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Cardiorespiratory Fitness and Coronary Artery Calcification in Young Adults: The CARDIA Study

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Abstract

Whether cardiorespiratory fitness relates to early subclinical atherosclerotic vascular disease remains unknown. We investigated the relation of cardiorespiratory fitness to coronary artery calcification (CAC) in 2373 African-American and White young adults from the Coronary Artery Risk Development in Young Adults (CARDIA) Study. We measured cardiorespiratory fitness in 1985-1986 (baseline) using a symptom-limited exercise test on a treadmill. Coronary calcium scores were measured in 2001-2002 (year 15) using electron-beam or multi-detector computed tomography. CAC was classified as present or absent, while cardiorespiratory fitness was classified as sex-specific low, moderate, and high fitness categories. After adjustment for age, sex, race, clinical center, education, cigarette smoking, waist girth, alcohol intake, physical activity, systolic blood pressure, antihypertensive medication use, diabetes mellitus, and fasting insulin, baseline cardiorespiratory fitness was inversely associated with prevalence of CAC in young adults (P for trend = 0.03). The odds ratios of having CAC for persons in the moderately and highly fit individuals were 0.80 (95% confidence interval (CI), 0.55-1.15) and 0.59 (95% CI, 0.36-0.97), respectively, as compared with the low-fit individuals. High levels of cardiorespiratory fitness were associated with a lower risk of having coronary calcification 15 years later in African-American and White young adults.

Keywords

Coronary artery calcification; Cardiorespiratory fitness; Physical activity

Introduction

Atherosclerosis is a major cause of stroke and coronary heart disease (CHD). Coronary artery calcification (CAC) is a subset of atherosclerosis that is positively associated with CHD and cardiovascular disease (CVD) events [1,2]. Cardiorespiratory fitness, an objective marker of

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physical activity, is also determined by genetics, subclinical disease, and behavioral and environmental factors [3]. Cardiorespiratory fitness is a strong predictor of all-cause and CVD mortality [4-6]. Improvements in fitness reduce blood pressure [7,8] and improve lipid profile [7,8], sensitivity to insulin [9], blood coagulation [10], platelet aggregation [11], fibrinolysis [12,13], and antioxidant defense systems [14-16]. However, the effects of cardiorespiratory fitness on the progression of early subclinical atherosclerotic vascular disease remain less clear. An inverse association between cardiorespiratory fitness and carotid artery intima-media thickness has been reported [17,18]. Although no association was seen between coronary calcium scores and physical activity [19,20], a close correlate of fitness [21], several clinical trials have also shown that exercise training coupled with other lifestyle modifications slowed progression of coronary atherosclerosis in CHD patients [22-26]. To address atherosclerotic vascular disease prevention strategies, it is important to investigate whether cardiorespiratory fitness is associated with reduced early atherosclerotic vascular disease risk in young adults. We therefore investigated whether cardiorespiratory fitness relates to CAC in African-American and White young adults from the Coronary Artery Risk Development in Young Adults (CARDIA) Study. Because physical activity is the most important behavioral determinant of fitness, we also studied habitual physical activity in relation to CAC.

2. Methods

2.1. Study population

The CARDIA study is a population-based cohort study to investigate the etiology of atherosclerosis in a young biracial population from 4 United States communities: Birmingham, Ala; Chicago, Ill; Minneapolis, Minn; and Oakland, Calif. The baseline study population comprises 5,115 African-American and White men and women, ages 18 to 30 years, recruited in 1985 to 1986 (Year 0). The participants were selected using a balanced design by race, gender, educational attainment (high school or less and more than high school), and age groups (18-24 and 25-30). The complete study design, sampling strategy, and examination techniques have been reported previously [27]. The participants were reexamined during 1987-1988 (Year 2), 1990-1991 (Year 5), 1992-1993 (Year 7), 1995-1996 (Year 10), and 2000-2001 (Year 15), with retention rates of 90%, 86%, 81%, 79%, and 74%, respectively. At year 15 examination, 3672 participants returned to examination. Of these, 3042 participants had a coronary artery scan to determine the presence or absence of calcium deposits in the arteries. The current study is based on those participants who had a baseline treadmill test (year 0) and a coronary artery scan at the year 15 examination. The participants' age ranged from 33 to 45 years at year 15 examination.

