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Effect of exercise training on plasma levels of C-reactive protein in healthy adults: the HERITAGE Family Study

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Aims To study the effect of exercise training on plasma C-reactive protein, a marker of inflammation.
Methods and results We performed a 20 week standardized exercise training programme in 652 sedentary healthy white and black men and women. C-reactive protein was measured with a high sensitivity assay. The study sample was stratified according to baseline C-reactive protein levels using a recommended classification (low <1.0 mg/L, $n = 265$; moderate 1.0–3.0 mg/L, $n = 225$; high >3.0 mg/L, $n = 162$). The median C-reactive protein reduction was 1.34 mg/L in the high baseline C-reactive protein group. C-reactive protein levels did not change in the low or moderate baseline C-reactive protein groups. The difference among the C-reactive protein groups was significant adjusting for all correlates of baseline C-reactive protein ($P < 0.001$) and additionally for changes in body weight, glucose, insulin, LDL cholesterol, HDL cholesterol, triglycerides, systolic and diastolic blood pressure, and maximal oxygen uptake ($P < 0.001$). The C-reactive protein reduction in the high baseline C-reactive protein group was consistent across all population groups ($P < 0.001$ for difference among baseline C-reactive protein groups).
Conclusion Plasma C-reactive protein levels are reduced in response to exercise training in sedentary healthy adults with high initial C-reactive protein levels. This finding may partly explain the effectiveness of regular physical activity in the prevention and treatment of cardiovascular and metabolic diseases.

Introduction

C-reactive protein is a sensitive marker of systemic low-grade inflammation and is currently recommended as the principal inflammatory marker in research and clinical practice.[1] Elevated plasma levels of C-reactive protein have been associated with an increased risk of coronary heart disease,[2,3] ischaemic stroke,[4] peripheral artery disease,[5] hypertension,[6] and any cardiovascular disease[3,7] in individuals who have no prior cardiovascular disease. C-reactive protein has also found to predict the risk of recurrent myocardial infarction[8] and mortality[9] in patients with coronary heart disease. Moreover, elevated plasma C-reactive protein levels have been associated with obesity,[7,10,11] insulin resistance,[10,11] the metabolic syndrome,[7,10] endothelial dysfunction,[11] and an increased risk of developing Type 2 diabetes.[12] A clinically important finding is that C-reactive protein predicts cardiovascular disease independent of traditional risk factors and adds prognostic information to these risk factors.[3,7]

Regular physical activity and good cardiorespiratory fitness have been associated with a reduced risk of coronary heart disease,[13,14] ischaemic stroke,[15,16] and premature cardiovascular and total mortality[17,18] in people who have no prior cardiovascular disease. Exercise training has also been shown to reduce cardiac and total mortality in patients with coronary heart disease[19] and to be effective in the treatment of peripheral artery disease.[20] Moreover, exercise has been found to decrease body adiposity,[21] increase insulin sensitivity,[21] improve glucose tolerance,[21] decrease plasma triglyceride levels,[21] increase plasma HDL cholesterol levels,[21] reduce blood pressure,[21] improve haemostatic factors,[21] improve endothelial function,[22] and reduce the risk of developing the metabolic syndrome[23] and Type 2 diabetes.[24] Nevertheless, these health effects only partly explain the reduced morbidity and mortality in physically active individuals.

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The results of cross-sectional epidemiological studies[25–30] and small clinical trials[31–33] suggest that the beneficial effects of regular physical activity could be partly mediated by the suppression of systemic low-grade inflammation. However, there are no reports on the effect of exercise training on inflammation in large study samples of sedentary individuals of different ages, genders, and races and who do not have diseases or take medications that potentially affect the inflammatory process. We therefore investigated the effect of exercise training on plasma C-reactive protein levels in 652 sedentary healthy, young and middle-aged, white and black women and men in the HERITAGE Family Study. We stratified the study sample according to baseline C-reactive protein levels by using a classification recently recommended by the Centers for Disease Control and Prevention and the American Heart Association.[1] We hypothesized that the exercise-induced C-reactive protein reduction is stronger among individuals who have higher baseline C-reactive protein levels and who therefore are at an increased risk of cardiovascular and metabolic diseases.[1] We also evaluated whether conditions known to be associated with inflammation modify the effect of exercise training on plasma C-reactive protein levels and whether the effect is mediated by exercise-induced changes in these conditions.

Methods

Study design

The HERITAGE Family Study is a 20 week exercise intervention trial that was carried out by a consortium of five universities in the US and Canada.[34] The study was designed to investigate the contribution of exercise training to changes in risk factors for Type 2 diabetes and cardiovascular diseases and the role of genetic factors in cardiovascular, metabolic, and hormonal responses to exercise training in white and black families. The study protocol was approved by each of the Institutional Review Boards of the research consortium of the HERITAGE Family Study. A written informed consent was obtained from each participant.

