Inflammatory Markers and Exercise: Differences Related to Exercise Type

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ABSTRACT

KING, D. E., P. CAREK, A. G. MAINOUS III, and W. S. PEARSON. Inflammatory Markers and Exercise: Differences Related to Exercise Type. *Med. Sci. Sports Exerc.*, Vol. 35, No. 4, pp. 575–581, 2003. **Purpose:** To examine the relationship between elevated inflammatory markers (CRP, fibrinogen, and white blood cell levels) and various forms of exercise for the adult U.S. population while controlling for factors that might influence the relationship. **Methods:** An analysis of the adults age 17 and over who participated in the National Health and Nutrition Examination Survey (NHANES) III was conducted. The main goal of the analysis was to determine whether exercise type was associated with systemic markers of inflammation. Bivariate statistics using chi-square to evaluate different types of exercise according to the presence of elevated and nonelevated inflammatory markers was initially performed. In addition, multivariate models were constructed using each type of exercise activity as the predictor variable and each inflammatory marker as the dependent variable. **Results:** A total of 4072 people were included in the analysis. In bivariate analyses, compared with nonexercisers in a specific exercise type, a significant lower likelihood of elevated inflammatory markers was found among regular participants in jogging, swimming, cycling, aerobic dancing, calisthenics, and weight lifting but not for gardening. After controlling for possible confounding factors including age, race, sex, body mass index, smoking, and health status in logistic regression analysis, only regular participants in jogging and aerobic dancing remained significantly less likely to have elevated cardiovascular markers. **Conclusions:** The results of this study indicate that some forms of physical activity are associated with a lower likelihood of elevation of inflammatory markers, although we cannot exclude the possibility that differences may be due to exercise intensity or duration. Future research should be directed toward further exploration of the effects of different types of exercise activity on inflammatory markers and the role of exercise in the prevention of cardiovascular disease. **Key Words:** CARDIOVASCULAR, FIBRINOGEN, WHITE BLOOD CELL, C-REACTIVE PROTEIN

Regular physical activity has many benefits including a reduced risk of cardiovascular and all-cause mortality (4,8). Benefits have been attributed to improved weight control, reduced LDL cholesterol, and increased insulin sensitivity, and accrue to a greater degree with increased intensity and duration of the activity (16,34). Although people often choose physical and sporting activity for enjoyment and fitness, reduction of cardiovascular risk is also a prime consideration (18).

Simultaneous with the growth of research evidence regarding the benefits of exercise in preventing cardiovascular disease has been the emergence of inflammation as an important independent risk factor for cardiovascular disease. Elevated levels of inflammatory markers, such as C-reactive protein (CRP), have been directly related to the risk of myocardial infarction (1,26). Chronically elevated levels of CRP have been shown to contribute independently to later risk of cardiovascular disease (25).

Recent attention to the inflammatory process and its role in cardiovascular risk has heightened interest in the inflammatory response to exercise (2,9,20). Several studies have explored the response of inflammatory biomarkers to muscle contraction and exercise activity. Physiologic studies have demonstrated that contracting skeletal muscle acutely produces interleukin-6 (IL-6), an inflammatory protein and biologic precursor of CRP, to help regulate glucose homeostasis during exercise (10,21,27). Increased levels of inflammatory markers also have been demonstrated in the bloodstream acutely after weight lifting and marathon running (20,29). These elevated levels may be due to intense exercise or a substantial mechanical load on the muscle. Regular exercise training appears to modify this response, possibly due to a training effect (22). For example, Fallon et al. (9) has found that CRP levels declined with regular

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soccer training, and Mattusch et al. (17) has found reductions in CRP in athletes after 9 months of endurance running. Further, Abramson and Vaccarino (2) used data from the Third National Health and Nutrition Examination Survey and found that regular physical activity is independently associated with lower odds of elevated inflammation markers, particularly CRP. After controlling for potential confounders including demographic factors, blood pressure, cholesterol, glucose levels, and body mass index (BMI), physical activity (>21 times per month) remained a significant predictor of lower odds of elevated inflammatory markers. Geffken et al. (12) similarly found lower levels of CRP, white blood cells (WBC), and fibrinogen with higher levels of total physical activity.

