Cardiorespiratory Fitness and C-Reactive Protein Among a Tri-Ethnic Sample of Women

Michael J. LaMonte, PhD, MPH; J. Larry Durstine, PhD; Frank G. Yanowitz, MD; Tobin Lim, BS; Katrina D. DuBose, MS; Paul Davis, PhD; Barbara E. Ainsworth, PhD, MPH

Background—Elevated C-reactive protein (CRP) is associated with increased coronary heart disease (CHD) risk. Cardiorespiratory fitness (“fitness”) is related with lower CHD risk; however, its relationship with CRP is relatively unknown.

Methods and Results—Cross-sectional associations between fitness and plasma CRP were examined among 135 African American (AA), Native American (NA), and Caucasian (CA) women (55±11 year; 28±6 kg/m²). Fitness was assessed with a maximal treadmill exercise test. Plasma CRP concentrations were determined with the Dade Behring high-sensitivity immunoassay. Geometric mean CRP levels were 0.43, 0.25, and 0.23 mg/dL, and average maximal MET levels of fitness were 7.2, 9.1, and 10 METs for AA, NA, and CA, respectively. CRP decreased across tertiles of fitness (P=0.002), increased across tertiles of BMI (P=0.0007), and varied by race (P=0.002). After adjustment for covariates, lower CRP (P<0.05) was observed across tertiles of fitness among NA and CA, but not AA. Among all women, after adjusting for race and covariates, the odds of high-risk CRP (>0.19 mg/dL) were 0.67 (95% CI=0.19 to 2.4) among fit (>6.5 METs) versus unfit women.

Conclusions—The health benefits from enhanced fitness may have an antiinflammatory mechanism. (Circulation. 2002;106:●●●-●●●.)

Key Words: exercise ■ C-reactive protein ■ coronary disease ■ women ■ inflammation

C-reactive protein (CRP) is a marker of subclinical inflammation. Elevated CRP is associated with a 2- to 5-fold increased risk of coronary events.1,2 CRP is inversely related with insulin sensitivity,3 directly related with type 2 diabetes risk,4 and elevated among individuals with excessive body fat.5 Fewer data exist on CRP and health for women and race-ethnic minorities, among whom CHD, diabetes, and obesity incidence is rising.6 Also, few studies5,6 have considered the influence of physical activity on associations between CRP and health outcomes.

Regular physical activity is associated with lower CHD and diabetes risk.7 Self-reported physical activity is inversely related with CRP concentrations.8,9 Cardiorespiratory fitness (“fitness”), assessed with maximal exercise testing, is stronger than self-reported physical activity as a predictor of several health outcomes.7,10 We showed higher fitness correlates with lower CHD risk factors.11-13 Blair and associates observed lower cardiovascular mortality14 and type 2 diabetes15 rates with higher fitness, irrespective of obesity status. Data on fitness and health parameters are particularly sparse among women and minorities.7,10,12,13 In the present study, we describe the cross-sectional association between fitness and CRP in a tri-ethnic sample of healthy women.

Methods
Informed consent was obtained from 44 African American (AA), 45 Native American (NA), and 46 Caucasian (CA) women who volunteered to be in the Cross-Cultural Activity Participation Study (CAPS). The aim of CAPS was to develop physical activity surveys for diverse populations of women.11,13,16,17 CAPS inclusion criteria were self-reported: AA, NA, or CA ethnicity, absence of symptoms of disease, and the absence of conditions that would preclude daily physical activity. Interview-based health histories, body mass index (BMI, kg/m²), waist girth (cm), and resting blood pressure measures have been described.8,13,16,17

After a 12-hour fast and 24-hour abstinence from exercise and smoking, antecubital blood was collected in EDTA, centrifuged, and frozen at −80°C until analysis. Plasma CRP concentrations were measured with the Dade-Behring high-sensitivity immunoassay (detection range=0 to 6.5 mg/dL).1,2 Additional CHD risk factor concentrations were obtained with standard automated assay procedures described elsewhere.11,13,17

Fitness was quantified as the duration of a maximal treadmill exercise test consisting of 2-minute stages graded by 1 MET (1 MET=3.5 mL O₂·kg⁻¹·min⁻¹) per stage.13 Exercise tests were conducted in the presence of a physician, and maximal exertion was seen as achieving ≥85% age-predicted maximal heart rate and perceived exertion ≥17 on a 20-point Borg scale.13,14

Summary statistics (mean, SD, frequency, Pearson correlation) were computed for variables in general accord with the assumptions of normal distribution. CRP values were skewed; therefore, log

