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# The associations between leisure-time physical activity and inflammatory and coagulation markers related to cardiovascular disease: the ATTICA Study

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**Abstract**

*Background*. As coronary heart disease is increasingly seen as an inflammation process, we evaluated the hypothesis whether physical activity reduces coronary heart disease risk by modifying the levels of inflammatory and coagulation markers.

*Methods*. From May 2001 to December 2002, we randomly enrolled 1524 adult men and 1518 women, without any evidence of cardiovascular disease, stratified by age–gender (census 2001), from the greater area of Athens, Greece. We assessed the relationship between self-reported physical activity status and inflammation markers (high sensitivity C-reactive protein, serum amyloid-A, fibrinogen, interleukin-6, tumor necrosis factor-α, and white blood cell counts), after taking into account the effect of several confounders.

*Results*. Eight hundred seventy-four (57%) of men and 903 (59%) of women were classified as sedentary. Multivariate statistical analysis after adjustment for gender, age, smoking habits, body mass index, total cholesterol, blood glucose, and systolic and diastolic blood pressure levels showed that participants devoted to high physical activity (>7 kcal/min expended) had 29% lower levels of C-reactive protein, 19% of white blood cell counts, 22% lower concentrations of amyloid-A, 20% lower levels of tumor necrosis factor-α, 32% of interleukin-6, and 11% of fibrinogen (all $P < 0.05$) as compared to those who were devoted to sedentary life.

*Conclusions*. Our findings suggest that the adoption of a physically active lifestyle modifies the inflammation process in healthy individuals.


*Keywords:* Physical activity; Inflammation; Atherosclerosis

## Introduction

In recent years, health care professionals have focus on prevention and therapy of the cardiovascular diseases through the evaluation and modification of several risk factors. Among the factors that may influence the occurrence of cardiovascular disease, the beneficial effect of physical activity on human health has been underlined in several studies, but the exact mechanisms are not well understood [1–5]. Recent findings support that inflammation plays a role in the pathogenesis of cardiovascular disease [6–8]. For example, some suggest that levels of C-reactive protein (CRP) in apparently healthy persons or patients with stable angina pectoris constitute an independent risk factor for cardiovascular events [9]. Moreover, since coronary heart disease (CHD) is increasingly seen as an inflammatory process, it is reasonable to hypothesize that physical activity reduces risk of coronary heart disease by reducing or preventing inflammation [10]. However, the strength of the association between several inflammation markers and physical activity is not fully investigated, since several potential confounders may influence it.

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The aim of this work is to investigate the association between leisure-time physical activity and inflammation markers related to coronary heart disease [high sensitivity CRP, interleukin (IL)-6, tumor necrosis factor (TNF)-α, fibrinogen, serum amyloid-A (SAA), and white blood cell (WBC) counts], in a population-based sample of healthy adults.

## Methods

### *Study's sample and design*

The "ATTICA" study is a health and nutrition survey, carried out in the province of Attica (including 78% urban and 22% rural areas), where Athens is a major metropolis. The sampling was random, multistage, and on the city–gender–age distribution of the province of Attica provided by the National Statistical Service (census of 2001). The study's design anticipates enrolling only one participant per household. The number of the participants was determined by power analysis and chosen to evaluate two-sided differences between the investigated parameters and physical activity levels greater than 10%, achieving statistical power of >0.80 at <0.05 probability level (*P* value). Also, those living in institutions were excluded from the sampling.

From May 2001 to August 2002, 4056 inhabitants from the above area were randomly asked to participate in the study. Of those, 3042 agreed to participate (75% participation rate). The participants had no clinical evidence of cardiovascular or any other atherosclerotic disease, as well as chronic viral infections dental problems or any type of surgery in the past week. They also exhibited no signs of cold, flu, or any acute respiratory infection.

There were only minor differences in distribution by gender and age between the study population and the target population. All participants were interviewed by trained personnel using a standard questionnaire that developed for the purposes of the study.