However, these studies did not compare the effect of different types of physical activity, which is particularly important in light of recent evidence of the relationship between exercise type and subsequent coronary heart disease (28). In a cohort study of 44,452 men, Tanasescu and colleagues (28) found that running, walking, and weight training were associated with a lower risk of nonfatal myocardial infarction and coronary mortality, whereas cycling, swimming, and racquet sports were not. Thus, the type of exercise as well as the intensity and duration appear to influence cardiovascular risk.

However, it is unclear whether different types of physical activity have different effects on inflammatory markers that, in turn, are known to affect cardiovascular risk. The current study sought to characterize elevated CRP, fibrinogen, and WBC levels for various forms of exercise for the adult U.S. population while accounting for factors that might influence the relationship. This knowledge will be helpful in improving our understanding of the relationships between exercise type and cardiovascular inflammatory markers.

METHODS

Study Design and Participants

The study was an analysis of the adults age 17 and over who participated in the National Health and Nutrition Examination Survey (NHANES) III, a national public use data set that does not require IRB approval for use. The NHANES III collected multistage, stratified, clustered samples from a civilian, noninstitutionalized population. The National Center for Health Statistics administered the survey to a randomly selected group of approximately 40,000 residents in 89 communities across the United States. The survey was conducted in two phases. The first phase was administered out of 44 different locations from October 1988 to October 1991. The second phase took place from September 1991 to October 1994 out of 45 different locations. Most (86%; 33,994) of surveyed residents were interviewed in their homes. All surveyed residents were invited to examination centers for additional data collection including physical examination and laboratory measures; 79% (31,311) of those surveyed completed all or some of the physical exam and laboratory data collection. Detailed information on the plan and operation of the NHANES III has been previously published (19).

To examine the relationship between CRP and exercise, three of the five NHANES data files were selected for analysis: the household adult data file, examination data file, and laboratory data file. All NHANES III public use data files are linked by a common survey participant variable. The variable consistently identifies the same participant in each different data file. We excluded any person who did not participate in all three parts of the survey.

The household adult data file contains the results of the questionnaire administered to all adults in the survey population described above. Adults (20,500) completed the household survey during the 6 yr of NHANES III data collection. The adult interviews were conducted in English and Spanish by highly trained field staff. The staff was continuously retrained throughout the 6-yr period to ensure that the appropriate standard was maintained.

The examination and lab data files contain the results of the exams and labs performed on survey participants who followed up their household interview as requested with a visit to one of the NHANES mobile examination centers. Survey participants were examined within a month of completing their household interview. A less comprehensive home examination was available to those participants who were unable to leave their home.

Of those who filled out an adult household survey, 96% (N = 19,760) also completed the lab tests and physical exam. People who had used anti-inflammatory drugs within the last 30 d also were excluded from the analysis, due to the possible effects such use might have on inflammatory markers. The use of antiinflammatory drugs was measured by questions regarding the use of prescription medications along with specific questions about the nonprescription use of aspirin and ibuprofen. Prescribed nonsteroidal anti-inflammatory drugs and corticosteroids were classed as anti-inflammatory medications.

Study Measures

Exercise type. Each respondent was asked if they participated in the following list of activities within the past month: walking a mile without stopping, jogging or running, swimming, regular dancing, aerobic exercise or aerobic dancing, riding a bicycle or exercise bicycle, calisthenics, garden or yard work, or weight lifting. Respondents were asked about how often they had participated in the activity in the past month. No information was collected regarding the duration or intensity of the activity. Respondents were compared with people not participating in that activity but who may have been participants in other exercise activities.

Markers of inflammation. Standard phlebotomy techniques were used to obtain specimens. Serum specimens were frozen to −20°C until being analyzed later.

