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Timothy S. Church

Carolyn E. Barlow

Conrad P. Earnest

James B. Kampert

Elisa L. Priest

See next page for additional authors

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Author(s)
Timothy S. Church, Carolyn E. Barlow, Conrad P. Earnest, James B. Kampert, Elisa L. Priest, and Steven N. Blair

Associations Between Cardiorespiratory Fitness and C-Reactive Protein in Men

T.S. Church, C.E. Barlow, C.P. Earnest, J.B. Kampert, E.L. Priest, S.N. Blair

Objective—This study examined the association between cardiorespiratory fitness and C-reactive protein (CRP), with adjustment for weight and within weight categories.

Methods and Results—We calculated median and adjusted geometric mean CRP levels, percentages of individuals with an elevated CRP (≥2.00 mg/L), and odds ratios of elevated CRP across 5 levels of cardiorespiratory fitness for 722 men. CRP values were adjusted for age, body mass index, vitamin use, statin medication use, aspirin use, the presence of inflammatory disease, cardiovascular disease, and diabetes, and smoking habit. We found an inverse association of CRP across fitness levels (P for trend<0.001), with the highest adjusted CRP value in the lowest fitness quintile (1.64 [1.27 to 2.11] mg/L) and the lowest adjusted CRP value in the highest fitness quintile (0.70 [0.60 to 0.80] mg/L). Similar results were found for the prevalence of elevated CRP across fitness quintiles. We used logistic regression to model the adjusted odds for elevated CRP and found that compared with the referent first quintile, the second (odds ratio [OR] 0.43, 95% CI 0.22 to 0.85), third (OR 0.33, 95% CI 0.17 to 0.65), fourth (OR 0.23, 95% CI 0.12 to 0.47), and fifth (OR 0.17, 95% CI 0.08 to 0.37) quintiles of fitness had significantly lower odds of elevated CRP. Similar results were found when examining the CRP-fitness relation within categories of body fatness (normal weight, overweight, and obese) and waist girth (<102 or ≥102 cm).

Conclusions—Cardiorespiratory fitness levels were inversely associated with CRP values and the prevalence of elevated CRP values in this sample of men from the Aerobics Center Longitudinal Study. **(*Arterioscler Thromb Vasc Biol*. 2002; 22:1869-1876.)**

Key Words: C-reactive protein ■ cardiorespiratory fitness ■ men

Elevated plasma C-reactive protein (CRP) levels have been prospectively associated with increased risk of cardiovascular disease (CVD) in apparently healthy individuals.[1–4] There is an abundance of reports on the positive association between weight and CRP, and investigators have also shown that reduction in weight produces a reduction in CRP concentrations.[5–11] We have reported previously that fitness has beneficial effects on mortality and CVD risk factors that are independent of weight and evident within weight classifications.[12–16] Thus, when the relationship between weight and CVD risk factors or clinical outcomes is assessed, it is important to account for exercise habits or fitness level.

There are only a few available studies examining the effect of regular exercise or exercise training on resting levels of CRP.[10,17,18] Geffken et al[17] found the amount of regular physical activity to be inversely related to CRP in a healthy elderly population, and Rohde et al[18] reported that healthy men who exercise >1 time a week had lower mean CRP than men who did not exercise at least once a week. Mattusch et al[19] found that 9 months of marathon training resulted in a 31% decrease in CRP (n=12), and Smith et al[20] reported a nonsignificant (P=0.12) decrease in CRP (−35%) after 6 months of exercise training in individuals (n=43) at high risk for ischemic heart disease. Although these studies provide evidence that regular exercise may reduce CRP values, each lacks either generalizability, adjustment for weight, a reliable measure of regular physical activity, or an adequate number of participants.

Cardiorespiratory fitness is an objective laboratory measurement that reduces the misclassification bias that often results from self-reports of physical activity. Although cardiorespiratory fitness has a genetic component, it is primarily determined by habitual physical activity.[21,22] To our knowledge, there are no available reports on the association of cardiorespiratory fitness and CRP. The purpose of the present study was to examine the association between cardiorespiratory fitness and CRP, with adjustment for weight and also within weight categories. Understanding the relationship between fitness and inflammatory markers may provide insight into the potential of exercise as a therapeutic option to reduce CRP.

Methods

Patient Data

The Aerobics Center Longitudinal Study (ACLS) is an epidemiological study of patients who received a preventive medical examination

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From The Cooper Institute, Dallas, Tex.
Reprint requests to Timothy S. Church, The Cooper Institute, 12330 Preston Rd, Dallas TX 75230. E-mail tchurch@cooperinst.org

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at the Cooper Clinic in Dallas, Tex. Participants for the analyses reported in the present study are 722 men examined during 2001. Most of the participants are non-Hispanic whites, residents of the United States, and well educated. All participants gave their informed consent to participate in the clinical examination and follow-up and to use their examination data for research purposes. The Cooper Institute Institutional Review Board annually reviewed and approved the study protocol.