Subjects

The subjects came from 97 white and 96 black families that included the natural mother and father ($\leq$65 years of age) and their offspring ($\geq$17 years of age). The white families had at least three offspring; the black families were smaller. The subjects included 236 parents (124 mothers, 112 fathers) and 416 offspring (234 daughters, 182 sons). The subjects were required to be sedentary, defined as not having participated in regular physical activity over the previous 6 months, and not having chronic diseases or taking medications that could have prevented their participation in a structured exercise training programme or could have affected their laboratory test results. The criteria for participation in the study have been explained in detail elsewhere.[34]

Of 855 eligible participants, 742 were considered to have complied with the study, because they had successfully finished the training programme (had participated in $\geq$95% of 60 required training sessions) and had undergone thorough examinations before and after training. Reasons for not completing the study included an illness or an injury ($n = 6$), a pregnancy ($n = 7$), a re-location ($n = 1$), a voluntary refusal to continue the study ($n = 22$), a dropout because one or more members of the family dropped out or were dropped rendering the rest of the family ineligible for the study ($n = 10$), too many missing training sessions ($n = 18$), an inability to complete all examinations ($n = 33$), and other reasons ($n = 16$).

Of the 742 subjects who complied with the study, 68 had missing data on C-reactive protein and 12 had missing data on other variables needed for the present analyses and were excluded. We also excluded eight subjects whose C-reactive protein value before or after training separated by $\geq$4 standard deviations from the mean or by $\geq$1 standard deviation from the next highest value. Thus, the final study sample with complete data on all variables needed for the present analyses included 652 individuals (439 whites and 213 blacks, 358 women and 294 men).

Exercise training programme

The 20 week exercise training programme included three training sessions per week on cycle ergometers in the laboratory. The intensity of exercise was customized for each subject based on the relationship between heart rate and oxygen uptake measured at baseline. During the first 2 weeks, the subjects were trained for 30 min per session at a heart rate corresponding to 55% of the maximal oxygen uptake measured at baseline. The duration of each exercise session was gradually increased to 50 min and heart rate was increased to the level corresponding to 75% of the baseline maximal oxygen uptake. This level was sustained for the last 6 weeks. The heart rate was monitored during all training sessions by a computerized cycle ergometer system, which adjusted ergometer resistance to maintain the target heart rate. The subjects were instructed not to change their lifestyle during the exercise intervention. Maximal oxygen uptake increased by 17.8% (from 37.1 to 42.5 mL/kg^{-1} min^{-1}) during 20 weeks of exercise, indicating that the training programme was effective for cardiorespiratory system. Changes in maximal oxygen uptake were not correlated with changes in C-reactive protein levels.

Measurements

All variables were assessed at baseline and after the exercise training programme by using the same study protocols and methods. Plasma C-reactive protein was measured with a high-sensitivity solid-phase chemiluminescent immunometric assay (IMMULITE 2000 High Sensitivity C-reactive protein, Diagnostic Products Corporation, Los Angeles, CA, USA) implemented on an automated immunoassay instrument (Diagnostic Products Corporation, Los Angeles, CA, USA). In 48 randomly selected subjects, the intraclass correlation between two C-reactive protein measurements during the same study visit was 0.98 and the coefficient of variation was 6.4%. The methods for assessing diet, smoking, alcohol consumption, the use of hormone replacement therapy or oral contraceptives, body mass index, maximal oxygen uptake, plasma HDL and LDL cholesterol, triglycerides, glucose, and insulin, as well as systolic and diastolic blood pressure have been presented previously.[34]

Statistical methods

Baseline characteristics are presented as means and standard deviations or per cents. Differences in the medians of baseline C-reactive protein in the groups of baseline characteristics were analysed by Wilcoxon test or Kruskal–Wallis test. Because of skewed distributions, a logarithmic transformation was done for C-reactive protein, insulin, HDL cholesterol, and triglyceride values. All these variables were normally distributed after logarithmic transformation. The strongest correlates of baseline C-reactive protein were determined by comparing the magnitude of standardized regression coefficients derived from univariate linear regression analyses performed separately for each correlate of baseline C-reactive protein. The associations of baseline C-reactive protein with C-reactive protein changes in response to exercise training were analysed with MIXED models, that take into account non-independence among family members. Data were adjusted first for all correlates of baseline C-reactive protein and second for exercise-induced changes in body weight, glucose, insulin, HDL and LDL cholesterol, triglycerides, systolic and diastolic blood

pressure, and maximal oxygen uptake. The associations of baseline C-reactive protein with C-reactive protein changes in response to exercise training in baseline subgroups were also analysed with MIXED models. We used established clinical cut-offs for body mass index (<25.0, 25.0–29.9, and ≥30.0 kg/m^2), glucose (<5.6 and ≥5.6 mmol/L), and LDL cholesterol (<2.6 and ≥2.6 mmol/L). Because no clinical cut-offs are available for maximal oxygen uptake or insulin and the use of clinical cut-offs for HDL cholesterol, triglycerides, or blood pressure would have provided unequal group sizes, we used medians for these variables. All statistical analyses were two-sided. *P*-values <0.05 were defined statistically significant. All statistical analyses were performed with SAS 8.2.

Results

Baseline characteristics

Baseline characteristics are shown in *Table 1*. The median C-reactive protein was higher in Blacks, women, and parents and tended to be higher in women who used hormone replacement therapy or oral contraceptives and in current smokers (*Table 2*). The median C-reactive protein was also higher in individuals who were overweight or obese or had lower maximal oxygen uptake, higher glucose, insulin, triglycerides, LDL cholesterol, or diastolic blood pressure and tended to be higher in those who had lower HDL cholesterol or higher systolic blood pressure (*Table 2*).