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transformed values are included in all analyses and geometric means are reported descriptively. Differences in CRP concentrations across categories of race, fitness, and BMI were analyzed with the general linear model. Fitness was quantified as treadmill exercise times that were adjusted for age with linear regression. Fitness varied by race (P<0.0001); therefore, race-specific treadmill time distributions were used to categorically define fitness as low (<33rd percentile), moderate (33rd to 67th percentile), and high (>67th percentile). BMI and waist girth were defined categorically as 18.5 to 24.9, 25 to 29.9, and ≥30 kg/m², and <88 or ≥88 cm, respectively. For the entire sample, multiple logistic regression was used to model the race and covariate adjusted association between fitness (fit, >6.5 METs versus unfit, ≤6.5 METs) and high-risk CRP (>0.19 mg/dL). Maximum METs were estimated from maximal treadmill speed and grade and used to standardize fitness scores. Women in the upper 75th percentile of maximal METs were defined as fit. Probability values are two-sided with an α rate of 0.05.

### Results

Participants were middle-aged, overweight, and had relatively low CHD risk factors (Table 1). Among all women, CRP correlated significantly (P<0.05) with fitness (r = −0.25), BMI (r = 0.25), waist girth (r = 0.21), insulin (r = 0.26), and triglyceride (r = 0.27). Higher CRP (P<0.05) was observed among CA estrogenic medication users and NA diabetics. Age-adjusted maximal treadmill exercise times were higher (P<0.0001) for both CA and NA compared with AA, and for CA compared with NA. Table 2 shows CRP varied by race (P = 0.002), decreased across tertiles of fitness (P = 0.002), and increased with higher BMI (P = 0.0007) and waist girth (P = 0.004). After adjusting for BMI, smoking, diabetes, and estrogen status, lower CRP (P < 0.05) was observed across tertiles of race-specific treadmill times among NA and CA, but not AA (Table 3). This association persisted among women with higher than race-specific median levels of insulin, triglyceride, and low-density lipoprotein cholesterol (LDL-C), and waist girth ≥ 88 cm in NA and CA (data not shown). Although not statistically significant, after adjusting for race, BMI, insulin, and triglyceride, the odds of high-risk CRP (>0.19 mg/dL [prevalence = 46%]) were 0.67

### TABLE 1. Characteristics of Study Participants (Mean±SD)

<table>
<thead>
<tr>
<th>Race</th>
<th>n</th>
<th>Age, y</th>
<th>BMI, kg/m²</th>
<th>Waist girth, cm</th>
<th>Systolic BP, mm Hg</th>
<th>Diastolic BP, mm Hg</th>
<th>Insulin, pmol/L</th>
<th>Glucose, mmol/L</th>
<th>Triglycerides, mmol/L</th>
<th>HDL-C, mmol/L</th>
<th>LDL-C, mmol/L</th>
<th>ApoB, g/L</th>
<th>Homocysteine, nmol/mL</th>
<th>Treadmill time, min</th>
<th>Maximal METs</th>
</tr>
</thead>
<tbody>
<tr>
<td>African American</td>
<td>44</td>
<td>56.6±10.1</td>
<td>30.9±6.1</td>
<td>89.0±13.1</td>
<td>129±18.6</td>
<td>79.4±8.7</td>
<td>79.9±57.7</td>
<td>5.2±1.8</td>
<td>0.9±0.4</td>
<td>1.7±0.5</td>
<td>2.3±0.9</td>
<td>0.8±0.4</td>
<td>8.3±3.3</td>
<td>11.0±2.7</td>
<td>7.2±1.4</td>
</tr>
<tr>
<td>Native American</td>
<td>45</td>
<td>50.7±8.9*</td>
<td>28.7±5.7</td>
<td>88.9±11.5</td>
<td>118±12.7*</td>
<td>76.7±9.2</td>
<td>74.9±57.7</td>
<td>5.2±2.1</td>
<td>1.5±0.9*</td>
<td>1.3±0.9*</td>
<td>2.4±0.7</td>
<td>0.8±0.2</td>
<td>6.9±1.9*</td>
<td>13.5±3.3</td>
<td>9.1±1.8</td>
</tr>
<tr>
<td>Caucasian</td>
<td>46</td>
<td>54.3±10.1</td>
<td>25.2±4.8†</td>
<td>78.4±11.2†</td>
<td>116.3±18.7*</td>
<td>76.6±9.2</td>
<td>74.9±57.7</td>
<td>4.7±0.6</td>
<td>1.3±0.6</td>
<td>1.6±0.4†</td>
<td>2.3±0.7</td>
<td>0.7±0.2</td>
<td>7.7±2.2</td>
<td>15.7±3.4†</td>
<td>10.0±1.9†</td>
</tr>
</tbody>
</table>

HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ApoB, apolipoprotein B; CVD, prevalent cardiovascular disease; and diabetes, prevalent diabetes. *P<0.05 with African Americans; †P<0.05 with Native Americans.