2.1.1. Measurements—All participants signed informed consent for the clinical examination, and were asked to fast for 12 hours before the clinical examination. The site institutional review committees approved the protocol. Body height and weight were measured with a calibrated scale and a vertical ruler, respectively, and body mass index (BMI, kg/m²) was calculated as weight in kilograms divided by height in meters squared. Waist girth was measured midway between the iliac crest and the lowest lateral portion of the rib cage and anteriorly midway between the xiphoid process of the sternum and the umbilicus, and further classified as sex-specific tertiles. Seated blood pressure was measured after 5 minutes of rest using a random-zero sphygmomanometer, and the average of the last 2 of 3 consecutive measurements was used for analysis. Serum, plasma, and whole blood samples were drawn from an antecubital vein and stored at -70° C until analysis. Plasma total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglycerides were measured with an enzymatic method [28]. HDL-C was measured after dextran-magnesium precipitation [29], and LDL-C was calculated using the Friedewald equation [30]. Fasting insulin was measured by radioimmunoassay (Linco). Test-retest laboratory reliability coefficients for total cholesterol,

HDL-C, LDL-C, and triglycerides were > 0.98 [31]. Additional details of examination procedures are published elsewhere [31-32].

CAC was determined at the year 15 examination by using computed tomography (CT) of the chest. Trained technicians scanned the root of aorta to the apex of the heart and obtained 40 contiguous 2.5- to 3 mm thick transverse images using electron beam CT (Chicago and Oakland field centers) and multidetector CT (Birmingham and Minneapolis field). All participants were scanned twice over a hydroxyapatite phantom to allow monitoring of image brightness and noise and adjusting for scanner differences. Obtained scans were electronically sent to the CARDIA Reading Center, and a radiologist identified the courses of the coronary arteries using specially developed image-processing software, programmed to define a calcific focus as four adjacent pixels comprising an area of at least 1.87 mm^2 . A calcium score was calculated for each calcified lesion by multiplying the area of focus by a coefficient based on the peak CT number in the focus. The coefficient ranges from 1 to 4 (1 = 131 to 200 HU, 2 = 201 to 300 HU, 3 = 301 to 400 HU, and 4 = 401 or greater HU). Total calcium scores were obtained by summing all lesions within a given artery and across all arteries (left main, left anterior descending, left circumflex, and right coronary artery). Each scan set with at least 1 non-zero score and a random sample of those with 0 score was reviewed by an expert investigator without knowledge of the scan scores to verify the presence of CAC. The overall score was calculated as the average of the two scans if the investigator adjudicated as positive, and was set to zero for those adjudicated as negative. Details on the CAC examination techniques and procedures have been described previously [33]. Coronary calcium was classified as a dichotomous variable (0 = absence; 1 = if calcium score > 0)

Cardiorespiratory fitness was measured by a maximal treadmill exercise test using a modified Balke protocol [34]. The test consisted of up to nine 2-minute stages of progressively increasing difficulty. The treadmill speed was $3.0 \text{ miles} \cdot \text{h}^{-1}$ for the first stage; $3.4 \text{ miles} \cdot \text{h}^{-1}$ for stages 2 to 6; $4.2 \text{ miles} \cdot \text{h}^{-1}$ for stages 7 to 8; and $5.6 \text{ miles} \cdot \text{h}^{-1}$ for stage 9. The grade was 2% for the first stage; 6% for the second stage and increased by 4% in each stage up to stage 6; 22% for the stage 7; and 25% for the stages 8 and 9. We determined medically eligible participants for the treadmill test, excluding those with a history of ischemic heart disease, and exercise-induced asthma at baseline, and those who were pregnant or had elevated resting blood pressure (systolic blood pressure $> 160 \text{ mmHg}$ or diastolic blood pressure $> 90 \text{ mmHg}$), acute illness with a fever, personal injury, or current use of cardiovascular medications (except high blood pressure medication). We also excluded those who had an abnormal electrocardiogram or equipment malfunction during the treadmill test. Total endurance time was used as an index of aerobic power, and sex-specific quartiles were used to classify cardiorespiratory fitness category. Men and women in the lowest quartile was classified as low fit, the next 2nd and 3rd quartiles as moderately fit, and the highest quartile as high fit.

Cigarette smoking, alcohol intake, physical activity, education level, and parental history of coronary artery disease (CAD) were assessed by standardized questionnaires. Smoking status was classified as never smoked, former smoker, or current smoker. Ever smoking was a statement that the participant had smoked at least 5 cigarettes per week, almost every week, for at least 3 months. Current smoking was an affirmative response to the question "do you still smoke cigarettes regularly". Alcohol intake was a continuous variable (ethanol intake, ml/day). Physical activity was assessed by the CARDIA physical activity questionnaire [35], which measured the frequency of participation in 13 different categories of recreational sports and exercise in the past 12 months. Self-reported physical activity scores were computed by multiplying the frequency of participation by intensity of activity and were classified as low, moderate, and high activity categories, which correspond to $< 25^{\text{th}}$, 25 to 75th, $\geq 75^{\text{th}}$ sex-specific percentile scores. Education level was classified by number of years of education: less than high school, completion of high school, or college graduation or more. Antihypertensive

medication use was noted. Diabetes mellitus was defined as a fasting glucose level ≥ 126 mg/dL or use of hypoglycemic agents.