The strongest correlates of baseline C-reactive protein

The strongest correlates of baseline C-reactive protein in women were body mass index, maximal oxygen uptake, triglycerides, LDL cholesterol, glucose, age, insulin, systolic blood pressure, the use of hormone replacement therapy or oral contraceptives, diastolic blood pressure, and smoking (*Table 3*). The strongest correlates of baseline C-reactive protein in men were maximal oxygen uptake, body mass index, age, LDL cholesterol, smoking, glucose, insulin, triglycerides, HDL cholesterol, and diastolic blood pressure. Alcohol consumption was not associated with C-reactive protein in either gender.

The effect of exercise training on C-reactive protein levels

There was no change in C-reactive protein levels in the whole study population (*Table 4*). C-reactive protein reduced by 1.34 mg/L in individuals who had high (>3.0 mg/L) baseline C-reactive protein levels (25% of the whole study population), but did not change among those with low (<1.0 mg/L) or moderate (1.0–3.0 mg/L) baseline C-reactive protein levels (*Table 4*). The difference in the C-reactive protein change among the baseline C-reactive protein groups was statistically significant after adjustment for all correlates of baseline C-reactive protein shown in *Table 3* ($P < 0.001$). Additional adjustment for changes in body weight, glucose, insulin, LDL cholesterol, HDL cholesterol, triglycerides, systolic and diastolic blood pressure, and maximal oxygen uptake had no effect on the association ($P < 0.001$). The exclusion of nine subjects who reported a change in smoking habits during the study did not have an effect on the results either.

The C-reactive protein reduction in the high baseline C-reactive protein group was consistent across all population groups, including whites and blacks, women and men, parents and offspring, women who did not use hormone replacement therapy or oral contraceptives and those who did, non-smokers and current smokers, individuals who were normal weight and overweight or obese, and those who had lower and higher levels of maximal oxygen uptake, glucose, insulin, LDL cholesterol, HDL cholesterol, triglycerides, systolic blood pressure and diastolic

Table 1 Baseline characteristics

	All ($n = 652$)	Women ($n = 358$)	Men ($n = 294$)
Age (years)	35.6 (13.7)	34.8 (13.0)	36.6 (14.4)
Race (% of blacks)	32.7	38.0	26.2
Gender (% of men)	45.1	–	100.0
Generation (% of offspring)	63.8	62.0	61.9
Hormone use[a] (%)	18.9	34.4	–
Smoking status			
Never (%)	64.4	67.3	60.9
Former (%)	22.7	18.4	27.9
Current (%)	12.9	14.3	11.2
Alcohol consumption (g/week)	5.1 (9.7)	3.1 (5.9)	7.5 (12.5)
Body mass index (kg/m^2)	26.6 (5.2)	26.3 (5.5)	27.0 (4.9)
Maximal oxygen uptake (mL/kg/min)	31.1 (8.8)	27.2 (7.0)	35.7 (8.5)
Plasma glucose (mmol/L)	5.1 (0.6)	4.9 (0.5)	5.2 (0.6)
Plasma insulin (pmol/L)	70.8 (50.4)	68.8 (50.2)	73.5 (51.2)
Plasma LDL cholesterol (mmol/L)	3.0 (0.8)	2.9 (0.7)	3.1 (0.8)
Plasma HDL cholesterol (mmol/L)	1.05 (0.28)	1.14 (0.27)	0.95 (0.25)
Plasma triglycerides (mmol/L)	1.29 (0.77)	1.10 (0.56)	1.51 (0.91)
Systolic blood pressure (mmHg)	118.6 (11.7)	116.5 (12.2)	121.1 (10.6)
Diastolic blood pressure (mmHg)	68.3 (8.7)	67.3 (8.9)	69.5 (8.4)

Data are presented as means and standard deviations or per cents.
[a]Hormone replacement therapy or oral contraceptives.

Table 2 Medians and interquartile ranges for baseline C-reactive protein in the whole study population and in the groups of baseline characteristics

	n	Median	Interquartile range	*P*-value for difference[b]
All subjects	652	1.30	0.60–2.99	
Race				
Whites	439	1.22	0.58–2.69	
Blacks	213	1.55	0.67–3.85	0.014
Gender				
Women	358	1.64	0.65–4.10	
Men	294	1.13	0.57–2.27	0.020
Generation				
Parents	236	1.77	0.94–3.47	
Offspring	416	1.04	0.48–2.65	<0.001
Hormone use[a]				
No	235	1.31	0.59–3.64	
Yes	123	2.13	0.80–5.11	0.069
Smoking status				
Never	420	1.20	0.59–2.82	
Former	148	1.43	0.63–3.13	
Current	84	1.85	0.70–4.88	0.125
Body mass index				
<25.0 kg/m^2	288	0.77	0.38–1.66	
25.0–29.9 kg/m^2	208	1.53	0.75–2.82	
≥30.0 kg/m^2	156	3.02	1.42–5.99	<0.001
Maximal oxygen uptake				
<30.2 mL/kg/min	327	2.11	0.97–4.45	
≥30.2 mL/kg/min	325	0.85	0.41–1.77	<0.001
Fasting plasma glucose				
<5.6 mmol/L	520	1.22	0.58–2.84	
≥5.6 mmol/L	82	2.41	1.11–4.36	<0.001
Fasting plasma insulin				
<60.0 pmol/L	311	0.98	0.47–2.29	
≥60.0 pmol/L	314	1.67	0.83–4.10	<0.001
Plasma LDL cholesterol				
<2.6 mmol/L	214	0.83	0.41–2.27	
≥2.6 mmol/L	438	1.53	0.75–3.27	<0.001
Plasma HDL cholesterol				
<1.02 mmol/L	327	1.40	0.68–2.86	
≥1.02 mmol/L	325	1.23	0.51–3.23	0.197
Plasma triglycerides				
<1.07 mmol/L	327	1.03	0.48–2.63	
≥1.07 mmol/L	325	1.56	0.80–3.39	<0.001
Systolic blood pressure				
<118 mmHg	326	1.25	0.56–2.67	
≥118 mmHg	326	1.40	0.66–3.16	0.148
Diastolic blood pressure				
<68 mmHg	324	1.16	0.52–2.67	
≥68 mmHg	328	1.49	0.69–3.33	0.017