Clinical Examination

The clinical examinations were administered in the morning after an overnight fast. The participants were also instructed to refrain from exercise during the day before their examination. Trained laboratory technicians, supervised by clinic physicians, administered the examinations according to a protocol specified in a manual of operations. The examination consisted of the following: a physical examination by a clinic physician; obtaining blood by venipuncture of an antecubital vein for blood chemistry analyses; measurement of blood pressure; anthropometry; completion of an extensive questionnaire on demographic characteristics, health history, family medical history, and a health habit inventory; and a maximal exercise test on a treadmill. Clinic technicians measured blood pressures with mercury manometers according to the American Heart Association protocol.[23] Height and weight were measured on a standard physician's balance beam scale and stadiometer. Body mass index (BMI), used as an index of body fatness, was calculated as weight in kilograms divided by height in meters squared. Percent body fat was assessed by summing 7 skinfold measurements and by using a generalized body density equation.[24] The correlation between body fat assessed by skinfold measurement and BMI within this study population was 0.55 ($P<0.0001$).

The Cooper Clinic laboratory, which participates in and meets quality control standards of the US Centers for Disease Control and Prevention Lipid Standardization Program, performed the blood chemistry analyses. CRP was measured by a high-sensitivity assay on a Prospect nephelometer (Dade Division of Baxter Healthcare Corp).

We assessed cardiorespiratory fitness with a maximal treadmill test by following a modified Balke protocol.[25] Patients began walking at 88 m/min (3.3 mph) with no elevation. After the first minute, the incline was increased to 2% and was increased 1% each minute thereafter until the 25th minute. For the few participants still able to continue the test beyond 25 minutes, the elevation was maintained at 25%, and the speed was increased by 5.4 m/min (0.2 mph) each minute until the end of the test. The test was terminated when the participants were exhausted or when the physician stopped the test for medical reasons.

Time on the treadmill test with this protocol is highly correlated ($R=0.92$) with measured maximal oxygen uptake.[26] Thus, cardiorespiratory fitness in the present study is analogous to maximal aerobic power and is used here as an objective laboratory marker for exercise participation in the several weeks before the treadmill test. We assigned men to age-group–specific fitness quintiles based on their total time on the treadmill test. We expressed cardiorespiratory fitness as maximal metabolic equivalents (METs, assessed as work metabolic rate/resting metabolic rate$=3.5\ mL \cdot kg^{-1} \cdot min^{-1}$) attained during the treadmill test. METs were calculated from estimated VO_{max} for the Balke protocol by using the formula $VO_{max}=1.44\times(\text{minutes on treadmill})+14.99$.[26] The maximal MET cut points for fitness quintiles are derived from the entire ACLS male population.

Statistical Methods

We computed the arithmetic mean±SD of each variable by CRP quartiles and by fitness quintiles. For CRP, we presented the median and interquartile range with significant differences in distributions assessed by the Kruskal-Wallis Test. For dichotomous variables, we presented percentages.

Because of the skewed distribution of CRP, we logarithmically transformed CRP values for statistical analyses on the basis of the general linear model, with results expressed as geometric means. We compared geometric mean CRP values across fitness quintiles adjusted for age, BMI, smoking (current, past, or never), vitamin use (multivitamins or antioxidants), statin use, aspirin use, and presence of inflammatory disease (asthma, bronchitis, arthritis, or emphysema), CVD (previous stroke or myocardial infarction), or diabetes (a previous diagnosis or fasting glucose >125 mg/dL). We defined a high CRP value as ≥2.00 mg/L and calculated the percentage of individuals with a high CRP value (adjusted for all the above covariates) for each fitness category.[3] Additionally, to avoid the potential effect modification due to smoking and chronic illness, analyses limited to never smokers with no history of CVD, diabetes, or inflammatory disease who were not taking statin medications (n=410) were repeated.

We examined the dose-response gradient of high CRP values across fitness levels, with the use of multiple logistic regression models with high CRP value as the dependent variable and with quintiles of fitness (lowest as referent) and potential confounders as independent variables.

