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Cardiorespiratory fitness and coronary artery calcification in women

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ABSTRACT

Introduction: Cardiorespiratory fitness (fitness) has been shown to be inversely associated with coronary heart disease morbidity and mortality. The cardioprotective mechanisms of fitness are not well defined. The goal of this study was to assess the relationship between coronary artery calcification as a measure of atherosclerotic burden and fitness in a large population of generally healthy women.
Methods: 5341 women ages 40–90 years seen between 1997 and 2007 underwent maximal treadmill exercise testing and coronary artery calcium (CAC) scanning. Fitness was reported in METs estimated from maximal treadmill time, grade, and speed. CAC was characterized dichotomously as CAC = 0 versus CAC > 0, and CAC < 100 versus CAC ≥ 100. Multiple logistic regression models were used to calculate the adjusted odds ratio of any CAC (CAC > 0) and CAC ≥ 100. Fitness was added to these models continuously and categorically based on standard and sample-specific cut-points.
Results: With a mean age of 52.0 years, the overall prevalence of detectable CAC was 19.9% and CAC ≥ 100 was 6.8%. Univariable analysis showed a modest inverse relationship between fitness and CAC > 0 (24% in low fit versus 19% in high fit, *p*-trend = 0.006), with a similar trend observed for CAC ≥ 100. In multivariable models, age adjustment diminished this association and the relationship was no longer statistically significant after adjustment for traditional risk factors.
Conclusions: The cardioprotective benefit of fitness does not appear to be mediated by an effect independent of traditional risk factors on the development of calcified coronary atherosclerosis as measured by electron beam tomography.

1. Introduction

Cardiorespiratory fitness (fitness) in women has been shown to be inversely associated with cardiovascular mortality [1] and coronary heart disease morbidity and mortality [2]. The underlying mechanisms of this favorable association have not been completely defined. The relationship between fitness and coronary heart disease events may be mediated through effects on intermediary cardiovascular risk factors, which are more common in unfit women [3], or could be mediated by other factors which affect the burden and progression of atherosclerosis independent of traditional risk factors. Currently, there are few data addressing the relationship between fitness and the development of calcified coronary atherosclerosis as quantified by coronary artery calcium (CAC) [4] in women.

The goal of this study was to assess the relationship between measured fitness and the burden of subclinical calcified coronary atherosclerosis as reflected by CAC in a large population of generally healthy women in order to better understand the cardioprotective mechanisms of fitness in preventing the development of coronary heart disease in women.

2. Methods

This study was a cross-sectional analysis of data collected during preventive medical examinations of patients evaluated at the Cooper Clinic in Dallas, Texas between 1997 and 2007. Data were entered into the Cooper Center Longitudinal Study database, which is maintained by The Cooper Institute. Patients signed an informed consent and approved the use of their data for research. Privacy precautions were maintained through The Cooper Institute policies, and all data were de-identified prior to analysis. The data collection and informed consent are reviewed and approved annually by The Cooper Institute's Institutional Review Board.

The study population consisted of 5341 women, ages 40–90, who underwent electron beam tomography scanning and fitness testing. Cooper Clinic patients are generally healthy, college-educated,

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primarily non-Hispanic white, and have access to preventive medical care by self-referral or referral from their employer. To be included in this analysis, participants were required to have complete data at one visit for medical history, anthropometric measurements, and laboratory studies that included lipids and glucose in addition to electron beam tomography scanning and fitness testing. Participants were excluded if they had a history of prior myocardial infarction or cerebrovascular accident. If patients had more than one evaluation, the earliest visit in this time period was included in the analysis. At the time of these analyses, medication data was not available in the database; hence, this variable was not utilized in the analysis.

The Cooper Clinic evaluation consists of an extensive medical history, physical examination, measurement of anthropometric features, laboratory studies including lipoprotein profile and fasting blood glucose, treadmill testing, and coronary artery calcium screening in some patients over age 40, depending on one's coronary risk profile and individual or physician preferences. Of note, the data acquired at Cooper Clinic for the CCLS is not based on a systematic research protocol but rather on the basic evaluation as outlined above, corporate designated evaluations, and clinical recommendations. Thus, the availability of particular measurements may be based on physician's clinical discretion and vary from patient to patient. Definitions for history of diabetes, hypertension, hyperlipidemia, current tobacco use, and family history of coronary heart disease were based on self-report in the medical history and confirmed by the clinic physician. Height and weight were measured using a standard clinical scale and stadiometer. Body mass index (BMI) was calculated as weight/height^2 (kg/m^2). Seated resting blood pressure was obtained with a mercury sphygmomanometer using the American Heart Association protocol. After a 12-h fast, venous blood was assayed for serum cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and glucose using standard automated techniques at the Cooper Clinic Laboratory.