The study focused on three markers of inflammation: serum CRP, WBC count, and fibrinogen. These markers were chosen because each of them has been associated with

cardiovascular risk (6,13,25,33), and they have been correlated with overall level of physical activity (2).

CRP was measured using a Behring Nephelometer Analyzer System (Behring Diagnostics Inc., Somerville, NJ). The lower limit of detection was truncated at 0.30 $mg \cdot dL^{-1}$ due to the limits of the diagnostic technique used, levels. Values below 0.30 were assigned a value of 0.21 $mg \cdot dL^{-1}$. This lower limit of detection limited statistical analysis of CRP to elevated or nonelevated, because CRP was noncontinuous across the full range and did not have a normal distribution.

An elevated level of CRP was defined prospectively, using a cutoff point based on previous studies of cardiovascular disease. Our purpose was to use levels that have prognostic significance as predictors of cardiovascular disease and cardiovascular events, recognizing that the levels selected are not clinical thresholds for the occurrence of cardiovascular events. Previous studies have chosen 0.30 $mg \cdot dL^{-1}$ as a cutoff of clinical significance, a level that corresponds to the 75th percentile in the NHANES III adult population. In a study by Abdelmouttaleb et al. (1) that compared CRP levels in groups at risk for cardiovascular disease, mean C-reactive protein levels were 0.23 in healthy controls. In another investigation, values in excess of 0.30 $mg \cdot dL^{-1}$ were associated with increased cardiovascular risk (25). Thus, after considering these factors and for the purposes of statistical analyses, values above 0.30 $mg \cdot dL^{-1}$ were considered elevated.

WBC count was included as part of the complete blood count performed using the Coulter Counter Model S-PLUS JR automated hematology analyzer (Coulter Electronics, Hialeah, FL). The level that was considered elevated was $>9550\ mm^{-1}$ (3) to be consistent with the previous study by Abramson (2). Elevated WBC is a known risk factor for heart disease (35)

Fibrinogen was analyzed using the Coagamate XC Plus automated coagulation analyzer (Organon Teknika, Durham, NC). Further details about the specific methods for laboratory procedures in the NHANES III have been described previously (15). Fibrinogen was considered elevated at a level $>373\ mg \cdot dL^{-1}$ as used in the Abramson and Vaccarino (2) study.

Other Measures

Demographics. Age, sex, race, smoking status, BMI, and self-reported health status were included in the analysis as control variables. Race included four categories: non-Hispanic white, non-Hispanic black, Mexican-American, and other. BMI was computed on the basis of weight in kilograms divided by the height in meters squared. Smoking status was determined by self-report as current, past, or never smokers. Self-reported health status (poor, fair, good, or excellent) was included to account for overall health and the presence of acute or chronic illnesses that might influence CRP (24).

Statistical Analysis

Because NHANES III was a complex, stratified cluster sample, standard statistical techniques could not be used. Therefore, we used SUDAAN (Research Triangle Institute, Research Triangle, NC), a specialized statistical program that accounts for the complex weighting of the NHANES III sample. Using SUDAAN allowed us to correct for unequal probabilities of selection and different response rates, ensuring that the results can be generalized to the noninstitutionalized civilian population of the United States. Thus, the percentages and odds ratios in this study represent weighted values. SUDAAN also adjusts the standard errors to account for the weighting, stratification, and clustering of the complex sampling design, to ensure that expressed *P* values are valid.

The main goal of the analysis was to determine whether exercise type was associated with markers of inflammation. We first computed bivariate statistics using chi-square to evaluate the presence of elevated and nonelevated inflammatory markers according to different types of exercise, comparing regular exercisers ($\geq 12\times\ month^{-1}$) to infrequent ($1–11\times\ month^{-1}$) and nonparticipants ($0\times\ month^{-1}$) of that specific exercise activity.