Established clinical cut-offs were used for body mass index, glucose, and LDL cholesterol. Medians were used for maximal oxygen uptake, insulin, HDL cholesterol, triglycerides, and systolic and diastolic blood pressures.

[a]Hormone replacement therapy or oral contraceptives. Only women included.

[b]From Wilcoxon test or Kruskal–Wallis test.

blood pressure (*Table 5*). In each of these population groups, the difference in the C-reactive protein change among the baseline C-reactive protein groups was statistically significant after adjustment for the correlates of baseline C-reactive protein ($P < 0.001$). Further adjustment for changes in body weight, glucose, insulin, LDL cholesterol, HDL cholesterol, triglycerides, systolic and diastolic blood pressure, and maximal oxygen uptake had no effect on these associations ($P < 0.001$).

Discussion

The main finding of the present study is that plasma C-reactive protein reduced by about 1.3 mg/L in response to 20 weeks of exercise training in sedentary healthy adults with high initial C-reactive protein levels (>3.0 mg/L). The C-reactive protein reduction was consistent across all population groups and varied between 1.2 and 2.2 mg/L. This observation is potentially important from a public

Table 3 The strongest correlates of baseline C-reactive protein

	Women ($n = 358$)		Men ($n = 294$)	
	B^a	*P*-value	B^a	*P*-value
Body mass index (kg/m^2)	0.476	<0.001	0.457	<0.001
Maximal oxygen uptake (mL/kg^{-1} min^{-1})	−0.402	<0.001	−0.478	<0.001
Plasma triglycerides (mmol/L)	0.269	<0.001	0.198	<0.001
Plasma LDL cholesterol (mmol/L)	0.234	<0.001	0.254	<0.001
Plasma glucose (mmol/L)	0.199	<0.001	0.240	<0.001
Age (years)	0.197	<0.001	0.337	<0.001
Plasma insulin (pmol/L)	0.182	<0.001	0.238	<0.001
Systolic blood pressure (mmHg)	0.164	0.002	0.039	0.505
Hormone use (users)	0.140	0.008	–	–
Diastolic blood pressure (mmHg)	0.122	0.021	0.154	0.008
Smoking (cigarette years)	0.099	0.062	0.246	<0.001
Plasma HDL cholesterol (mmol/L)	−0.063	0.235	−0.155	0.008

[a]Standardized regression coefficient from a univariate linear regression analysis.

Table 4 Medians and interquartile ranges for C-reactive protein before and after exercise training and for C-reactive protein changes in response to exercise training (in mg/L) in the whole study population and in the low, moderate, and high baseline C-reactive protein groups.

		Before exercise training		After exercise training		Change in response to exercise training	
	n	Median	Interquartile range	Median	Interquartile range	Median	Interquartile range
Whole study population	652	1.31	0.60–3.00	1.50	0.68–3.38	+0.05	−0.44 to +0.70
Low (<1.0 mg/L)	265	0.50	0.32–0.72	0.62	0.39–1.11	+0.14	−0.06 to +0.56
Moderate (1.0–3.0 mg/L)	225	1.66	1.29–2.27	1.79	1.20–2.87	+0.18	−0.44 to +0.94
High (>3.0 mg/L)	162	5.60	4.17–8.65	4.56	2.89–7.18	−1.34	−3.10 to +0.39

The subjects were categorized as having low (C-reactive protein <1.0 mg/L), moderate (C-reactive protein 1.0–3.0 mg/L), or high (C-reactive protein >3.0 mg/L) risk of cardiovascular disease by using a recent recommendation of the Centers for Disease Control and Prevention and the American Heart Association.[1] In a MIXED model, $P < 0.001$ for the difference in the C-reactive protein changes in response to exercise training in the low, moderate, and high baseline C-reactive protein groups after adjustment for all correlates of baseline C-reactive protein shown in *Table 3*.

health and clinical point of view. Individuals with C-reactive protein >3.0 mg/L represent about one-fourth of adult population and are known to have a markedly increased risk of cardiovascular diseases and Type 2 diabetes.[1] A C-reactive protein reduction of 1–2 mg/L can significantly decrease the risk of cardiovascular diseases and Type 2 diabetes in individuals who have high C-reactive protein levels. The possible inflammation suppressing effect of exercise training may partly explain the effectiveness of regular physical activity in the prevention and treatment of cardiovascular and metabolic diseases.[13–24]