### TABLE 2. CRP Levels by Race, Fitness, BMI, and Waist Girth

<table>
<thead>
<tr>
<th>Race</th>
<th>n</th>
<th>Geometric Mean</th>
<th>SE</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>African American</td>
<td>44</td>
<td>0.43</td>
<td>0.03</td>
<td>0.03</td>
</tr>
<tr>
<td>Native American</td>
<td>45</td>
<td>0.25*</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>46</td>
<td>0.23*</td>
<td>0.13</td>
<td>0.002</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fitness (treadmill time, min)</th>
<th>n</th>
<th>Geometric Mean</th>
<th>SE</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (&lt;11.1)</td>
<td>45</td>
<td>0.43</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Moderate (11.1 to 14.5)</td>
<td>46</td>
<td>0.26†</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>High (&gt;14.5)</td>
<td>44</td>
<td>0.23†</td>
<td>0.04</td>
<td>0.002</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BMI, kg/m²</th>
<th>n</th>
<th>Geometric Mean</th>
<th>SE</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>18.5 to 24.9</td>
<td>50</td>
<td>0.19</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>25 to 29.9</td>
<td>40</td>
<td>0.34§</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>≥30</td>
<td>45</td>
<td>0.42§</td>
<td>0.04</td>
<td>0.0007</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Waist girth, cm</th>
<th>n</th>
<th>Geometric Mean</th>
<th>SE</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;88</td>
<td>83</td>
<td>0.25</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>≥88</td>
<td>52</td>
<td>0.42</td>
<td>0.03</td>
<td>0.004</td>
</tr>
</tbody>
</table>

CRP reported as mg/dL. Fitness is shown as sample tertiles of treadmill time. BMI and waist categories defined according to current NIH standards. *P<0.05 with African Americans; †P<0.05 with Native Americans; §P<0.05 with low fitness; ¶P<0.05 with 18.5 to 24.9 BMI.
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Caucasian§
Native American‡

The highest level of fitness among AA was generally less than the
might have been a contributory factor. The fact that the
variation in treadmill exercise time among AA (Table 1)
the other CHD risk factors (data not shown). The restricted
consistent with the pattern of association between fitness and
lack of association between fitness and CRP among AA was
for BMI and other covariates among NA and CA women. The
CRP and fitness are inversely related even after accounting
for race and covariate adjusted odds of CRP
might exist.7,10 The

In our study, AA women had higher BMI
and insulin levels and were less fit than CA and NA. BarinbasMitchell et al21 found the effect of race on CRP was
strongest among estrogen users who had lower BMI, fasting
glucose, and physical activity levels compared with women
not using estrogen. We found estrogen use was similar
between AA and CA, but only related with CRP among CA.
Studies are needed to understand the effects of race and
estrogenic medication on CRP.

Our data confirm a significant association between CRP
and adiposity measures. The correlation for CRP with BMI
(r=0.25) and waist girth (r=0.21) was similar to previous
reports.3,5,8,9 CRP concentrations rose sharply across higher
BMI and waist categories (Table 2). The inverse association
between CRP and fitness (Table 3) seen in our study persisted
in models adjusted for race, BMI, and waist girth. This
relationship suggests fitness may be an important determinant
of plasma CRP even among women with increased body fat,
and carries important public health implications given the
recent increase in CHD, obesity, and type 2 diabetes rates
among women and minorities.6