Then, using logistic regression, multivariate models were constructed using each type of exercise activity as the predictor variable and each inflammatory marker as the dependent variable. Initially the same three levels of exercise participation were used in the regression models; however, there were too few participants in the many of the low ($1–11\times\ month^{-1}$) groups to evaluate the model. Consequently, because we were most interested in the associations between frequent exercise and inflammatory markers, the nonparticipant ($0\times\ month^{-1}$) and low ($1–11\times\ month^{-1}$) participant groups were combined in the regression analyses to form the reference group. Exercise 12 or more times a month was chosen as the focus because it corresponds to the recommended level of exercise ($3\times\ wk^{-1}$) for people at cardiovascular risk (25).

The dependent variables of markers of inflammation (CRP, fibrinogen, and WBC) were analyzed as dichotomous variables (elevated vs nonelevated) to be consistent with previous studies focusing on cardiovascular risk. Further, the distribution of the CRP is skewed, making linear model techniques inappropriate (12,24). The models were adjusted for possible confounders including age, race, gender, smoking, BMI, and self-reported health status. Standardized betas, *P* values, odds ratios, and 95% confidence intervals were obtained from the logistic regression output. Statistical significance was defined as $P \leq 0.05$.

RESULTS

A total of 4072 people with physical activity, history, and laboratory data available were included in this analysis. The demographics of the respondents are highlighted in Table 1.

Data for all exercise types are shown in Table 2, stratified by the presence of elevation of the three inflammatory

TABLE 1. Demographics of population (N = 4072).

	%
Age (yr)	
17–34	39.7
35–49	25.0
50–64	20.1
65+	15.2
Sex	
Male	49.6
Female	50.4
Race	
Non-Hispanic white	68.3
Non-Hispanic black	14.1
Mexican-American	6.9
Other	10.7
Self-reported health status	
Excellent	20.6
Very good	27.2
Good	35.8
Fair	13.1
Poor	3.4
BMI	
>30	22.3
≤30	77.7
Smoking status	
Current	26.0
Past	25.5
Never	48.5

markers included in the study. Compared with nonparticipants in the given type of exercise, there was a significantly lower likelihood of elevation of systemic inflammatory markers among participants in all activities except gardening. Frequent ($>12\times$ month^{-1}) jogging and dancing were associated with lower percentage of elevation for all three markers. Cycling was associated only with lower fibrinogen, but not CRP or WBC.

Results of the logistic regression analyses are shown in Table 3. After adjustment, people who participated in jogging or aerobic dancing 12 or more per month showed the lowest odds for having elevated levels of CRP. Participants in aerobic dancing also were found to have significantly reduced odds of having elevated fibrinogen levels and reduced odds of an elevated WBC. None of the other types of physical activity were associated with elevation of CRP, fibrinogen, or WBC count in the regression models.

DISCUSSION

The most important finding of the current study is that different types of physical activity have different associations with inflammatory markers. After controlling for age, BMI, smoking, and other confounding factors in the analysis, only participants in regular jogging and aerobic dancing had significantly lower likelihood of elevated inflammatory markers. Participation in the other types of exercise activity, including cycling and swimming, was not associated with levels of inflammatory markers in adjusted analyses. If confirmed in further studies, the finding that cardiovascular inflammatory markers are less likely to be elevated with specific types of exercise may have important implications for people at risk of cardiovascular disease.

Lower levels of inflammatory markers, particularly CRP, have been associated with regular participation in exercise or physical activity (2,12,32). However, the reductions in inflammatory markers observed in these studies were not analyzed by specific exercise type. In the current study, the beneficial association with overall physical activity was seen only among regular participants of jogging or aerobic dancing, activities that emphasize running, jogging, or repetitious weight-bearing movement. There was no association with inflammatory markers observed in the current study with participation in cycling, swimming, calisthenics, gardening, or weight lifting >12 times per month after controlling for possible confounders.