To examine the association of fitness and CRP within levels of body fatness, we created fitness-fatness categories. We categorized individuals as normal weight ($18.5\ kg/m^2 \le BMI < 25.0\ kg/m^2$), overweight ($25.0\ kg/m^2 \le BMI < 30.0\ kg/m^2$), or obese ($BMI \ge 30.0\ kg/m^2$) according to the *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults*.[27] No participants in the present study had a BMI $<19.0\ kg/m^2$. We classified the participants in fitness quintile 1 as low fit, in fitness quintiles 2 and 3 as moderately fit, and in fitness quintiles 4 and 5 as high fit. We then cross-classified the 3 fitness categories with the 3 fatness categories to create 9 fitness-fatness categories (low-fit–normal weight, low-fit–overweight, . . ., high-fit–obese). We calculated the adjusted (age, BMI, vitamin use, statin, aspirin use, inflammatory disease, CVD, diabetes, and smoking) geometric mean CRP and prevalence of high CRP for each fitness-fatness category.

To examine the effect of body composition and fat distribution assessed by means other than BMI, the above analyses were repeated with body fatness quantified by percent body fat and with fat distribution quantified by waist girth for those individuals who had these measurements taken. Participants were assigned to 1 of 3 categories of percent body fat based on the cutoffs <18.2%, 18.2% to 25.2%, and >25.2%, which correspond to the <25th, 25th to <75th, and ≥75th percentile scores. We calculated the adjusted geometric mean CRP for each fitness-body fat category. For waist girth, participants were categorized as <102 cm or ≥102 cm, the waist girth criteria for "high risk" as defined in the *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults*.[27] We calculated the adjusted geometric mean CRP and prevalence of high CRP for the 6 fitness–waist girth categories. Additionally, it has been reported that waist girth ≥90 cm combined with triglyceride levels ≥175.0 mg/dL (2.0 mmol/L) is associated with the metabolic triad of hyperinsulinemia, hyperapolipoprotein B, and small dense LDL, as well as with the risk of coronary heart disease.[28] Therefore, we categorized individuals with a waist girth ≥90 cm and a triglyceride level ≥175.0 mg/dL as having a "hypertriglyceridemic waist."[28] We calculated and compared the adjusted geometric mean CRP for individuals with and without hypertriglyceridemic waist and then repeated this comparison with an additional adjustment for fitness. Furthermore, we compared the adjusted geometric mean CRP of individuals with hypertriglyceridemic waist in the lowest 2 fitness quintiles with that of individuals with hypertriglyceridemic waist in the highest 3 fitness quintiles.

The Pearson product moment correlation coefficients and partial correlations (controlling for age) were calculated to examine pairwise associations between variables. For all statistical tests, the α level adopted for significance was a 2-tailed $P \le 0.05$. Statistical analysis was performed with SAS version 8.2.

Results

Table 1 presents the participant characteristics and clinical variables by quartiles of CRP. There was a direct association

TABLE 1. Cardiovascular Disease Risk Factors Across Quartiles of CRP for 722 Men in the Aerobics Center Longitudinal Study

	CRP Quartiles				*P* for Trend*
	≤0.45	0.46–0.85	0.86–1.84	>1.84	
No. of Subjects	183	179	180	180	
Age, y	50.4 (10.1)	50.5 (10.8)	53.2 (10.1)	51.8 (9.9)	0.07
BMI, kg/m^2	25.5 (3.0)	26.6 (3.1)	28.1 (3.4)	29.5 (5.0)	<0.0001
Exercise tolerance, METs	12.4 (1.8)	11.9 (1.7)	11.1 (1.6)	10.5 (2.0)	<0.0001
Systolic blood pressure, mm Hg	121.8 (12.9)	123.7 (11.7)	126.6 (13.9)	127.7 (15.7)	<0.0001
Diastolic blood pressure, mm Hg	82.1 (8.7)	82.8 (8.5)	85.2 (8.9)	85.6 (9.3)	<0.0001
Fasting glucose, mg/dL	95.0 (10.0)	98.3 (19.0)	98.5 (14.0)	100.3 (15.4)	0.001
Total cholesterol level, mg/dL	187.7 (34.0)	193.4 (34.0)	192.3 (31.8)	195.9 (39.2)	0.12
Triglyceride level, mg/dL	111.3 (55.2)	132.8 (95.4)	147.9 (92.0)	148.6 (95.3)	<0.0001
HDL cholesterol level, mg/dL	52.2 (13.3)	50.7 (12.4)	46.0 (11.0)	45.4 (12.8)	<0.0001
Multivitamin use	38	32	42	32	0.16
Antioxidant use	26	17	23	17	0.09
Statin medication use	15	15	19	13	0.43
Aspirin use	21	16	17	13	0.40
Inflammatory disease	20	21	17	23	0.46
Cardiovascular disease	1	1	1	2	0.76
Diabetes	1	1	3	4	0.06
Smoking	14	8	13	17	0.12

Values presented as mean (SD) or %.