2.1.2. Statistical analyses—We included 2373 men and women who participated the CARDIA study from 1987 to 2001. All participants had a year 0 treadmill test in which they achieved at least 85% of age-predicted maximal heart rate and a coronary artery scan at the year 15. We excluded 669 participants who did not complete the exercise treadmill test at baseline ($n = 173$), who were pregnant ($n = 3$), who failed to achieve at least 85% of age-predicted maximal heart rate ($n = 413$), and those missing covariates ($n = 80$). General linear models were used to test mean differences across fitness categories after adjustment for age, sex, race, and clinical center, and education. A chi-square test was used to compare frequency differences across fitness categories. Multiple logistic regression models were used to investigate the association of baseline cardiorespiratory fitness levels to year 15 presence of CAC after adjustment for age, sex, race, clinical center, and education (model 1), additional adjustment for cigarette smoking, waist girth, alcohol intake, and physical activity (model 2), and additional adjustment for systolic blood pressure (SBP), antihypertensive medication use, diabetes mellitus, and fasting insulin (model 3). All covariates were measured at year 0. Trends across exposure categories were tested by treating those categories as an ordinal scale with adjustment for covariates. The lowest fitness quartile was the reference category. We carried out parallel analyses with physical activity as the exposure of interest. We also examined the race- and sex-adjusted partial Pearson correlations between treadmill duration with HDL-C, total cholesterol, LDL-C, triglycerides, and fasting insulin. All statistical procedures were performed by Statistical Analysis Systems, version 9 (SAS Institute, Cary, NC).

3. Results

As Table 1 shows, African Americans tended to be less fit than whites. The prevalences of CAC ($P < 0.001$), antihypertensive medication use ($P < 0.001$), and current smoking ($P < 0.001$) and the mean scores of systolic blood pressure ($P < 0.001$), triglycerides ($P < 0.001$), fasting insulin ($P < 0.001$), LDL-C ($P < 0.001$) and total cholesterol levels ($P < 0.001$) were progressively lower across low, moderate, and high cardiorespiratory fitness levels. The means scores of physical activity and HDL-C ($P < 0.001$) were higher across fitness groups (Table 1). We observed similar trends when the analyses were stratified by race and sex (data not shown).

Race- and sex-adjusted partial correlation coefficients with treadmill duration were 0.23 for HDL-C ($P < 0.001$), -0.14 for total cholesterol ($P < 0.001$), -0.17 for LDL-C ($P < 0.001$), -0.25 for triglycerides ($P < 0.001$), and -0.33 for fasting insulin ($P < 0.001$).

Table 2 shows the association between cardiorespiratory fitness and year 15 presence of CAC. After adjustment for age, sex, race, clinical center, and education, there was an inverse association between cardiorespiratory fitness levels and CAC (P for trend < 0.001). Associations persisted after additional adjustment for cigarette smoking, waist girth, alcohol intake, physical activity (model 2), and additional adjustment for systolic blood pressure (SBP), antihypertensive medication use, diabetes mellitus, and fasting insulin (model 3). The odds ratios of having CAC for persons in the moderately and highly fit individuals were 0.80 (95% confidence interval, 0.55-1.15) and 0.59 (95% confidence interval, 0.36-0.97), respectively, as compared with the low-fit individuals (model 3, P for trend = 0.03). We further analyzed the association between baseline physical activity and CAC (Table 3), finding no association after minimal adjustment for age, sex, race, clinical center, and education (P for trend = 0.67). Associations remained null after further adjustment for other multiple risk factors (models 2 and 3, $P > 0.05$).

Supplemental analyses were run. We carried out sensitivity analyses concerning the effect of a more stringent exclusion for achieved treadmill heart rate. Findings were similar if we included only those who achieved 80%, 85%, and 88% of age predicted maximum heart rate. The estimated magnitude of this relation was unaltered but became nonsignificant when we included only those who failed to achieve these age-predicted maximal heart rates (85% and 88%), possibly due to the decreased sample size (data not shown). Second, we examined the association between cardiorespiratory fitness and CAC after additional adjustment for blood lipids (HDL-C and total cholesterol levels, and triglycerides) in model 3, and found that the association was attenuated to nonsignificance. The odds ratios across low, moderate, and high fitness categories were 1.00 (low, reference), 0.95 (0.65, 1.39), and 0.78 (0.46, 1.28) (P for trend = 0.35). Third, we examined year 15 physical activity in relation to CAC. CAC was unrelated to year 15 physical activity or to the average of all available physical activity measurements (data not shown). Fourth, we assessed a possible race $\times$ sex interaction; the P -value for the race $\times$ sex interaction was 0.37. There was no interaction for the fitness $\times$ race (P = 0.54) or fitness $\times$ sex (P = 0.52).

