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Physical Fitness and C-Reactive Protein Level in Children and Young Adults: The Columbia University BioMarkers Study

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ABSTRACT. Objective. To examine the association of physical fitness with C-reactive protein (CRP) level in children and young adults.

Methods. Subjects (N = 205) aged 6 to 24 years were enrolled in the Columbia University BioMarkers Study (1994–1998). Physical fitness was assessed using a non-effort-dependent treadmill testing protocol (physical work capacity at heart rate of 170 beats per minute). CRP level was measured using a high-sensitivity assay.

Results. Subjects were 54% female and 65% of Hispanic origin. Mean fitness level was higher in boys than in girls, but CRP levels did not differ by gender. Fitness level was inversely correlated with CRP ($r = -0.22$). This relationship was significant in boys ($r = -0.32$) but not in girls ($r = -0.15$). After multivariate regression adjustment for age, race/ethnicity, body mass index, and family history of early-onset ischemic heart disease, physical fitness remained inversely associated with CRP level in boys ($β = -0.02$; standard error $= 0.01$).

Conclusions. These findings indicate that physical fitness is inversely related to CRP level in children and that this relationship is more pronounced in boys than in girls. Pediatrics 2003;111:332–338; children, C-reactive protein, fitness, obesity, physical fitness.

ABBREVIATIONS. CRP, C-reactive protein; IL-6, interleukin-6; PWC170, physical work capacity at heart rate of 170 beats per minute; BMI, body mass index; SE, standard error.

Recent data implicate systemic inflammatory factors, including fibrinogen, C-reactive protein (CRP), and interleukin-6 (IL-6), as important risk factors for atherosclerosis and cardiovascular disease events.1–14 There is evidence of participation of inflammatory factors in the early stages of atherogenesis, including impairment of endothelial function15 and the formation of fatty streaks and plaque,10–12 as well as in the thrombotic events that trigger myocardial infarction and some strokes.9 Two specific mechanisms involving CRP that have been described relate to monocyte activation10,16 and to promotion of synthesis of adhesion molecules that recruit leukocytes to the endothelial surface, thereby amplifying the inflammatory process in the vascular endothelium.17 In addition, inflammatory factors interact with other risk factors for atherosclerosis in complex ways. For example, CRP and IL-6 levels predict development of type 2 diabetes,18 possibly attributable in part to the established relationship of obesity to IL-6 and CRP levels.19,20 Obesity is a strong predictor of CRP,19,20–24 and other inflammatory markers.25–28 IL-6, which stimulates hepatic production of fibrinogen and CRP, is synthesized in adipose tissue, particularly by visceral adipose tissue.29,30 Synthesis of tumor necrosis factor-$α$, another proinflammatory cytokine, is also increased in obese subjects.31 Physical activity and physical fitness levels are inversely correlated with fibrinogen22–38 and with CRP levels in adults.39

The presence of early-stage atherosclerosis has been documented extensively in children and young adults,40–43 but data regarding inflammatory factors in children are not so well developed as in adults. Studies in children have shown that fibrinogen level is positively correlated with obesity25–28 and inversely correlated with physical activity44,45 and physical fitness.46 One study of CRP in children found an inverse relation with physical activity.47 To our knowledge, this is the only published study to address this relationship in children, and no published study has focused on the relationship of physical fitness with CRP level in children.

METHODS

Subjects

The Columbia University BioMarkers Study is a cross-sectional study of children and their parents conducted from 1994 to 1998. Families were recruited from lists of cardiac patients generated through the Presbyterian Hospital Clinical Information System, private cardiology practices, lipid clinics, pediatric practices at Columbia-Presbyterian Medical Center, and fliers posted within the medical center. Families with at least 1 healthy child, 4 to 25 years of age, were eligible for participation. Healthy was defined as not having any chronic medical condition under treatment by a pediatrician, other than high blood pressure or high lipids (referral criteria to the Children’s Cardiovascular Health Center). A total of 612 children and young adults from 351 eligible families were recruited for the study. Subjects with intercurrent infections were rescheduled and examined at a time when they were not ill. The study design called for complete examination of 1 child or...
young adult per family, specifically, the oldest child ≤25 years of age. Physical fitness assessments and anthropometric measures (body mass index, skinfold thickness, and waist and hip circumferences) were therefore not obtained in 196 children who had older siblings in the study. Additional exclusions were 32 children in whom CRP level was not measured, 43 in whom the fitness assessment was not performed, 74 who did not complete the fitness assessment, and 62 who completed the assessment but had data that did not meet criteria for extrapolation to heart rate of 170 beats per minute. Thus, 205 children were included in this relating fitness level to CRP. Informed consent was obtained from all participating families. The study was approved by the Institutional Review Board of Columbia Presbyterian Medical Center.