*P for trend for Pearson Correlation between continuous variables and log CRP. χ^2 analysis used for dichotomous variables.

between CRP levels and each of the variables BMI, systolic blood pressure, diastolic blood pressure, fasting glucose, and triglycerides. There was an inverse association between CRP levels and the variables fitness and HDL cholesterol. There were no statistically significant trends across the CRP quintiles for any of the dichotomous variables.

Table 2 shows the participant characteristics by fitness quintiles. In general, the age distributions across fitness quintiles are similar, with the better metabolic profiles found in the higher fitness quintiles. Multivitamin and antioxidant vitamin use was lowest and smoking prevalence was highest in the lower fitness quintiles. Statin medication use, aspirin use, prevalence of inflammatory disease, and prevalence of CVD varied across fitness quintiles, with no obvious trends. Only 15 men had diabetes, and 11 of them were in quintiles 1 and 2. Median CRP values were significantly different across fitness quintiles ($P<0.0001$), with the lower fitness quintiles having the highest median CRP values and the higher fitness quintiles having the lowest median CRP values.

The first (lowest) and fifth (highest) fitness quintiles had the highest and lowest adjusted geometric mean CRP values, respectively (Figure 1, top). There was a significant inverse trend for CRP level across fitness quintiles ($P<0.001$). After full adjustment, 49% of the men in the lowest fitness quintile had a high CRP value compared with only 16% of men in the highest fitness quintile (Figure 1, middle). There was a significant inverse trend for prevalence of high CRP values across fitness quintiles ($P<0.0001$). Compared with men in the lowest fitness quintile, men in the 2nd, 3rd, 4th, and 5th fitness quintiles had significantly lower adjusted odds of having a high CRP value (Figure 1, bottom). The lowest risk of having a high CRP value was found in the highest fitness category (odds ratio [OR] 0.17, 95% CI 0.08 to 0.37; $P=0.001$). There was a significant inverse trend across fitness quintiles ($P<0.0001$). The OR of having a high CRP for men in the lowest fitness quintile compared with all other quintiles was 3.2 (95% CI 1.8 to 5.8, $P<0.0001$).

We obtained similar results for adjusted geometric mean CRP values and for the prevalence of high CRP across fitness quintiles when limiting the analysis to 410 never-smoking men who were free of CVD, inflammatory disease, and diabetes and not taking statin medications. The adjusted mean CRP values across fitness quintiles (low to high) were 1.82, 1.07, 1.03, 0.79, and 0.70 mg/L (P for trend <0.0001), and the prevalence of elevated CRP was 48%, 27%, 24%, 22%, and 15% across the fitness quintiles (P for trend <0.0001).

Figure 2 presents the adjusted geometric mean CRP values and prevalence of elevated CRP by fitness and body mass categories. The low-fit–normal weight group had an insufficient (n=6) number of individuals to generate representative data, and their data are not presented. In normal weight (18.5≤BMI<25.0 kg/m^2) participants, the high-fit men had significantly lower CRP than did the moderate-fit men. In the overweight (25.0 kg/m^2≤BMI<30.0 kg/m^2) and obese (BMI ≥30.0 kg/m^2) participants, the moderate-fit and high-fit men had significantly lower CRP than did the low-fit men. The highest prevalence of elevated CRP was found in the low-fit men of the overweight and obese categories, whereas the lowest prevalence was in the high-fit groups. There was a significant inverse trend for prevalence of elevated CRP

TABLE 2. Characteristics of the 722 Men in the Aerobics Center Longitudinal Study

	Age-Specific Fitness Quintiles				
	1	2	3	4	5
METs per fitness quintiles by age*					
20–39 y	4.4–10.4	10.4–11.7	11.7–12.6	12.6–14.0	>14.0
40–49 y	4.4–9.8	9.8–10.9	10.9–12.1	12.1–13.3	>13.3
50–59 y	4.4–8.8	8.8–9.9	9.9–10.9	10.9–12.2	>12.2
60+ y	4.4–7.5	7.5–8.6	8.6–9.7	9.7–11.0	>11.0
No. of subjects	64	116	161	190	191
Age, y	49.7 (10.6)	49.9 (10.2)	51.1 (10.7)	52.3 (10.4)	52.5 (9.6)
BMI, kg/m^2	32.1 (5.9)	29.4 (3.9)	27.5 (3.3)	26.9 (2.9)	25.1 (2.6)
Exercise tolerance, METs	8.5 (1.3)	10.0 (1.0)	10.8 (1.0)	11.7 (1.1)	13.6 (1.2)
Median CRP (IQR), mg/L	2.29 (1.06–4.90)	1.28 (0.62–2.31)	0.86 (0.46–1.75)	0.80 (0.49–1.51)	0.52 (0.26–1.05)
Systolic blood pressure, mm Hg	131.0 (17.0)	125.3 (14.4)	123.7 (11.7)	124.8 (14.2)	123.8 (13.1)
Diastolic blood pressure, mm Hg	88.5 (9.6)	84.5 (9.2)	83.9 (8.6)	83.8 (8.7)	82.3 (8.7)
Fasting glucose, mg/dL	103.6 (16.1)	102.2 (18.8)	96.7 (11.0)	98.6 (18.3)	94.1 (9.5)
Total cholesterol level, mg/dL	195.2 (30.6)	199.5 (37.5)	198.3 (31.8)	189.9 (37.0)	184.3 (33.5)
Triglyceride level, mg/dL	160.1 (64.9)	156.8 (94.0)	152.8 (98.9)	133.2 (97.8)	100.6 (49.2)
HDL cholesterol level, mg/dL	41.7 (11.8)	44.0 (11.6)	47.6 (12.0)	48.9 (11.7)	54.2 (13.1)
Multivitamin use	27	34	38	33	41
Antioxidant use	16	21	19	22	24
Statin Medication use	16	19	16	16	13
Aspirin use	23	16	16	13	23
Inflammatory disease	28	21	27	17	15
Cardiovascular disease	0	2	1	2	0
Diabetes	6	5	0	3	1
Smoking	25	23	14	15	12