Previous studies suggest that regular physical activity could suppress inflammation by reducing body adiposity and improving insulin sensitivity.[32,35] In a recent study, however, the exercise-induced C-reactive protein reduction was not associated with weight loss.[36] The present data suggest that the C-reactive protein reduction in response to exercise training is not mediated by changes in body weight or other metabolic factors. One explanation is that the 20 week exercise training programme in the HERITAGE Family Study resulted in only modest changes in body adiposity,[37] insulin sensitivity,[38] plasma lipids and lipoproteins,[39] and blood pressure,[40] and individual differences in response to exercise training were large.[37–40] A longer intervention and larger changes in metabolic factors could have resulted in a larger C-reactive protein reduction. The C-reactive protein reduction was not associated with or explained by improvement in cardiorespiratory fitness either. Exercise training may also reduce C-reactive protein through more direct effects on the inflammatory process. Some previous studies suggest that exercise training reduces the expression and blood levels of leukocyte adhesion molecules, inhibits interactions between monocytes and endothelial cells,[41] decreases the production of pro-inflammatory cytokines, and increases the production of anti-inflammatory cytokines by mononuclear cells,[31] maintains balance between the production of pro-inflammatory and anti-inflammatory cytokines in skeletal muscles,[42,43] improves antioxidative defences,[44] and reduces the susceptibility of LDL to oxidation.[45]

The strengths of the present study include the standardized exercise training programme, the large study sample of previously sedentary white and black men and women, the careful exclusion of individuals who had chronic diseases or took medications that could have affected plasma C-reactive protein levels and thus confounded the statistical analyses, and the comprehensive adjustment for conditions known to be associated with plasma C-reactive protein levels. These characteristics of the study allowed us to evaluate the independent effect of exercise training on

Table 5 Medians and interquartile ranges for C-reactive protein changes in response to exercise training (in mg/L) according to baseline C-reactive protein and other baseline characteristics

	Baseline C-reactive protein levels								
	Low (<1.0 mg/L)			Moderate (1.0–3.0 mg/L)			High (>3.0 mg/L)		
Population group	*n*	Median	Interquartile range	*n*	Median	Interquartile range	*n*	Median	Interquartile range
Race									
Whites	184	+0.19	−0.03 to +0.59	158	+0.28	−0.27 to +1.13	97	−1.35	−3.10 to −0.20
Blacks	81	+0.01	−0.13 to +0.49	67	−0.08	−0.65 to +0.79	65	−1.31	−2.99 to +0.68
Gender									
Women	133	+0.05	−0.10 to +0.54	112	+0.20	−0.32 to +1.06	113	−1.31	−3.08 to +0.41
Men	132	+0.21	−0.04 to +0.63	113	+0.15	−0.46 to +0.87	49	−1.36	−3.10 to +0.04
Generation									
Parents	63	+0.11	−0.09 to +0.37	104	+0.40	−0.29 to +1.43	69	−1.19	−2.99 to +0.66
Offspring	202	+0.15	−0.06 to +0.58	121	+0.01	−0.48 to +0.68	93	−1.47	−3.58 to +0.23
Hormone use[a]									
No	97	+0.02	−0.11 to +0.48	70	+0.17	−0.48 to +0.94	68	−1.42	−3.40 to +0.42
Yes	36	+0.18	−0.09 to +0.74	42	+0.13	−0.09 to +1.09	45	−1.19	−2.66 to +0.26
Smoking status									
Non-smokers	234	+0.13	−0.07 to +0.49	198	+0.17	−0.44 to +1.02	136	−1.30	−2.97 to +0.46
Current smokers	31	+0.26	−0.05 to +1.12	27	+0.32	−0.27 to +0.77	26	−1.57	−4.86 to −0.10
Body mass index									
<25.0 kg/m^2	171	+0.12	−0.07 to +0.58	79	+0.15	−0.57 to +0.77	38	−2.23	−4.86 to −0.64
≥25.0 kg/m^2	94	+0.18	−0.06 to +0.54	146	+0.23	−0.31 to +1.15	124	−1.19	−2.91 to +0.57
Maximal oxygen uptake									
<30.2 mL/kg/min	85	+0.10	−0.09 to +0.57	120	+0.36	−0.31 to +1.20	122	−1.31	−2.91 to +0.44
≥30.2 mL/kg/min	180	+0.16	−0.05 to +0.54	105	+0.07	−0.57 to +0.70	40	−1.59	−4.89 to −0.56
Fasting plasma glucose									
<5.6 mmol/L	223	+0.15	−0.05 to +0.58	177	+0.25	−0.33 to +0.94	120	−1.43	−3.16 to +0.21
≥5.6 mmol/L	19	+0.09	−0.16 to +0.49	36	−0.05	−0.55 to +1.27	27	−1.13	−2.49 to +0.73
Fasting plasma insulin									
<60.0 pmol/L	158	+0.10	−0.08 to +0.52	95	+0.19	−0.46 to +1.05	58	−1.57	−3.08 to −0.37
≥60.0 pmol/L	91	+0.22	−0.01 to +0.76	125	+0.19	−0.31 to +0.94	98	−1.31	−3.10 to +0.26
Plasma LDL cholesterol									
<2.6 mmol/L	122	+0.13	−0.06 to +0.54	49	+0.04	−0.58 to +0.68	43	−1.62	−3.65 to +0.48
≥2.6 mmol/L	143	+0.15	−0.07 to +0.60	176	+0.22	−0.33 to +1.15	119	−1.23	−2.99 to +0.39
Plasma HDL cholesterol									
<1.02 mmol/L	121	+0.19	−0.05 to +0.66	128	+0.19	−0.34 to +1.08	78	−1.21	−2.90 to +0.48
≥1.02 mmol/L	144	+0.11	−0.08 to +0.48	97	+0.17	−0.49 to +0.91	84	−1.61	−3.64 to +0.24
Plasma triglycerides									
<1.07 mmol/L	162	+0.12	−0.07 to +0.58	93	+0.08	−0.64 to +0.94	72	−1.70	−4.68 to +0.34
≥1.07 mmol/L	103	+0.19	−0.03 to +0.56	132	+0.26	−0.27 to +0.98	90	−1.18	−2.49 to +0.39
Systolic blood pressure									
<118 mmHg	138	+0.15	−0.06 to +0.64	112	+0.16	−0.31 to +1.13	76	−1.51	−3.64 to −0.22
≥118 mmHg	127	+0.14	−0.07 to +0.48	113	+0.24	−0.46 to +0.91	86	−1.25	−2.99 to +0.66
Diastolic blood pressure									
<68 mmHg	142	+0.19	−0.03 to +0.60	107	+0.15	−0.31 to +1.09	75	−1.58	−3.62 to +0.39
≥68 mmHg	123	+0.09	−0.09 to +0.37	118	+0.23	−0.47 to +0.91	87	−1.30	−2.99 to +0.41