These results add to the growing literature on the influence of exercise on inflammatory markers. Acute elevation of inflammatory markers has been seen after intense exercise, presumably as a result of joint and muscle inflammation associated with vigorous physical activity (2,9,10,17,21,27). However, although markers have generally been high when measured soon after exercise, long-term effects appear to lower inflammatory markers. Tisi and colleagues (30,31) have cautioned that exercise may induce a low-grade repetitive inflammation that increases vascular endothelial injury, but walking regularly appears to reduce rather than increase levels of inflammatory markers. Thomas et al. (29) studied the inflammatory response after running compared with weight training and found sporadically higher values of CRP in weight lifters immediately after the training session but no changes in runners. Other studies have found that CRP significantly increases in the period 2–5 d after running rather than immediately. Castell et al. (5) found increased CRP measured 16 h after a marathon but not immediately after the event. Neidhart et al. (20) have found elevated CRP levels at 24 and 48 h after a marathon run. In studies evaluating other activities, Dufaux et al. (7) found lower levels of CRP in swimmers and rowers, whereas levels in runners did not differ significantly from controls. The variable results found in previous studies may be due to differences in sample size, exercise intensity, and lack of controlling for possible confounding factors.

Lower levels of inflammatory markers have been documented after regular participation in sports and exercise activity, and may be the result of a training effect. In a study by Fallon et al. (9), regular soccer training led to lower CRP levels several months later. Mattusch et al. (17) documented similar reductions in CRP in athletes after 9 months of an endurance running program. Our study in a large national sample of people regularly participating in many different types of physical activity found that people in jogging or aerobic dancing exercise activity ≥ 12 times a month were less likely to have elevated inflammatory markers. This finding lends support to a "training effect" on inflammation and needs evaluation in further studies.

The beneficial effects of exercise are well documented and are not being put into doubt by the findings of the current study. Regular exercise has been shown to decrease cardiovascular risk and the risk of developing diabetes (15,28). However, the mechanism of how physical activity prevents cardiovascular disease has not been well elucidated. Physical activity has beneficial effects on many car-

TABLE 2. Percent with elevated CRP, fibrinogen, and WBC, by exercise type and frequency [times(×) per month].

	CRP (>0.3 mg·dL^{-1})	*P*	Fibrinogen (>373 mg·dL^{-1})	*P*	WBC (>9550 cells·mm^{-3})	*P*
Jogging		<0.01		<0.01		<0.01
≥12× month^{-1}	6.9		1.3		2.6	
1–11× month^{-1}	13.2		1.1		2.9	
0× month^{-1}	28.6		10.1		10.7	
Swimming		0.04		<0.01		0.21
≥12×	14.8		5.6		5.4	
1–11×	20.5		2.3		5.5	
0×	27.1		9.7		10.2	
Cycling		0.24		<0.01		0.30
≥12×	29.6		8.9		6.9	
1–11×	21.2		2.8		7.0	
0×	26.7		9.9		10.1	
Aerobic dancing		0.11		0.01		<0.01
≥12×	11.6		2.8		1.2	
1–11×	25.7		3.8		14.4	
0×	26.4		9.2		9.5	
Other dancing		0.02		<0.01		0.02
≥12×	1.0		3.1		1.0	
1–11×	10.1		4.3		10.2	
0×	89.0		9.6		88.8	
Calisthenics		0.04		0.02		0.09
≥12×	18.5		8.6		4.8	
1–11×	21.3		4.1		8.2	
0×	27.6		9.3		10.3	
Gardening		0.15		0.28		0.99
≥12×	30.4		12.6		9.6	
1–11×	22.4		8.0		9.7	
0×	27.7		8.6		9.4	
Weight lifting		<0.01		<0.01		0.15
≥12×	15.1		6.3		5.9	
1–11×	14.1		1.5		5.2	
0×	27.5		9.4		10.1	

diovascular disease risk factors, including total and HDL cholesterol, hypertension, BMI, insulin sensitivity, and diabetes mellitus type 2 (11). However, the beneficial effects of physical activity are not fully accounted for by risk factor reduction. A role for vascular inflammation is suggested by studies that show lower CRP with physical activity (2) and improved vascular endothelium-dependent vasodilatation with exercise training (23). The protective effect of physical activity against cardiovascular disease may be mediated by a combination of cardiovascular responses including the vascular-mediated inflammatory response. Thus, a differential inflammatory response to different types of exercise may have important implications for cardiovascular risk.