Values presented as mean (SD) or % unless otherwise indicated.

IQR indicates interquartile range.

*Standards from previously published Aerobics Center Longitudinal Study reports. METs calculated from time on treadmill (Balke protocol): METs=([1.44×minutes on treadmill]+14.00)/3.5 mL×kg^{-1}×min^{-1}.

across fitness levels in the overweight ($P=0.0006$) and obese ($P=0.007$) categories.

We found that within BMI categories, there were differences in body fat percentage (and waist girth) across levels of fitness. In general, the high fitness groups had lower body fat percentage and smaller waist girths than did the lower fitness groups in the same BMI categories. For example, in the overweight category, the body fat percentage was 24.8%, 23.5%, and 22.4% (P for trend<0.04), and waist girth was 98.9, 04.9, and 92.5 cm (P for trend$=0.0008$) for the low-, moderate-, and high-fit groups, respectively. To assess whether the inverse relation between fitness and CRP within BMI categories was due to differences in body fat percentage or waist girth, we added the latter 2 variables to the regression models. The additional adjustment for body fat percentage and waist girth had little effect on predicted CRP values, and the CRP-fitness relationship within the BMI categories was not altered (data not presented).

We also assessed the relative importance of fitness and body fat distribution on CRP by using body fat percentage (n=637) and waist girth (n=636). The analyses we performed using percent body fat were very similar to analyses using BMI. For example, in the intermediate body fat category (18.2% to 25.2% fat), mean adjusted CRP values across the low, moderate, and high fitness groups were 1.92, 0.91, and 0.78 mg/L, respectively (P for trend$=0.0008$), and in the highest body fat category (>25.2% fat), the mean CRP values were 1.55, 1.07, and 0.87 mg/L for the low, moderate, and high fitness groups, respectively (P for trend$=0.01$). In the lowest body fat category (<18.2% fat), there were only 2 individuals in the low-fit category. For the moderate- and high-fit categories, the mean adjusted CRP values were 1.32 and 0.84 mg/L, respectively.

Data for body fat distribution assessed by waist girth are presented in Figure 3. In both waist girth categories, the adjusted (age, waist girth, vitamin use, statin use, aspirin use, inflammatory disease, CVD, diabetes, and smoking) mean CRP values of the high-fit group were significantly lower than those of the low-fit group. Additionally, there was a significant inverse trend for CRP across fitness levels for both waist girth groups ($P=0.01$ for waist girth <102 cm and $P=0.009$ for waist girth ≥102 cm).

In comparing individuals with (n=107) and without (n=527) hypertriglyceridemic waist, we found adjusted mean