The subjects were categorized as having low (C-reactive protein <1.0 mg/L), moderate (C-reactive protein 1.0–3.0 mg/L), or high (C-reactive protein >3.0 mg/L) risk of cardiovascular disease by using a recent recommendation of the Centers for Disease Control and Prevention and the American Heart Association.[1] Established clinical cut-offs were used for body mass index, glucose, and LDL cholesterol. Medians were used for maximal oxygen uptake, insulin, HDL cholesterol, triglycerides, and systolic and diastolic blood pressures. In MIXED models for each population group, $P < 0.001$ for the difference in the C-reactive protein changes in response to exercise training in the low, moderate, and high baseline C-reactive protein groups after adjustment for all correlates of baseline C-reactive protein shown in *Table 3*.

[a] Hormone replacement therapy or oral contraceptives. Only women included.

plasma C-reactive protein levels and to compare the effect in various population groups. A weakness of the study is the lack of a control group. The HERITAGE Family Study was originally designed to investigate the role of genetic factors in cardiovascular, metabolic, and hormonal responses to exercise training and a control group was not deemed necessary. Thus, it is difficult to conclude whether the observed C-reactive protein reduction in individuals with high baseline C-reactive protein levels was due to exercise training or changes in other correlates of C-reactive protein. In contrast, there are several reasons to believe that the C-reactive protein reduction in the high baseline C-reactive protein group is due to a true effect of exercise training. First, the C-reactive protein reduction

was strong, independent of a number of potential confounding factors, and evident in all population groups. Secondly, the participants were instructed not to change their lifestyle during the study, and reported changes in smoking habits in few subjects had no effect on the results. Third, over time variation in plasma C-reactive protein levels in healthy individuals with stable lifestyle is small,[1] suggesting that the large C-reactive protein reduction most likely reflects the true effect of exercise training. The C-reactive protein reduction in the high baseline C-reactive protein group may also be partly due to a regression towards the mean phenomenon. However, the interquartile ranges of C-reactive protein in the high baseline C-reactive protein group were similar before and after training, suggesting that regression towards the mean may not be a major reason for the observed C-reactive protein reduction.

In conclusion, plasma C-reactive protein levels reduced markedly in response to exercise training in sedentary healthy adults with high initial C-reactive protein levels, who are known to have an increased risk of cardiovascular diseases and Type 2 diabetes. Our finding supports the current recommendation to increase moderate intensity physical activity to reduce the risk of cardiovascular and metabolic diseases. Randomized controlled trials with sufficient sample sizes are needed to confirm the inflammation suppressing effect of exercise training, to detect biological mechanisms underlying the effect, and to verify whether the effect is evident among individuals with different levels of C-reactive protein and cardiovascular and metabolic risk factors.