Fitness was assessed by maximal time on a treadmill test using the modified Balke protocol, the standard testing mode since 1970. The treadmill speed began at 3.3 mph with a 0% grade for the first minute, a 2% grade for the second minute, and 1% increases in grade for each minute thereafter until the 25th minute. For participants who were able to exercise beyond 25 min, the elevation was maintained at 25% and the speed was increased by 0.2 mph each minute until volitional exhaustion. Time on the treadmill with this protocol has been shown to be highly correlated with measured maximal oxygen uptake in women [5]. Maximal metabolic equivalent (MET) levels (1 MET = 3.5 mL O_2 kg^{-1} min^{-1}) were estimated from the final treadmill speed and grade [6]. From prior work at The Cooper Institute, standard age- and gender-specific fitness "quintiles" were used for the following age groups: 40–49 years, 50–64 years, and ≥65 years [7]. Due to the fact that these are standard cut-points based on prior research, the distribution of participants within the five "quintiles" does not represent five equal groups [8]. The fitness "quintiles" were then grouped into traditional fitness categories: women in the lowest fit "quintile" (Q1) were considered "unfit"; women in "quintiles" 2 and 3 (Q2, 3) were considered "moderate fit"; and women in "quintiles" 4 and 5 (Q4, 5) were considered "high fit". Fitness was also analyzed continuously (in METs) and in present sample-specific quartiles.

CAC was assessed by the Imatron C-150XP or C-300 electron beam tomography scanner (GE Imatron, San Francisco, California). 3-mm thick slices were obtained with 2-mm table increments during a breath-holding protocol. Agatston score calculation and the related method for quantifying CAC score have been previously described [9]. CAC was characterized dichotomously as CAC = 0 versus CAC > 0 and CAC < 100 versus CAC ≥ 100.

We summarized selected demographic and clinical characteristics of the sample by standard categories of fitness and tested for trends across ordered fitness categories using the Jonckheere–Terpstra nonparametric method. Multiple logistic regression models of CAC > 0 were fit and summarized by odds ratios and 95% confidence intervals calculated from the profile likelihood. Co-variates included fitness, age, family history of premature coronary heart disease, current smoking, BMI, diabetes mellitus, hypertension and hyperlipidemia. Diabetes was defined as a self-reported history of diabetes and/or fasting blood glucose ≥ 126 mg/dL. Hypertension was defined as a self-reported history of hypertension and/or systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg. Hyperlipidemia was defined as a self-reported history of hyperlipidemia and/or total cholesterol ≥ 200 mg/dL. Fitness was entered in these models as a continuous variable, and also using standard Cooper Institute categories [7] as well as sample-specific quartiles for sensitivity analyses. In additional sensitivity analyses, the same models were fit for CAC ≥ 100, which corresponds to a higher atherosclerotic burden. The relationship between CAC > 0 and continuous fitness was also assessed in the subgroup with 10–<20% Framingham 10-year risk of coronary heart disease (i.e., moderate risk). To assess the relationship between CRF and continuous CAC, we fit multiple quantile regression models for the 75th and 90th percentiles of CAC, and we fit multiple linear regression models to log(CAC + 1). The sample of 5341 women provides 80% power to detect an unadjusted odds ratio as small as 1.06 for a 1 MET continuous fitness association and as small as 1.15 between the fourth and first quartiles of fitness. All analyses were conducted using SAS/STAT® statistical software, version 9.2.

3. Results

The baseline characteristics of the study cohort are shown in Table 1. The average functional capacity in the low fit group was 6.1

Table 1
Characteristics of 5341 women with EBT and modified Balke treadmill, stratified by cardiorespiratory fitness category.

Fitness category[a]	Low fit $n = 380$	Moderate fit $n = 1562$	High fit $n = 3399$	p-Trend
Age (yrs)	52.2 (8.6)	52.4 (8.4)	51.9 (7.8)	0.46
Post-menopausal	192 (50.5)	822 (52.6)	1729 (50.9)	0.42
History of hypertension	106 (27.9)	316 (20.2)	371 (10.9)	<0.0001
History of diabetes	17 (4.5)	33 (2.1)	35 (1.0)	<0.0001
History of hyperlipidemia	136 (35.8)	481 (30.8)	797 (23.4)	<0.0001
Family history coronary heart disease	195 (51.3)	713 (45.6)	1486 (43.7)	0.01
Current smoker	31 (8.2)	113 (7.2)	142 (4.2)	<0.0001
Body mass index (kg/m^2)	31.5 (6.3)	26.4 (4.7)	23.1 (3.2)	<0.0001
Systolic blood pressure (mmHg)	125.0 (16.7)	120.2 (16.0)	116.3 (15.4)	<0.0001
Diastolic blood pressure (mmHg)	83.2 (10.2)	80.1 (9.4)	77.9 (9.3)	<0.0001
Total cholesterol (mg/dL)	211.5 (38.3)	207.9 (36.2)	201.3 (33.9)	<0.0001
Low-density lipoprotein cholesterol (mg/dL)	125.6 (34.7)	120.4 (31.8)	112.3 (30.3)	<0.0001
High-density lipoprotein cholesterol (mg/dL)	58.1 (16.1)	63.6 (16.7)	70.9 (16.8)	<0.0001
Triglycerides[b] (mg/dL)	138.9 (91.5)	119.3 (72.0)	91.1 (52.0)	<0.0001
Glucose (mg/dL)	101.3 (23.1)	94.9 (15.8)	92.0 (8.4)	<0.0001
Framingham risk score[c] (%)	6.2 (4.3)	5.0 (3.6)	3.9 (2.6)	<0.0001
Fitness (METs[d])	6.1 (0.8)	7.9 (0.9)	10.2 (1.5)	<0.0001

Data are expressed as mean (±SD) or as number (column percentage).
[a] Low fit = Quintile 1; Moderate fit = Quintiles 2, 3; High fit = Quintiles 4, 5.
[b] Triglycerides Quartile range.
[c] Framingham risk score for coronary heart disease 10 year risk (%).
[d] METs = metabolic equivalents.