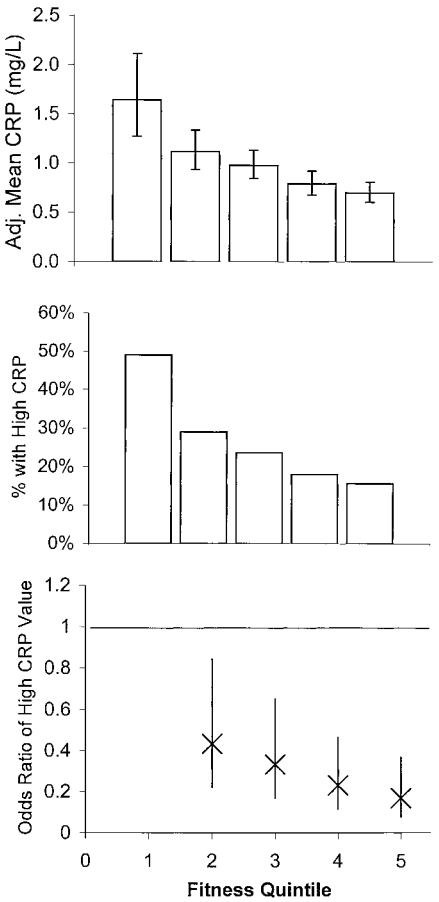

Figure 1. Data from 722 men in the ACLS. Data were adjusted for age, BMI, vitamin use, statin medication use, aspirin use, the presence of inflammatory disease, CVD, and diabetes, and smoking. The top panel presents adjusted geometric mean CRP values across fitness quintiles, the middle panel depicts the percentage of individuals with a high CRP (≥2.0 mg/L) across fitness quintiles, and the bottom panel presents the risk of having a high CRP across fitness quintiles, with the lowest quintile as the referent group. Error bars represent 95% CIs.

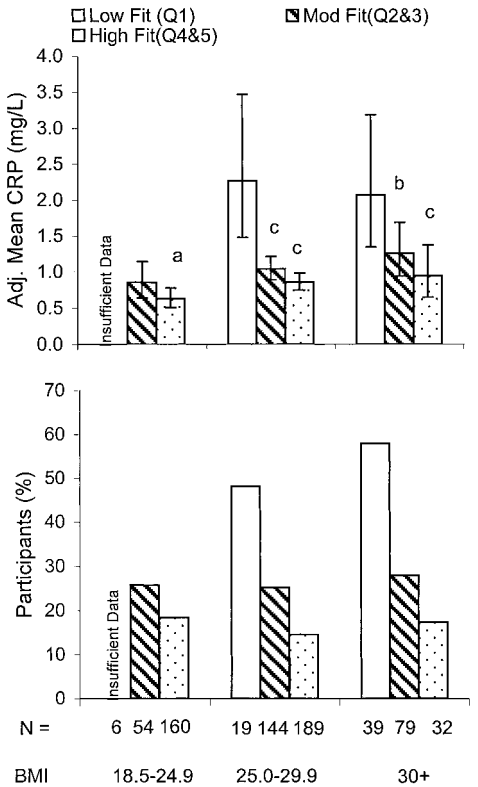

Figure 2. Adjusted geometric mean CRP values for categories of fitness and fatness. Data were adjusted for age, BMI, vitamin use, statin medication use, aspirin use, the presence of inflammatory disease, CVD, and diabetes, and smoking. Individuals with 18.5 kg/m^2≤BMI<25.0 kg/m^2 were classified as normal weight, individuals with 25.0 kg/m^2≤BMI<30.0 kg/m^2 were classified as overweight, and individuals with a BMI ≥30.0 kg/m^2 were classified as obese. We further categorized individuals as having low (fitness quintile 1), moderate (fitness quintiles 2 and 3), and high (fitness quintiles 4 and 5) fitness. We combined the 3 fatness categories with the 3 new fitness categories to create 9 fitness-fatness categories. There was an insufficient number (n=6) of individuals in the low-fit–normal weight category to generate a meaningful analysis. The top panel depicts the mean adjusted CRP value for each fitness-fatness category, and the bottom panel depicts the percentage of individuals in each category with high CRP (≥2.0 mg/L). Error bars represent 95% CIs. aP<0.05 compared with moderate-fit group; bP=0.01 compared with low-fit group; and cP≤0.001 compared with low-fit group.

CRP values to be significantly higher in the individuals with hypertriglyceridemic waist compared with normal individuals (1.31 versus 0.89 mg/L, respectively; P=0.0002). When fitness was added to the model, there was no longer a difference between the 2 groups (1.07 versus 0.93 mg/L, respectively; P=0.24), which suggests that fitness may account for the difference in CRP between individuals with and without hypertriglyceridemic waist. Among individuals with hypertriglyceridemic waist, the adjusted mean CRP values were significantly higher for individuals in the lowest 2 fitness quintiles compared with individuals in the upper 3 fitness quintiles (1.70 versus 1.07 mg/L, respectively; P=0.02).

Because BMI and waist girth are strongly correlated (r=0.87 and P<0.0001 for this cohort) and because both are correlated with fitness (and CRP), we sought to identify which of the 3 variables is independently associated with CRP when adjusted for the other 2. Individually, BMI (r=0.38, P<0.0001), waist girth (r=0.41, P<0.0001), and fitness as METS (r=0.37, P<0.0001) were associated with log CRP. However, in a multivariate model (adjusted for age), only fitness (partial r=0.186, P<0.0001) and waist girth (partial r=0.145, P<0.0001) remained statistically significant (r model=0.45, P<0.0001; n=635). Thus, in this cohort, when waist girth and fitness were taken into account, BMI was not associated with log CRP (P=0.95).