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References

1. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO III, Criqui M, Fadl YY, Fortmann SP, Hong Y, Myers GL, Rifai N, Smith SC Jr, Taubert K, Tracy RP, Vinicor F. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation* 2003;**107**:499–511.
2. Koenig W, Sund M, Frohlich M, Fischer HG, Lowel H, Doring A, Hutchinson WL, Pepys MB. C-reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men: results from the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Augsburg Cohort Study, 1984 to 1992. *Circulation* 1999;**99**:237–242.
3. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med* 2002;**347**:1557–1565.
4. Rost NS, Wolf PA, Kase CS, Kelly-Hayes M, Silbershatz H, Massaro JM, D'Agostino RB, Franzblau C, Wilson PW. Plasma concentration of C-reactive protein and risk of ischemic stroke and transient ischemic attack: the Framingham study. *Stroke* 2001;**32**:2575–2579.
5. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Plasma concentration of C-reactive protein and risk of developing peripheral vascular disease. *Circulation* 1998;**97**:425–428.
6. Sesso HD, Buring JE, Rifai N, Blake GJ, Gaziano JM, Ridker PM. C-reactive protein and the risk of developing hypertension. *JAMA* 2003;**290**: 2945–2951.
7. Ridker PM, Buring JE, Cook NR, Rifai N. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14 719 initially healthy American women. *Circulation* 2003;**107**: 391–397.
8. Ridker PM, Rifai N, Pfeffer MA, Sacks FM, Moye LA, Goldman S, Flaker GC, Braunwald E. Inflammation, pravastatin, and the risk of coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events (CARE) Investigators. *Circulation* 1998;**98**:839–844.
9. Lindahl B, Toss H, Siegbahn A, Venge P, Wallentin L. Markers of myocardial damage and inflammation in relation to long-term mortality in unstable coronary artery disease. FRISC Study Group. Fragmin during Instability in Coronary Artery Disease. *N Engl J Med* 2000;**343**:1139–1147.
10. Festa A, D'Agostino R Jr, Howard G, Mykkanen L, Tracy RP, Haffner SM. Chronic subclinical inflammation as part of the insulin resistance syndrome: the Insulin Resistance Atherosclerosis Study (IRAS). *Circulation* 2000;**102**:42–47.
11. Yudkin JS, Stehouwer CD, Emeis JJ, Coppack SW. C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? *Arterioscler Thromb Vasc Biol* 1999;**19**:972–978.
12. Freeman DJ, Norrie J, Caslake MJ, Gaw A, Ford I, Lowe GD, O'Reilly DS, Packard CJ, Sattar N. C-reactive protein is an independent predictor of risk for the development of diabetes in the West of Scotland Coronary Prevention Study. *Diabetes* 2002;**51**:1596–1600.
13. Lakka TA, Venalainen JM, Rauramaa R, Salonen R, Tuomilehto J, Salonen JT. Relation of leisure-time physical activity and cardiorespiratory fitness to the risk of acute myocardial infarction. *N Engl J Med* 1994;**330**: 1549–1554.
14. Leon AS, Connett J, Jacobs DR Jr, Rauramaa R. Leisure-time physical activity levels and risk of coronary heart disease and death. The Multiple Risk Factor Intervention Trial. *JAMA* 1987;**258**:2388–2395.
15. Sacco RL, Gan R, Boden-Albala B, Lin IF, Kargman DE, Hauser WA, Shea S, Paik MC. Leisure-time physical activity and ischemic stroke risk: the Northern Manhattan Stroke Study. *Stroke* 1998;**29**:380–387.
16. Kurl S, Laukkanen JA, Rauramaa R, Lakka TA, Sivenius J, Salonen JT. Cardiorespiratory fitness and the risk for stroke in men. *Arch Intern Med* 2003;**163**:1682–1688.
17. Paffenbarger RS Jr, Hyde RT, Wing AL, Lee IM, Jung DL, Kampert JB. The association of changes in physical-activity level and other lifestyle characteristics with mortality among men. *N Engl J Med* 1993;**328**:538–545.
18. Laukkanen JA, Lakka TA, Rauramaa R, Kuhanen R, Venalainen JM, Salonen R, Salonen JT. Cardiovascular fitness as a predictor of mortality in men. *Arch Intern Med* 2001;**161**:825–831.
19. Jolliffe JA, Rees K, Taylor RS, Thompson D, Oldridge N, Ebrahim S. Exercise-based rehabilitation for coronary heart disease. *Cochrane Database Syst Rev* 2001, CD001800.
20. Stewart KJ, Hiatt WR, Regensteiner JG, Hirsch AT. Exercise training for claudication. *N Engl J Med* 2002;**347**:1941–1951.
21. Thompson PD, Buchner D, Pina IL, Balady GJ, Williams MA, Marcus BH, Berra K, Blair SN, Costa F, Franklin B, Fletcher GF, Gordon NF, Pate RR, Rodriguez BL, Yancey AK, Wenger NK. Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease: a statement from the Council on Clinical Cardiology and the Council on Nutrition, Physical Activity, and Metabolism. *Circulation* 2003;**107**:3109–3116.
22. Hambrecht R, Wolf A, Gielen S, Linke A, Hofer J, Erbs S, Schoene N, Schuler G. Effect of exercise on coronary endothelial function in patients with coronary artery disease. *N Engl J Med* 2000;**342**:454–460.
23. Laaksonen DE, Lakka HM, Salonen JT, Niskanen LK, Rauramaa R, Lakka TA. Low levels of leisure-time physical activity and cardiorespiratory fitness predict development of the metabolic syndrome. *Diabetes Care* 2002;**25**:1612–1618.
24. Laaksonen DE, Lindström J, Lakka TA, Eriksson JG, Niskanen LK, Wikström K, Aunola S, Keinänen-Kiukaanniemi S, Laakso M, Valle TT, Ilanne-Parikka P, Louheranta A, Hämäläinen H, Rastas M, Salminen V, Cepaitis Z, Hakumäki M, Kaikkonen H, Härkönen P, Sundvall J, Tuomilehto J. Uusitupa M. Physical activity in the prevention of type 2 diabetes: The Finnish Diabetes Prevention Study. *Diabetes* 2005;**54**: 158–165.