 Measures

Physical fitness level was assessed using a treadmill (Quinton, Seattle, WA) following the physical work capacity at a heart rate of 170 beats per minute (PWC170) protocol.46,49 Children walked on a standard treadmill at a speed of 4 km/h starting at 0% grade for 2 minutes, after which the grade was increased by 5% every 2 minutes. Heart rate was monitored with a Polar Vantage XL Heart Rate Monitor (Port Washington, NY). The test was terminated when heart rate reached 170 beats per minute or when the child could no longer continue, at which point the grade was returned to 0% and the child continued to walk for 2 more minutes. Heart rate was plotted against work stage and extrapolated in a linear manner to the percentage grade corresponding to a heart rate of 170 beats per minute. This work load level was the index of aerobic fitness. Resting heart rate was measured with an automated monitor (Critikon Dinamap, Tampa, FL) before the exercise test and after 5 minutes of rest.

Height was measured to the nearest centimeter using a rigid stadiometer. Weight was measured to the nearest 0.1 kg using a calibrated balance scale. Body mass index (BMI) was calculated as body mass (in kilograms) divided by the height (in meters) squared. Circumferences at the waist (level of the maximum extension of the buttocks) were measured with a tape measure,50 and the waist-to-hip ratio was calculated. CRP levels were measured from fasting citrated plasma using an enzyme-linked immunoabsorbent assay. Specimens were frozen at −70°C for 3 to 5 years. This assay was standardized according to the World Health Organization First International Reference Standard and performed at the University of Vermont.51

RESULTS

Children who were excluded from the analysis (N = 196) were younger than children in the analysis (8.9 vs 10.3 years; P < .01), more likely to be Hispanic (77% vs 66%; P = .05), and less likely to have a positive family history (12% vs 22%; P < .05). However, mean CRP values were similar in excluded versus included children (1.5 vs 1.4 mg/L; not significant). Among the 205 children in whom fitness level was assessed, 54% (n = 110) were female and 65% (n = 134) were of Hispanic origin (Table 1). The mean age of this group was 10.2 years (standard deviation: 3.9). Mean CRP levels were similar in boys and girls (Table 2). For boys, the median CRP level was 0.98 mg/L (range: 0.6–9.36). For girls, the median CRP level was 0.98 mg/L (range: 0.4–10.27). Girls had lower levels of physical fitness than boys (20.3 vs 20.6% grade; P < .01) and higher resting heart rate (85.9 vs 77.4 beats per minute; P < .01). Hispanic children had higher mean levels of CRP than non-Hispanic white children (1.5 vs 1.3 mg/L; P < .01) and lower level of physical fitness (21.9 vs

Statistical Analyses

Frequencies, means, and standard deviations were calculated for each variable. Bivariate associations were analyzed using t tests and analysis of variance for differences in means between groups and Pearson’s correlation coefficient for continuous variables. Mean CRP levels were calculated for each tertile of fitness level, and linear trend was assessed using linear regression analysis. Multiple linear regression models were used to adjust for covariates including age, gender, race/ethnicity, family history of early-onset ischemic heart disease, source of recruitment, and measures of obesity. In all analyses, CRP levels were log transformed (natural logarithm) to approximate normality. Statistical analyses were performed with SPSS-PC software (SPSS for Windows, version 10.0, SPSS Inc, Chicago, IL).
25.3% grade; *P < .01*) but did not differ in resting heart rate or measures of obesity. CRP level tended to be higher in younger children (means of 1.5, 1.3, and 1.1 mg/L for children <10, 10–14, and ≥15 years, respectively). Conversely, mean physical fitness level, BMI, and sum of skinfolds were lower in children who were younger than 10 years, compared with older children. Eighty-three children (22%) had a positive family history of early-onset ischemic heart disease. This group of children had lower mean level of CRP compared with children with negative family history (1.1 vs 1.4 mg/L; *P < .01*) but higher mean level of fitness (25.5 vs 22.7% grade; *P < .05*).