Discussion

The primary finding of this cross-sectional study was an inverse association between CRP levels and cardiorespiratory fitness, which was independent of body composition and fat distribution, as assessed by BMI, percent body fat, and waist girth. Furthermore, within overweight and obese individuals, CRP values were significantly greater in the lowest fitness categories compared with higher fitness categories.

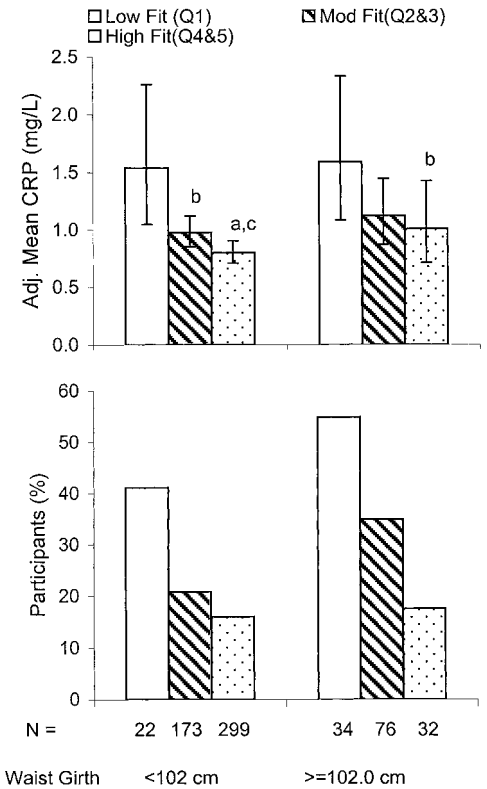

Figure 3. Adjusted geometric mean CRP values for categories of fitness and fatness for 636 men with available waist girth measures. Data were adjusted for age, waist girth, vitamin use, statin medication use, aspirin use, the presence of inflammatory disease, CVD, and diabetes, and 3 levels of smoking. Individuals were categorized by waist girth measurement into 2 groups: waist girth $<$102.0 cm or waist girth $\geq$102.0 cm. We further categorized individuals as having low (fitness quintile 1), moderate (fitness quintiles 2 and 3), and high (fitness quintiles 4 and 5) fitness. We combined the 2 waist girth categories with the 3 new fitness categories to create 6 fitness-waist girth categories. The top panel depicts the mean adjusted CRP value for fitness–waist girth category, and the bottom panel depicts the percentage of individuals in each category with a high CRP ($\geq$2.0 mg/L). Error bars represent 95% CIs. a$P<0.05$ compared with moderate-fit group; b$P<0.05$ compared with low-fit group; and c$P\leq0.01$ compared with low-fit group.

Elevated CRP is a strong risk factor for CVD events and mortality.[1–4] Additionally, in a post hoc analysis, Ridker et al[2] reported that reducing CRP levels in individuals with elevated CRP but normal LDL cholesterol results in a significant reduction in cardiac events. It must be emphasized that it was not the original aim of the present study to examine the therapeutic benefit of lowering CRP in individuals, and there have not been any randomized clinical trials specifically addressing this issue that have been completed to date. Regardless, there is mounting evidence that interventions to reduce CRP may have clinical benefit.[29] Statin medications, antioxidant vitamin use, and weight loss have all been shown to reduce CRP.[9,30–33] The difference in CRP values in men in the ACLS in the middle and lowest fitness quintiles was substantial and of a magnitude that results in significant differences in risk of CVD. For example, the median CRP level of 0.86 mg/L observed in the middle (third) fitness quintile is associated with mild CVD risk, whereas the CRP value of 2.29 mg/L in the lowest fitness quintile is associated with high risk of CVD.[3] Additionally, the largest difference in mean CRP between sequential fitness quintiles was found between the first and second fitness quintiles, with small stepwise decreases with each subsequent fitness quintile. Thus, if the goal is to minimize the risk of having a high CRP value, avoiding the low fitness category should be a priority.