### *Physical activity ascertainment*

Weekly energy expenditure was assessed by considering frequency (times per week), duration (in minutes), and intensity of sports-related physical activity during a usual week. Intensity was graded in qualitative terms such as light (expended calories <4 kcal/min, i.e., walking slowly, cycling stationary, light stretching, etc.), moderate (expended calories 4–7 kcal/min, i.e., walking briskly, cycling outdoor, swimming moderate effort, etc.), and high (expended calories >7 kcal/min, i.e., walking briskly uphill, long distance running, cycling fast or racing, swimming fast crawl, etc.) [11].

Participants who did not report any physical activities were defined as sedentary. For the rest, we calculated a combined score by multiplying the weekly frequency, duration, and intensity of physical activity. Then we calculated the tertiles of this score, and physically active participants were equally classified into three groups: low physical activity (1st tertile), medium physical activity (2nd tertile), and high physical activity (3rd tertile). Therefore, 1st, 2nd, and 3rd tertiles included 217 men and 205 women.

Although there are some concerns with self-reported physical activity, the introduced evaluation is now considered reliable, valid, and has been used by many other similar studies [12].

We have also recorded the type of exercise, that is, resistance (i.e., any technique that uses progressive resistance to increase muscular strength) or endurance training. The presence of occupational physical activity was recorded but was not taken into account for the analysis due to difficulties in evaluation and standardization. This exclusion may confound our findings, but the large sample size and the randomized procedure for the selection of the participants can spread the subjects who reported occupational exercise equally in both groups of the study.

### *Biochemical and clinical measurements*

The blood samples were collected from the antecubital vein between 8 and 10 AM, in a sitting position after 12 h of fasting and avoiding of alcohol. The biochemical evaluation was carried out in the same laboratory that followed the criteria of the World Health Organization Lipid Reference Laboratories. CRP and SAA were assayed by particle-enhanced immunonephelometry (N Latex, Date-Behring Marburg GmbH, Marburg, Germany) with a range from 0.175 to 1100 mg/L and 0.75 to 1000 mg/L, respectively. IL-6 was measured with high sensitivity enzyme-linked immunoassay (R & D Systems Europe Ltd., Abingdon, UK) with a range from 0.156 to 10 pg/mL. The intraassay and interassay coefficients of variation were <5% for CRP and SAA and <10% for IL-6. Plasma fibrinogen levels were measured using a BNII Dade Behring automatic nephelometry. For the determination of fibrinogen, blood was anticoagulated with 3.8% trisodium citrate (9:1 vol/vol) and cooled on ice until centrifugation. The intraassay and interassay coefficients of variation of fibrinogen did not exceed 9%. We also measured white blood cell counts using a Medicon analyzer (Medicon Ltd., Athens, Greece). We used the ELISA method for the quantitative determination of human TNF-α in duplicate in serum samples of the participants by Quantikine HS/human TNF-α immunoassay kit (R & D Systems, Inc. Minneapolis, USA).

Serum total cholesterol was measured using chromatographic enzymic method in a Technicon automatic analyzer RA-1000. The intraassay and interassay coefficients of variation of cholesterol levels did not exceed 5%.

Arterial blood pressure was measured at end of the physical examination with subject in sitting position for 25–30 min. Three measurements were obtained from the right arm (ELKA using aneroid manometric sphygmometer, Von Schlieben Co., West Germany). Patients whose average blood pressure levels were greater or equal to 140/90 mm Hg or taking antihypertensive medication were classified as hypertensives. Participants with total serum cholesterol levels greater than 200 mg/dL or those taking lipid-lowering agents were classified as hypercholesterolemic, and those with blood sugar of >125 mg/dL or those using antidiabetic medication were classified as diabetic. However, in all statistical analyses, continuous measurements of blood pressures and chemistries were used.

Also, the investigators of the study recorded a detailed medical history of the participants.