The recent study by Tanasescu et al. (28) demonstrated that specific exercise types (in addition to total physical activity) were associated with reduced risk of myocardial infarction and cardiovascular mortality. Walking, running, and weight training reduced the risk of subsequent heart disease, whereas cycling, swimming, and racquet sports did not. The results of the current study, which demonstrated a beneficial association with inflammatory markers for jogging and dancing, but not for cycling, swimming, or weight lifting, are largely consistent with Tanasescu's findings, with the exception of weightlifting. Because our study included both sexes and Tanasescu's only included men, some differences in findings may be due to gender. Further research is needed to clarify these findings.

TABLE 3. Adjusted logistic regressions for exercise type and CRP, fibrinogen, and white cell count: participating in activity ≥12 times per month (compared with 0–11 times per month)*.

	CRP		Fibrinogen		White Cell Count	
	OR	95% CI	OR	95% CI	OR	95% CI
Jogging	0.33	0.14–0.78**	0.33	0.04–3.11	0.46	0.10–2.09
Swimming	0.62	0.25–1.52	1.61	0.38–6.86	0.40	0.05–3.36
Cycling	1.30	0.76–2.22	1.11	0.58–2.13	0.80	0.26–2.47
Aerobic dancing	0.31	0.13–0.78**	0.29	0.09–0.99**	0.11	0.03–0.41**
Other dancing	0.76	0.33–1.73	2.06	0.22–19.01	0.45	0.08–2.42
Calisthenics	0.77	0.48–1.23	1.12	0.74–1.69	0.59	0.23–1.55
Gardening	1.36	0.87–2.12	1.02	0.55–1.90	1.26	0.71–2.24
Weight lifting	0.83	0.41–1.67	1.35	0.49–3.68	0.70	0.19–2.54

* Controlling for age, race, sex, body mass index, self-reported health status, and smoking. The reference group OR is 1.00 for each exercise type.
** $P < 0.05$.

Several limitations of the study need to be mentioned. First, the data on exercise activity and medical history factors are by self-report and are limited by recall and reporting bias. Participants may have under- or overestimated their levels of exercise activity. However, there is no reason to suspect that respondents exaggerated more on one type of exercise activity than another. Another limitation is that data on the duration and intensity of the activity were not collected, which made us unable to account for differences due to exercise dose. Therefore, some of the findings in the study may be due to a greater intensity of jogging and aerobic dancing as compared with swimming or cycling, even at similar number of times per week. However, the beneficial and nonbeneficial activities in the current study are similar to those in the coronary heart disease outcome study by Tanasescu et al. (28), which did include intensity and duration of exercise in addition to exercise type.

Another limitation is the potential inconsistency of laboratory measures. Although strict laboratory control measures were used to insure quality in the measurement of the

inflammatory markers (14), some inaccuracies are possible. Misclassification is therefore possible based on both exercise and inflammatory assessments, but such effects would likely be random rather than in a consistent direction and would not likely result in overestimation of differences. Finally, we analyzed the total population of adults without excluding people with chronic diseases. Thus, although we controlled for health status, the implications of our findings may not be equally applicable to people with and without chronic disease.

In conclusion, the results of this study indicate that varying forms of physical activity have different effects upon markers of inflammation. The study demonstrated a significant association between certain activities (jogging and aerobic dancing) and a lower likelihood of elevation of inflammatory markers, but no association for other types of exercise including gardening, swimming, cycling, calisthenics, and weight lifting. It is unclear whether these findings can be extrapolated to be a possible mechanism for the decreased risk of cardiovascular disease seen with certain forms of exercise. If such a mechanism is confirmed, then specific types of exercise may need to be recommended for people at cardiovascular risk. Future research should be directed toward further exploration of differences in inflammatory markers with different types of exercise activity and the role of exercise in the prevention of cardiovascular disease.

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