type and duration of PA, are associated with increased plaque calcium density for a given CAC volume, indicative of plaque stability to evaluate CV risk, is needed.[43]

On the contrary, others have challenged the extreme exercise hypothesis, viewing evidence as being relatively weak and not clinically important given the known benefits of exercise on cardiac and vascular structure and function.[44-49] For example, in a population-based cohort of nearly 75,000 nonelite-level Swedish skiers who participated in long-distance skiing races, those who finished more races (and presumably older and trained for more years) had lower mortality.[48] Earlier evidence has suggested that, physiologically, elite ultra-endurance athletes have increased diameter and dilation of the coronaries,[45,50] partly due to adaptations of the vascular structure, and possibly an increase in the caliber or number of resistance arterioles.[50] So, although there can be increased atherosclerosis in endurance athletes compared with sedentary males with a similar risk profile,[41] it may not necessarily translate into adverse clinical outcomes due to the presence of enlarged coronary artery size and dilatory capacity.[51,52] Similarly, it is argued that the risk of bradyarrhythmias and atrial fibrillation[53] is modest given that the coronaries of endurance athletes presumably have superior vasomotor reserve and reduced risk of plaque rupture leading to thrombosis.[45,49]

We noted a differential effect of higher levels of PA on odds of CAC. These findings demonstrate a greater odds of CAC>0 in white males engaged in 3 times PA guidelines, with similar trends observed in white females; however, interactions between race or across race/sex categories in the association between trajectory class and CAC>0 were not statistically significant. We, therefore, cannot completely explain why the associations between higher PA levels 3 times above guidelines and higher CAC prevalence was present in white men only. In this regard, another study by Erqou et al[54] showed that after adjustment for CVD risk factors, black race was significantly associated with greater carotid intima media thickness but less CAC (CAC>100) than white race. The authors further note that the higher concentration of various inflammatory mediators observed in the black participants suggests that the increased risk of CVD in black patients may be related to higher plaque vulnerability of less calcified coronary lesions.[54] Similar to the results of Erqou et al,[54] white males in the present analyses had the lowest HDL-C levels across all 4 race/sex groups. Given that HDL-C is positively associated with PA and has an essential role in protecting against CVD, it is possible that higher levels of HDL-C provide more protection against the development of CAC in black men, whereas lower HDL-C levels may not be sufficient to elicit similar protection against the development of CAC in white men. However, in the present analyses, additional adjustment for HDL-C revealed no difference in the reported associations between 25-year PA trajectories and CAC prevalence in white and black males and females; thus, additional data are needed to understand the role of HDL-C in CAC development. Furthermore, the lack of association of trajectory class with CAC in black participants may have been due to small sample sizes because very few black individuals were in the exceeded PA guidelines trajectory group. There are some data that suggest that plaque is less calcified in black than white individuals, which may be explained by differences in vitamin D and calcium metabolism, or bone regulatory factors, inflammatory markers, hemostasis, and fibrinolysis.[55] Previously, most studies assessing the impact of high levels of PA on cardiac outcomes did not include black participants, and further exploration on environmental, biochemical, and genetic factors are needed to asses any differences by race.

Engagement in PA is a continuously evolving process throughout life. However, no studies have examined the changes in PA with subclinical CAC development, a measure of atherosclerosis. Earlier studies showing that a high level of leisure-time PA delays coronary atherosclerosis progression have been restricted to older populations ranging from 52 to 80 years,[11,12,14] and many have been of cross-sectional design[9,10,12] and, therefore, are without data about changes in PA patterns and the interrelationships of aging and time as predictors of PA over the life span. Other prospective studies that have analyzed PA changes over time are limited in their methods to categorize

individuals, for example, by averaging repeated assessments of PA or through modeling change in PA relative to some baseline value.[11,12,14]

The strengths and limitations of this study are noteworthy. This study used innovative trajectory modeling methods that incorporate both the time and sequence of assessments to identify subgroups in the population that share similar trajectories of PA during young adulthood and middle age. Trajectories of PA levels were obtained based on measures from up to 8 follow-up examinations, with a minimum of 3 PA measures, thus reflecting long-term PA patterns. However, self-reported questionnaires were used to capture changes in PA, which are subject to participant recall and social desirability bias.[12] In addition, self-reported PA does not provide information regarding activity intensity but rather provides a more conservative estimate of minutes of PA engagement per week. Substantial evidence indicates that cardiorespiratory fitness (CRF) is one of the strongest predictors of atherosclerotic CVDs and mortality.[46] Presumably, higher PA contributes to higher CRF, which may obviate the risk associated with higher CAC scores and provide CV protection.[56] However, the extent to which these findings are explained by baseline CRF, family history of coronary artery disease, psychosocial or socioeconomic characteristics or related lifestyle factors, or genetics is yet to be assessed and may introduce additional confounding to this PA and CAC investigation. Likewise, we acknowledge the potential for misclassification bias regarding the self-reported use of cardioprotective medications because we are unable to confirm whether CARDIA participants were correctly reporting their medication use on questionnaires. Another limitation is that although trajectory modeling accounts for group variations, it does not capture individual variations in PA levels, which may exist within trajectory groups and, thus, may explain the nonsignificant associations between 25-year PA trajectories and CAC prevalence development, particularly in participants meeting PA guidelines (trajectory 2). Furthermore, the trajectory groups identified in this younger population may not be generalizable to other populations. Last, trajectory 3 participants (3 times PA guidelines) included relatively few black females because PA levels were generally lower in this group; therefore, we were underpowered to detect an association within this subgroup.

CONCLUSION

In summary, these results showed that white individuals who participated in 3 times the recommended guidelines for PA over 25 years had higher odds of developing coronary subclinical atherosclerosis by middle age. Collectively, these data suggest that the biological mechanisms associated with increased CAC and high levels of PA deserve further evaluation. Likewise, the impact of modestly higher levels of CAC in aging, highly active individuals on CV outcomes also deserves further attention.

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **AOR** = adjusted odds ratio; **BMI** = body mass index; **CAC** = coronary artery calcification; **CARDIA** = Coronary Artery Risk Development in Young Adults; **CHD** = coronary heart disease; **CRF** = cardiorespiratory fitness; **CT** = computed tomography; **CV** = cardiovascular; **CVD** = cardiovascular disease; **EU** = exercise unit; **HDL-C** = high-density lipoprotein cholesterol; **MET** = metabolic equivalent; **PA** = physical activity

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