### *Demographic and lifestyle characteristics*

In addition to the physical activity status, the study's questionnaire included demographic characteristics like age, gender, family status (married, divorced, widowed), financial status (average annual income during the past 3 years), and education level. The educational level of the participants (as a proxy of social status) was measured in years of school. Information about smoking habits was collected using a standardized questionnaire developed for the study. Current smokers were defined as those who smoked at least one cigarette per day. Never smokers are those who have never tried a cigarette in their life, and former smokers were defined as those who had stopped smoking more than 1 year previously. In all multivariate statistical analyses, cigarette smoking habits were taken into account using the pack-years (cigarette packs per day × years of smoking). However, to correct for the amount of nicotine containment in various types of cigarettes smoked (i.e., light, heavy, very heavy), we assigned a weight in each different type of cigarette-pack, using the 0.8 mg per cigarette as the standard.

Consumption of nonrefined cereals and products, vegetables, legumes, fruits, olive oil, dairy products, fish, pulses, nuts, potatoes, eggs, sweets, poultry, red meat, and meat products were measured as an average per week during the past year through a validated food-frequency questionnaire (FFQ) from the Department of Nutritional Epidemiology of our Institute [13]. The frequency of consumption was then quantified approximately in terms of the number of times a month a food was consumed. Alcohol consumption was measured by daily ethanol intake, in wineglasses (100 mL and 12-gr ethanol concentration). Based on the Mediterranean-diet pyramid [14], we calculated a special diet score ranged from 0 to 55. Higher values of this score indicates adherence to the traditional Mediterranean diet, characterized by moderate consumption of fat and high monounsaturated–saturated fat ratio), while lower values indicate adherence to the "Westernized" diet.

Body mass index was calculated as weight (in kilograms) divided by standing height (in meters squared). Obesity was defined as body mass index of >29.9 kg/m$^2$. Details about the aims and methods of the ATTICA study have been presented elsewhere [15].

### *Statistical analysis*

Continuous variables are presented as mean values ± standard deviation, while qualitative variables are presented as absolute and relative frequencies. Associations between categorical variables were tested by the use of contingency tables and the calculation of chi-squared test. Comparisons between normally distributed continuous variables and categorical were performed by the calculation of Student *t* test and one-way or multiway analysis of covariance (multiway ANCOVA), after controlling for homoscedacity. Kolmogorov-Smirnov criterion was used for the assessment of normality. In the case of asymmetric continuous variables, the tested hypotheses were based on the calculations of nonparametric tests, such as Mann–Whitney and Kruskal–Wallis. Correlations between inflammation variables and physical activity levels were tested through multiple linear regression analysis after the adjustment for several potential confounders and interactions. Due to its skewed distribution, CRP levels were log-transformed. The odds ratio of being at the higher quartile of inflammatory markers levels with respect to physical activity status was evaluated through multiple logistic regression analysis.

All reported *P* values are based on two-sided tests and compared to a significance level of 5%. However, due to multiple significance comparisons, we used the Bonferroni correction to account for the increase in type I error. SPSS 10.1 software (SPSS Inc. 2002, USA) was used for all the statistical calculations.

## Results

Table 1 presents the investigated characteristics of the participants according to their physical activity status. From physically active participants, 5% of men and 2% of women reported only resistance training, while 7% of men and 12% of women reported only endurance training. Eight hundred seventy-four (57%) of men and 903 (59%) of women were classified as sedentary. Physically active participants were significantly younger and were less frequent to be active smokers, as compared to sedentary. An inverse relationship was also observed between body mass index and physical activity status. No statistically significant associations were found between physical activity levels and indexes of social status (education level and annual income) and alcohol consumption (Table 1).