25. Geffken DF, Cushman M, Burke GL, Polak JF, Sakkinen PA, Tracy RP. Association between physical activity and markers of inflammation in a healthy elderly population. *Am J Epidemiol* 2001;**153**:242–250.
26. Abramson JL, Vaccarino V. Relationship between physical activity and inflammation among apparently healthy middle-aged and older US adults. *Arch Intern Med* 2002;**162**:1286–1292.
27. Wannamethee SG, Lowe GD, Whincup PH, Rumley A, Walker M, Lennon L. Physical activity and hemostatic and inflammatory variables in elderly men. *Circulation* 2002;**105**:1785–1790.
28. Albert MA, Glynn RJ, Ridker PM. Effect of physical activity on serum C-reactive protein. *Am J Cardiol* 2004;**93**:221–225.
29. Ford ES. Does exercise reduce inflammation? Physical activity and C-reactive protein among U.S. adults. *Epidemiology* 2002;**13**:561–568.
30. Pitsavos C, Chrysohoou C, Panagiotakos DB, Skoumas J, Zeimbekis A, Kokkinos P, Stefanadis C, Toutouzas PK. Association of leisure-time physical activity on inflammation markers (C-reactive protein, white cell blood count, serum amyloid A, and fibrinogen) in healthy subjects (from the ATTICA study). *Am J Cardiol* 2003;**91**:368–370.
31. Smith JK, Dykes R, Douglas JE, Krishnaswamy G, Berk S. Long-term exercise and atherogenic activity of blood mononuclear cells in persons at risk of developing ischemic heart disease. *JAMA* 1999;**281**:1722–1727.
32. You T, Berman DM, Ryan AS, Nicklas BJ. Effects of hypocaloric diet and exercise training on inflammation and adipocyte lipolysis in obese postmenopausal women. *J Clin Endocrinol Metab* 2004;**89**:1739–1746.
33. Rauramaa R, Halonen P, Väisänen SB, Lakka TA, Schmidt-Trücksass A, Berg A, Penttilä IM, Rankinen T, Bouchard C. Effects of aerobic physical exercise on inflammation and atherosclerosis in men: the DNASCO Study: a six-year randomized, controlled trial. *Ann Intern Med* 2004;**140**:1007–1014.
34. Bouchard C, Leon AS, Rao DC, Skinner JS, Wilmore JH, Gagnon J. The HERITAGE family study. Aims, design, and measurement protocol. *Med Sci Sports Exerc* 1995;**27**:721–729.
35. Esposito K, Pontillo A, Di Palo C, Giugliano G, Masella M, Marfella R, Giugliano D. Effect of weight loss and lifestyle changes on vascular inflammatory markers in obese women: a randomized trial. *JAMA* 2003;**289**:1799–1804.
36. Okita K, Nishijima H, Murakami T, Nagai T, Morita N, Yonezawa K, Iizuka K, Kawaguchi H, Kitabatake A. Can exercise training with weight loss lower serum C-reactive protein levels? *Arterioscler Thromb Vasc Biol* 2004;**24**:1868–1873.
37. Wilmore JH, Despres JP, Stanforth PR, Mandel S, Rice T, Gagnon J, Leon AS, Rao D, Skinner JS, Bouchard C. Alterations in body weight and composition consequent to 20 wk of endurance training: the HERITAGE Family Study. *Am J Clin Nutr* 1999;**70**:346–352.
38. Lakka TA, Rankinen T, Weisnagel SJ, Chagnon YC, Lakka H-M, Ukkola O, Boulé N, Rice T, Leon AS, Skinner JS, Wilmore JH, Rao DC, Bergman R, Bouchard C. Leptin and leptin receptor gene polymorphisms and changes in glucose homeostasis in response to regular exercise in nondiabetic individuals: the HERITAGE Family Study. *Diabetes* 2004;**53**:1603–1608.
39. Leon AS, Rice T, Mandel S, Despres JP, Bergeron J, Gagnon J, Rao DC, Skinner JS, Wilmore JH, Bouchard C. Blood lipid response to 20 weeks of supervised exercise in a large biracial population: the HERITAGE Family Study. *Metabolism* 2000;**49**:513–520.
40. Wilmore JH, Stanforth PR, Gagnon J, Rice T, Mandel S, Leon AS, Rao DC, Skinner JS, Bouchard C. Heart rate and blood pressure changes with endurance training: the HERITAGE Family Study. *Med Sci Sports Exerc* 2001;**33**:107–116.
41. Jordan J, Beneke R, Hutler M, Veith A, Haller H, Luft FC. Moderate exercise leads to decreased expression of beta1 and beta2 integrins on leucocytes. *Eur J Appl Physiol Occup Physiol* 1997;**76**:192–194.
42. Febbraio MA, Steensberg A, Starkie RL, McConell GK, Kingwell BA. Skeletal muscle interleukin-6 and tumor necrosis factor-alpha release in healthy subjects and patients with type 2 diabetes at rest and during exercise. *Metabolism* 2003;**52**:939–944.
43. Greiwe JS, Cheng B, Rubin DC, Yarasheski KE, Semenkovich CF. Resistance exercise decreases skeletal muscle tumor necrosis factor alpha in frail elderly humans. *FASEB J* 2001;**15**:475–482.
44. Powers SK, Ji LL, Leeuwenburgh C. Exercise training-induced alterations in skeletal muscle antioxidant capacity: a brief review. *Med Sci Sports Exerc* 1999;**31**:987–997.
45. Vasankari TJ, Kujala UM, Vasankari TM, Ahotupa M. Reduced oxidized LDL levels after a 10-month exercise program. *Med Sci Sports Exerc* 1998;**30**:1496–1501.