Physical fitness was inversely associated with CRP (*r = −0.22; *P < .01*). These correlations were *r = −0.32* (*P < .01*) in boys and *r = −0.15* (not significant) in girls (Table 3). Age was inversely correlated with CRP, whereas all 3 measures of obesity were positively correlated. There was an inverse graded relationship between physical fitness and CRP for the sample as a whole (trend *P < .01*; Table 4). This relationship was significant in boys (2.0, 1.6, and 1.1 mg/L for lowest, middle, and highest tertile of PWC<sub>170</sub>, respectively; trend *P = .002*) but not in girls (1.8, 1.4, and 1.1 mg/L for lowest, middle, and highest tertiles of PWC<sub>170</sub>, respectively; trend *P = .14*). Additional analysis within age groupings of children younger than 10 years (*n = 64*), 10 to 14 years (*n = 95*), and ≥15 years (*n = 40*), with boys and girls combined, showed significant linear trends for the inverse relation of physical fitness with CRP level for children age 10 to 14 years (trend *P < .05*) and age ≥15 years (trend *P < .05*; Table 4). Resting heart rate was not significantly related to CRP (mean values 1.3, 1.4, and 1.7 mg/L for lowest, middle, and highest tertiles of resting heart rate, respectively; trend not significant).

In multivariate analysis, after adjustment for age, gender, ethnicity, family history of ischemic heart disease, and source of recruitment, physical fitness (PWC<sub>170</sub>% grade) was inversely associated with CRP level (*β = −0.02*, standard error [SE] = 0.01, *P < .01*; Table 5). After additional adjustment for BMI or for sum of skinfolds, the coefficients for physical fitness were no longer significant (*β = −0.01, SE = 0.01, *P = .09*; and *β = −0.01, SE = 0.01, *P = .19*, respectively).

Separate regression analyses were conducted for boys and girls. In boys, physical fitness was inversely associated with mean CRP (*β = −0.03, SE = 0.01, *P = .01*), after adjustment for age, ethnicity, family history, and recruitment site. This association remained significant after BMI or sum of skinfolds was added to the model (*β for PWC<sub>170</sub> = −0.02, SE = 0.01, *P < .05*; *β for PWC<sub>170</sub> = −0.02, SE = 0.01, *P = .05*, respectively). In girls, no association of fitness with CRP was present.

The results of additional multivariate analyses using the BMI-age interaction variable described in “Methods” in place of BMI did not differ materially from those shown in Table 5. The regression coefficients (SE) for PWC<sub>170</sub>, after adjustment for this variable and the other variables shown in Table 5, were −0.02 (0.01; *P = .056*) for boys and girls combined, not significant in the girls, and −0.02 (0.01; *P = .03*) in the boys. We also performed multivariate analyses in which total cholesterol and systolic blood pressure were added to these models, but the findings for PWC<sub>170</sub> were not materially affected by this additional adjustment.

**DISCUSSION**

Using the PWC<sub>170</sub> treadmill protocol to assess physical fitness and a highly sensitive assay for CRP, we found a significant inverse association between physical fitness level and CRP in a sample of 205 children and young adults. This relation remained significant after adjustment for age, gender, race/ethnicity, family history of ischemic heart disease, and recruitment site. Fitness level was more strongly associated with CRP in boys, and in boys this relationship remained significant after additional multivariate adjustment for BMI or sum of skinfolds. The relationship of fitness level to CRP was not statistically significant in girls.