Multivariate statistical analysis (Table 2) after adjustment for gender, age, smoking habits, years of school, body mass index, total cholesterol, blood glucose, and systolic and diastolic blood pressure levels showed that highly physically active (3rd tertile) individuals had 29% lower levels of CRP, 19% lower levels of WBC counts, 22% lower levels of SAA, 20% lower levels of TNF-α, 32% lower levels of IL-6, and 11% lower levels of fibrinogen, when compared to sedentary ones. No differences were observed when we

Table 1
Demographic, anthropometric, and behavioral characteristics by physical activity status

| | Physical activity status | | | | |
|---|---|---|---|---|---|
| | Sedentary | 1st Tertile | 2nd Tertile | 3rd Tertile | *P* |
| *Men* | | | | | |
| Number | 874 | 217 | 217 | 216 | |
| Age (years) | 47 ± 13 | 48 ± 11 | 46 ± 9 | 45 ± 12 | <0.001 |
| Education (years of school) | 11 ± 4 | 12 ± 5 | 11 ± 4 | 12 ±4 | 0.244 |
| Annual income (#,000 Euros) | 17.8 ± 4 | 16.8 ± 3 | 15.2 ± 4 | 13.2 ± 9 | 0.348 |
| Body mass index (kg/m$^2$) | 28 ± 3 | 27 ± 3 | 26 ± 4 | 24 ± 3 | <0.001 |
| Current smoking | 55% | 54% | 54% | 48% | 0.895 |
| Alcohol intake (mL/d) | 280 ± 40 | 250 ± 55 | 190 ± 95 | 180 ± 90 | 0.256 |
| *Women* | | | | | |
| Number | 903 | 205 | 205 | 205 | |
| Age (years) | 47 ± 12 | 46 ± 9 | 46 ± 11 | 44 ± 10 | 0.001 |
| Education (years of school) | 12 ± 4 | 12 ± 3 | 13 ± 5 | 12 ± 2 | 0.359 |
| Annual income (#,000 Euros) | 15.4 ± 7 | 15.8 ± 7 | 18.2 ± 8 | 14.2 ± 6 | 0.335 |
| Body mass index (kg/m$^2$) | 26 ± 3 | 24 ± 3 | 24 ± 4 | 22 ± 3 | <0.001 |
| Current smoking | 46% | 44% | 36% | 29% | 0.041 |
| Alcohol intake (mL/d) | 120 ± 40 | 110 ± 55 | 90 ± 55 | 85 ± 50 | 0.224 |

stratified the analysis for the type of exercise, that is, resistance or endurance (*F* test for the interaction = 0.76, *P* = 0.8), the gender of the participants (*F* test for the interaction = 0.34, *P* = 0.9), as well as the educational (*F* test for the interaction = 0.50, *P* = 0.6) or the financial status (*F* test for the interaction = 1.3, *P* = 0.5). It is of interest that significant differences were observed between moderate and sedentary physical activity status in all inflammatory markers (Table 2).

Fig. 1 illustrates results from multivariate regression models that evaluated the association between physical activity status on inflammation markers, after controlling for various covariates including years of school, annual income, and diet score. The most prominent effect of physical activity was observed in CRP levels.

In addition, presence of physical activity was associated with 24% lower odds of classifying an individual at the higher quartile of CRP levels as compared with those who reported sedentary life (odds ratio = 0.76, 95% confidence interval 0.62–0.92), after controlling for the aforementioned covariates. Similar findings were obtained regarding the effect of physical activity on WBC counts (odds ratio = 0.79, 95% confidence interval 0.65–0.96), SAA (odds ratio = 0.70, 95% confidence interval 0.58–0.85), IL-6 (odds ratio = 0.68, 95% confidence interval 0.56–0.83), TNF-α (odds ratio=0.74, 95% confidence interval 0.56–0.97), and fibrinogen (odds ratio = 0.79, 95% confidence interval 0.64–0.98).

## Discussion

Our findings support that inflammatory markers are significantly lower in physically active individuals than those leading a sedentary lifestyle. More specifically, participants in the highest fitness tertile exhibited signifi-