CRP is strongly associated with BMI, and BMI is inversely associated with fitness.[8] Thus, it is critical when examining fitness or BMI data to account for possible confounding of the other variable. We too found BMI to be associated with CRP, but even after adjustment for BMI (and body fat percent), fitness was strongly associated with CRP concentration. We are unaware of studies on the relation of BMI or other measures of obesity to CRP in which fitness was measured and taken into account in the analyses. It is of particular clinical significance that within overweight and obese categories, individuals in the moderate fitness categories have substantially lower CRP levels than individuals in the low fitness categories. Although this result needs to be tested with intervention studies, these preliminary findings suggest that individuals may decrease CRP levels by increasing fitness, even without substantial weight loss. In examining the relative importance of body composition and fitness on CRP, we focused our analysis on BMI because it is a relatively easy measure to obtain in the clinical setting and because the majority of prior research related to body composition and CRP has focused on BMI. It is noteworthy that when waist girth and fitness were included in the multivariable model, BMI was no longer associated with CRP, suggesting, as others have noted, that measuring waist girth is important in assessing clinic risk.[28] Although waist girth was associated with CRP independently of fitness, within the level of waist girth ($<$102 or $\geq$102 cm), higher levels of fitness were associated with lower concentrations of CRP. Additionally, fitness appeared to account for the differences found in CRP when individuals with and without hypertriglyceridemic waist were compared.

It is not possible to determine whether exercise causes lower CRP levels from our cross-sectional study; however, there are preliminary intervention data that support our cross-sectional findings. Mattusch et al found[19] 9 months of marathon training (n=12) to reduce CRP levels by 31%, with no change in the nontraining control group (n=10). Although the level did not reach statistical significance ($P=0.12$), Smith et al[20] found 6 months of supervised exercise to reduce CRP by 35% in individuals (n=43) at high risk of ischemic heart disease.

Cardiorespiratory fitness is determined primarily by exercise habits, but there is also a genetic component, which accounts for 25% to 40% of the variation in fitness.[21,22] We have no data on how the genetic influence on fitness might be related to the findings of the present study. Therefore, we assume that the association between fitness and CRP is primarily mediated by the effect of regular exercise. The pathways whereby regular exercise and reduced adiposity improve CRP are subject to speculation and could be the result of a variety of mechanisms. A potential common pathway may be the interleukins; in particular, there is

evidence for the involvement of tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6). IL-6 and TNF-α are released in significant amounts from adipose tissue, particularly visceral adipose tissue.[34,35] Their release from adipose tissue is augmented by increased sympathetic stimulation, which is downregulated by regular physical activity.[36] TNF-α is a potent stimulator of IL-6 production, and IL-6 is a potent stimulator of CRP production.[37] Whereas a single bout of acute exercise increases plasma levels of IL-6, interluekin-1β, and associated inflammatory markers,[38] repeated exercise training may lower basal plasma interleukin concentrations.[39] In cross-sectional analyses, Volpato et al[40] found IL-6 levels to be inversely related to exercise tolerance in disabled older women, whereas Taaffe et al[41] reported an inverse relationship between accumulated moderate and strenuous activity with IL-6 in 880 adults aged 70 to 79 years. Smith et al[20] found that a 6-month exercise program reduced TNF-α (n=43, average age 49.0 years). Tsukui et al[42] reported that exercise training in 29 obese women (average age 56 years) reduced TNF-α with only a modest weight loss. Thus, the effect of regular exercise on TNF-α and IL-6 levels may be responsible for reduced lower CRP in individuals with higher levels of fitness.

Limitations of the Study

Diet may influence CRP, and regular exercisers may have healthier diets than nonexercisers.[43] However, we do not have sufficient dietary data on this group of participants to evaluate the influence of diet. We were able to control for several other potential confounders, including the use of multivitamins, antioxidant vitamins, and medication use; thus, it is unlikely that additional information on diet composition would have substantially changed the directionality of our findings.

The data set used in this analysis has a lower percentage of individuals (8.9%) in the lowest fitness quintile than anticipated. If the study population were a random sample of the larger ACLS database, which dates back to 1970, one would expect the lowest fitness quintile to constitute 20% of the sample. This may be the result of chance variation or of changing exercise habits in the study population. However, the lower than expected number of individuals in the lowest fitness quintile is of little significance because CRP was inversely associated with levels of fitness in a stepwise fashion across all fitness quintiles. Additionally, all available data were used in the analyses, eliminating the potential of a systematic selection biased against low-fit individuals. The predominantly white, middle-to-upper class study population limits the generalizability of the results of the present study but should not affect the internal validity. In fact, the homogeneity of our study group on socioeconomic factors is a benefit, because it reduces the likelihood of confounding by these factors.

The present study also has a number of strengths, including the large sample size, an objective measure of cardiorespiratory fitness, and detailed information on medical history, smoking, and medication and supplement use. Perhaps the most important strength is examining the fitness-CRP relationship with levels of body composition and fat distribution as assessed by BMI, percent body fat, and waist girth.

Conclusion

Cardiorespiratory fitness levels were inversely associated with CRP values and the prevalence of elevated CRP values in this sample of men from the ACLS. This association was independent of BMI and was evident in subgroups of overweight and obese men.

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