Mean fitness level was higher in the boys than in the girls, as measured both by PWC<sub>170</sub> work stage and resting heart rate, and it is possible that a threshold effect may explain our finding that physical fitness was related to CRP level in the boys but not in the girls. Several recent reports indicate that estrogen replacement therapy in postmenopausal women is associated with substantial increases in CRP level.53–56 The hormonal effects of puberty in children are different from those of estrogen replacement in postmenopausal women, but another possible explanation for the lack of an association in our data between physical fitness level and CRP in girls, while this relation was present in boys, may relate to hormonal changes specific to puberty in girls. We cannot address this possibility directly because sex hormone levels were not measured in our study. We did not obtain Tanner stage for the children in our study because of participant objections to this procedure, and we did not obtain self-reported information regarding onset of menses. We note, however, that mean CRP levels were 1.3 mg/L in the girls and 1.4 mg/L in the boys in our sample, making gender differences in CRP an unlikely explanation for the gender differences in the relationship to physical fitness level.
Our findings are consistent with those reported by Cook et al., who studied 699 children ages 10 to 11 years and found higher mean level of CRP in children in the top quintile of the ponderal index. These investigators used a questionnaire to assess physical activity and found an inverse relationship with CRP in bivariate analysis and after adjustment for the ponderal index. These investigators also measured resting pulse rate but found no correlation with CRP level. Physical fitness is inversely related to several established cardiovascular disease risk factors, including high cholesterol, blood pressure, and obesity, in both adults and children.57–64 Likewise, studies have reported inverse associations of physical fitness with inflammatory markers, mainly fibrinogen.32–38 Studies of physical fitness and CRP in adults are limited. Geffen et al.39 studied an elderly population and found lower levels of CRP in more physically active subjects. Mattusch et al.40 reported a decrease in CRP levels after a 9-month endurance training program in adults. The protective effects of physical activity and physical fitness on conventional cardiovascular risk factor profiles are well established in adults.57,66,67 Long-term exercise seems to decrease the proatherogenic activities of monocytes, including synthesis of proinflammatory inter-leukins and tumor necrosis factor-α.68 Other mechanisms may also be involved.

One limitation of our study could arise from exclusion from the analysis of children without anthropometric data. However, excluded children had a mean CRP level similar to those who were included. Smoking is a known predictor of CRP level1,2,6 and may also have been a source of confounding, if children who smoked were less likely to be fit and had higher levels of CRP. We did not gather information on smoking habits in our sample; thus, we cannot examine this possibility directly. However, the subgroup analysis in children who were younger than 10 years, in whom smoking is very uncommon,69 was consistent with the overall findings. We also did not collect information on nonsteroidal anti-inflammatory drug use, but chronic use of this class of drug...
in healthy children who are younger than 10 years is uncommon. The cross-sectional design of the study limits inferences about the causal relationship between fitness and CRP, although it seems more likely that fitness influences CRP level than that CRP level influences fitness. Unmeasured confounders, residual confounding, and the generalizability of the findings to other populations are other potential limitations. A strength of our study was the use of the PWC170 protocol to measure physical fitness in children. This measure of physical fitness is not effort levels in children.46,64

CONCLUSION

We found an inverse association between physical fitness and CRP level in children and young adults. This relationship was more pronounced in boys than in girls. Atherosclerosis has long been recognized as a progressive, sequential process12 that can begin in childhood.40–43 Recent studies have underscored the role of inflammatory factors in the pathophysiology of atherosclerosis.1–14 Thus, identifying factors that modify the inflammatory component of the atherosclerotic process in its early stages may contribute to the treatment and prevention of cardiovascular disease. Higher levels of physical fitness may be helpful in modifying the low-grade inflammatory state indexed by CRP level elevations within the ranges observed in epidemiologic studies in children and young adults.

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TABLE 5. Multiple Regression Models for Mean CRP Level in Relation to Age, Gender, Race/Ethnicity, Family History of Early-Onset Ischemic Heart Disease, Source of Recruitment, Physical Fitness Level, and BMI: Columbia University BioMarkers Study, New York, 1994 to 1998

<table>
<thead>
<tr>
<th>Variables Included in Model</th>
<th>Model 1*</th>
<th>Model 2†</th>
</tr>
</thead>
<tbody>
<tr>
<td>β (SE)‡</td>
<td>P Value</td>
<td>β (SE)‡</td>
</tr>
<tr>
<td><strong>Age (y)</strong></td>
<td>0.02 (0.02)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Gender (male vs female)</strong></td>
<td>0.12 (0.12)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Race/ethnicity (Hispanic vs non-Hispanic white)</strong></td>
<td>0.10 (0.15)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Family history (positive vs negative)</strong></td>
<td>-0.42 (0.15)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td><strong>Source of recruitment (high vs low risk)</strong></td>
<td>0.12 (0.14)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><strong>PWC170 (% grade)</strong></td>
<td>-0.02 (0.01)</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

NS indicates not significant.

* Model 1 tests the relation of fitness level (PWC170) to CRP after adjustment for covariates but not including BMI.

† Model 2 tests the relation of fitness level (PWC170) to CRP after adjustment for covariates including BMI.

‡ Regression coefficients (β) for continuous variables are the unit increase in the natural logarithm of CRP per unit increase in the covariate, and mean differences in the natural logarithm of CRP for dichotomous variables.

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