4. Discussion

Although cardiorespiratory fitness is a strong predictor of all-cause and cardiovascular disease mortality and mediates atherosclerotic risk [3-16], there has been little research on the association between cardiorespiratory fitness and subclinical atherosclerotic vascular disease in young adults. Our major finding was that cardiorespiratory fitness was inversely associated with early atherosclerosis in African-American and White young adults. This finding is consistent in direction with the Kuopio Ischemic Heart Disease Risk Factor (KIHDRF) Study in which Finnish men who had higher aerobic capacity had slower progression of mean carotid artery wall thickness with adjustment for age and cigarette smoking [17]; their findings were attenuated by further adjustment for apolipoprotein B and diabetes. Regular physical activity leads to increased cardiorespiratory fitness; about 35% of the variance in cardiorespiratory fitness is explained by physical activity [21]. Therefore this finding is also consistent in direction with several clinical trials including the Heidelberg Regression Study [22,23], the Stanford Coronary Risk Intervention Project [24], and the Lifestyle Heart Trial [25,26], in which coronary artery disease (CAD) patients who had exercise training with a low-fat diet [22,23] or exercise training with other lifestyle modification (stop smoking, low-fat diet, and stress management) [24-26] had a slower progression of coronary atherosclerosis, as compared with control patients with CAD. In contrast, our findings indicate that there is no association between baseline physical activity and CAC, consistent with reports from the US Army Personnel Study and the Atherosclerosis Risk in Communities (ARIC) Study both of which showed no association between physical activity and CAC [19,20]. This may be due to imprecise measurement of physical activity in both observational and cross-sectional studies, which may have underestimated the true odds ratios. Further studies are needed to determine with more accurate measurement of physical activity such as accelerometer or pedometer in relation to CAC.

It is known that some factors (e.g., blood lipids) improve after fitness training [7-8,11-12,39], consistent with correlations observed in the present study; blood lipids are not confounders if they are in the causal pathway. In our study, a dose-response relation between cardiorespiratory fitness and CAC persisted without adjustment for blood lipids, but this association became nonsignificant with adjustment for blood lipids indicating that these lipids are likely in the causal pathway.

Besides improving blood lipid profile, there are several plausible ways by which cardiorespiratory fitness might reduce atherosclerotic vascular disease risk. Vascular function, platelet activity, and coagulant factors may determine both hemostasis and thrombosis in the

vessels. Physical activity or exercise improves nitric oxide and prostacyclin production, which improve endothelial function by enhancing vasodilation and vasomotor function in the vessels [36]. Exercise also prevents platelet aggregation and adhesion in the endothelium [37,38]. Exercise can play an antithrombotic role by enhancing fibrinolysis [13] and improving lipid profiles [39], and by reducing blood pressure [8], blood viscosity [39] and fibrinogen levels [40], all of which might contribute to slow the progression of early atherosclerosis.

A strength of this study is that our data represent population-based samples of United States African-American and White young men and women. To our knowledge, this is the first study to investigate the relation of cardiorespiratory fitness to subclinical atherosclerosis in young adults. Further studies are needed to determine whether cardiorespiratory fitness is associated with presence of CAC across different ethnic and age groups. A limitation of our study is that we did not assess CAC at baseline, but we included only asymptomatic healthy individuals at baseline excluding those patients with a history of ischemic heart disease; those who had elevated resting blood pressure or current use of cardiovascular medications; and those with an abnormal electrocardiogram during the treadmill test. In addition, we included only participants who achieved at least 85% of their age-predicted maximal heart rate. We focused on prediction of CAC from measurements 15 year earlier. We did not study changes in fitness or other exposure variables during the follow-up; future CARDIA reports will do so.

In conclusion, we found that high levels of cardiorespiratory fitness were associated with a lower risk of having coronary calcification 15 years later in African-American and White young adults.

Our findings suggest that cardiorespiratory fitness may play a role in preventing early atherosclerotic vascular disease risk in young adults.

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Table 1

Characteristics of the study participants across cardiorespiratory fitness levels: The CARDIA study, 1985-2001.