Several mechanisms could account for lower CRP in active
and fit individuals. Significant reductions in CRP and other
inflammatory markers have been shown among individuals
completing prolonged exercise training.19,20 Elevated CRP
has been associated with infectious viral pathogens;1 however,
enhanced natural killer cell activity may confer a
resistance to acute infections in fit individuals.7 Higher levels
of physical activity and fitness are associated with improved
inflammatory markers have been shown among individuals
postmenopausal Caucasian women. Significantly
higher submaximal fitness and lower CRP concentrations
were recently reported among 14 German men after 9 months
of exercise training.19 Our cross-sectional data showed that
CRP and fitness are inversely related even after accounting
for BMI and other covariates among NA and CA women. The
lack of association between fitness and CRP among AA was
consistent with the pattern of association between fitness and
the other CHD risk factors (data not shown). The restricted
variation in treadmill exercise time among AA (Table 1)
might have been a contributory factor. The fact that the
highest level of fitness among AA was generally less than the
lowest fitness score among NA and CA implies that a
cardioprotective threshold level of fitness might exist.7,10 The
race and covariate adjusted odds of CRP >0.19 mg/dL
among all women were 0.67 for fit versus unfit women;
however, this association did not reach statistical significance
(95% CI=0.19 to 2.4), possibly due to sample size
limitations. Prospective studies are needed to determine whether
the cardioprotective effect of fitness is mediated through
inflammatory pathways.

Another important observation from our data was the
variation in plasma CRP by race (Table 2). Geometric mean
CRP concentrations were significantly higher among AA
(0.43 mg/dL) compared with NA (0.25 mg/dL) and CA (0.23
mg/dL) women. This relationship was maintained after con-
trolling for BMI, insulin, TG, smoking, and diabetes. Higher
CRP concentrations have been reported among AA versus
CA adults.5,9 Potential mechanisms for racial differences in
CRP are unknown. In our study, AA women had higher BMI
and insulin levels and were less fit than CA and NA. Barinas-Mitchell et al21 found the effect of race on CRP was
strongest among estrogen users who had lower BMI, fasting
glucose, and physical activity levels compared with women
not using estrogen. We found estrogen use was similar
between AA and CA, but only related with CRP among CA.
Studies are needed to understand the effects of race and
estrogenic medication on CRP.

Discussion

Inverse associations have been reported between inflammatory
markers, like plasma CRP and fibrinogen, and self-
reported physical activity.5,9 Cardiorespiratory fitness is an
objective measure of recent physical activity.7,10,12 Reports on
fitness and inflammatory markers are sparse. Haddock et al18
showed fitness was an independent determinant of fibrinogen
among postmenopausal Caucasian women. Significantly
higher submaximal fitness and lower CRP concentrations
were recently reported among 14 German men after 9 months
of exercise training.19 Our cross-sectional data showed that
CRP and fitness are inversely related even after accounting
for BMI and other covariates among NA and CA women. The
lack of association between fitness and CRP among AA was
consistent with the pattern of association between fitness and
the other CHD risk factors (data not shown). The restricted
variation in treadmill exercise time among AA (Table 1)
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highest level of fitness among AA was generally less than the
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race and covariate adjusted odds of CRP >0.19 mg/dL
among all women were 0.67 for fit versus unfit women;
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(95% CI=0.19 to 2.4), possibly due to sample size
limitations. Prospective studies are needed to determine whether
the cardioprotective effect of fitness is mediated through
inflammatory pathways.

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CRP concentrations were significantly higher among AA

TABLE 3. CRP Levels by CRF Stratified on Race Adjusted for Covariates

<table>
<thead>
<tr>
<th>Fitness (treadmill time, min)</th>
<th>n</th>
<th>Geometric Mean</th>
<th>SE</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>African American§</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (&lt;10.2)</td>
<td>13</td>
<td>0.43</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>Moderate (10.2 to 11.9)</td>
<td>15</td>
<td>0.46</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>High (&gt;11.9)</td>
<td>18</td>
<td>0.43</td>
<td>0.08</td>
<td>0.99</td>
</tr>
<tr>
<td>Native American‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (&lt;11.2)</td>
<td>14</td>
<td>0.31</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Moderate (11.2 to 14.5)</td>
<td>16</td>
<td>0.26</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>High (&gt;14.5)</td>
<td>15</td>
<td>0.18*†</td>
<td>0.05</td>
<td>0.01</td>
</tr>
<tr>
<td>Caucasian§</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (&lt;14.1)</td>
<td>16</td>
<td>0.30</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>Moderate (14.1 to 17.5)</td>
<td>15</td>
<td>0.19*</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>High (&gt;17.5)</td>
<td>15</td>
<td>0.17*</td>
<td>0.03</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Fitness shown as race-specific tertiles of treadmill time.

*P<0.05 with low fitness; †P<0.05 with moderate fitness; §Model adjusted for BMI, smoking, diabetes and estrogen status; ‡Model adjusted for BMI, screening, and estrogen status. Diabetes was not reported by CA women; therefore, it was not included as a covariate.

(95% CI=0.19 to 2.4) among fit (>6.5 METs) versus unfit women.

Acknowledgments

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markers of inflammation in prediction of cardiovascular disease in


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