Characteristics	Baseline cardiorespiratory fitness levels [*]			P Value [†]
	Low	Moderate	High	
No. of participants (N = 2373)	575	1204	594	
Baseline mean Levels [‡]				
Age	25.2	24.3	24.1	<0.001
Treadmill time (min)				
White men (n = 692)	9.8	12.4	14.8	<0.001
Black men (n = 430)	9.0	11.7	13.8	<0.001
White women (n = 690)	7.2	9.7	12.3	<0.001
Black women (n = 561)	5.6	7.6	9.9	<0.001
Systolic blood pressure (mmHg)	112.2	110.2	108.7	<0.001
Total cholesterol (mg/dL)	185.3	177.5	172.7	<0.001
HDL cholesterol (mg/dL)	48.5	53.4	56.6	<0.001
LDL cholesterol (mg/dL)	118.5	109.7	104.1	<0.001
Triglycerides (mg/dL)	91.3	72.1	60.2	<0.001
Fasting insulin level (uU/mL)	14.7	9.9	8.3	<0.001
Alcohol intake (ml/day)	14.1	14.7	13.3	0.43
Waist girth (cm)	85.0	76.8	73.1	<0.001
Physical activity score	341.4	416.8	554.7	<0.001
Baseline percent frequency				
Male (%)	45.0	47.3	49.3	0.34
African American (%)	63.1	43.3	18.0	<0.001
Antihypertensive medication use (%)	2.6	1.4	0.5	0.01
Current smoking (%)	27.0	24.0	14.7	<0.001
Education level (< 12 years) (%)	7.7	5.7	2.7	<0.001
Year 15 percent frequency				
Coronary artery calcification (%)	12.0	9.2	6.6	0.006

^{*} Sex-specific cardiorespiratory fitness (treadmill time, min.): men, <11, 11 to <13.5, ≥13.5; women, <7.3, 7.3 to <10, ≥10.

[†] P value based on F test with 2 degrees of freedom for any difference among the 3 fitness level groups.

[‡] Adjusted for age, sex, race, clinical center, and education.

Odds ratios (95% CI) of year 15 presence of coronary artery calcification by baseline cardiorespiratory fitness levels in White and African-American young adults: the CARDIA study, 1985-2001.

Variables	No. of Cases	Baseline cardiorespiratory fitness levels*			P for trend
		Low	Moderate	High	
Coronary calcification	219	69	111	39	
Adjusted for age, sex, race, clinical center, and education (model 1)		1.00	0.72 (0.51, 1.01)	0.46 (0.29, 0.71)	<0.001
Multivariable adjusted (model 2) [†]		1.00	0.78 (0.54, 1.10)	0.56 (0.34, 0.90)	0.02
Multivariable adjusted (model 3) [‡]		1.00	0.80 (0.56, 1.16)	0.59 (0.36, 0.97)	0.03

* Sex-specific cardiorespiratory fitness levels (treadmill time, min.): men, <11, 11 to <13.5, ≥13.5; women, <7.3, 7.3 to <10, ≥10. Covariates were used from the year 0 examination.

[†] Adjusted for age, sex, race, clinical center, education, cigarette smoking, waist girth, alcohol intake, and physical activity.

[‡] Adjusted for age, sex, race, clinical center, education, cigarette smoking, waist girth, alcohol intake, physical activity, systolic blood pressure, antihypertensive medication use, diabetes mellitus, and fasting insulin.

Odds ratios (95% CI) of year 15 presence of coronary artery calcification by baseline physical activity levels in White and African-American young adults: the CARDIA study, 1985-2001.

Table 3

Variables	No. of Cases	Baseline physical activity levels*			P for trend
		Low	Moderate	High	
Coronary calcification	219	62	109	51	
Adjusted for age, sex, race, clinical center, and education (model 1)		1.00	0.84 (0.59, 1.18)	0.92 (0.61, 1.39)	0.67
Multivariable adjusted (model 2) [†]		1.00	0.83 (0.58, 1.18)	0.95 (0.62, 1.44)	0.76
Multivariable adjusted (model 3) [‡]		1.00	0.83 (0.58, 1.19)	0.96 (0.63, 1.47)	0.82

* Sex-specific physical activity levels (units): men, <272, 272 to <688, ≥688; women, <150, 150 to <478, ≥478. Covariates were used from the year 0 examination.

[†] Adjusted for age, sex, race, clinical center, education, cigarette smoking, waist girth, and alcohol intake.

[‡] Adjusted for age, sex, race, clinical center, education, cigarette smoking, waist girth, alcohol intake, systolic blood pressure, antihypertensive medication use, diabetes mellitus, and fasting insulin.