Table 2
Inflammatory markers and physical activity status

| | Physical activity status | | | | |
|---|---|---|---|---|---|
| | Sedentary | 1st Tertile | 2nd Tertile | 3rd Tertile | *P* |
| White blood cell (×1000 counts) | 7.4 ± 1.3 | 7.1 ± 1.1 | 6.5 ± 1.8† | 6.0 ± 1.2** | 0.001 |
| C-reactive protein (mg/dL) | 2.2 ± 1.4 | 1.8 ± 1.4 | 1.8 ± 1.8†† | 1.7 ± 1.2** | 0.02 |
| Fibrinogen (mg/dL) | 323 ± 69 | 317 ± 77 | 304 ± 72† | 287 ± 67** | 0.02 |
| Interleukin-6 (pg/mL) | 2.5 ± 1.2 | 2.0 ± 0.4 | 1.7 ± 1.3†† | 1.7 ± 0.9** | 0.03 |
| Tumor necrosis factor-α (pg/mL) | 6.1 ± 1.4 | 5.5 ± 1.1 | 5.1 ± 1.2†† | 4.9 ± 2.2** | 0.03 |
| Amyloid-A (mg/L) | 5.5 ± 2.4 | 5.1 ± 2.1 | 4.4 ± 2.1†† | 4.3 ± 2.4* | 0.05 |

Overall *P* values derived from multiway ANCOVA models in which physical activity entered as an ordered variable according to kcal/min expended per week (i.e., sedentary, low, medium, and high). Covariates entered in all models are gender, age (years), pack-years of smoking, years of school, body mass index (kg/m$^2$), total cholesterol (mg/dL), blood glucose (mg/dL), systolic and diastolic blood pressure levels (mm Hg), alcohol consumption (mL/day), and dietary habits (diet score).

* 2nd Tertile significantly differs from sedentary at Bonferroni α* < 0.05.
** 3rd Tertile significantly differs from sedentary at Bonferroni α* < 0.01.
† 2nd Tertile significantly differs from sedentary at Bonferroni α* < 0.01.
†† 3rd Tertile significantly differs from sedentary at Bonferroni α* < 0.05.

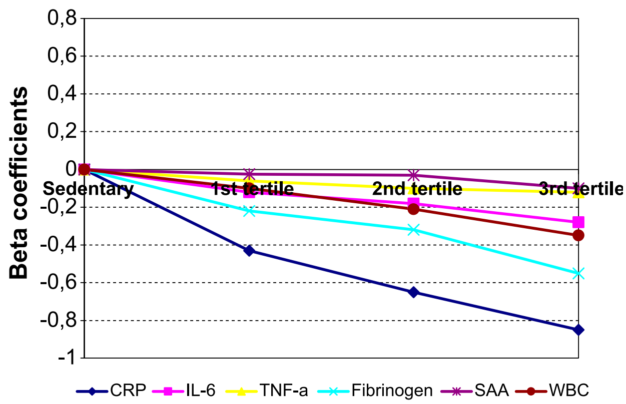


Fig. 1. Values of the standardized beta coefficients by physical activity status (sedentary, 1st, 2nd, and 3rd tertiles) on C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-a (TNF-a), fibrinogen, serum amyloid-A (SAA), and white blood cell (WBC) counts. All regression models were adjusted for gender, age, smoking habits, body mass index, years of school, annual income, diet score, total cholesterol, blood glucose, and systolic and diastolic blood pressure levels.

cantly lower concentrations of CRP, SAA, TNF-α, IL-6, WBC, and fibrinogen than the sedentary group.

The health benefits of a physically activity lifestyle are well recognized. In particular, the risk of coronary heart disease mortality or morbidity is inversely related to the level of physical activity [1–5]. The protective role of physical activity on cardiovascular morbidity is, at least in part, attributed to the favorable effects of physical exercise on several "traditional" coronary risk factors, like blood pressure levels and body mass index [1,2]. Although the duration, intensity, and volume of physical activity are still being refined, it is becoming more apparent that most of the health benefits at a minimal risk are derived from low to moderate intensity physical activities [16]. Indeed, recent statements from the Surgeon General [3], the National Institutes of Health Consensus Development Panel on Physical Activity and Cardiovascular Health [17], and the Center for Disease Control and Prevention and the American College of Sports Medicine [11] recommend at least 30 min of moderate-intensity physical activity on most, preferably all, days of the week to prevent coronary heart disease and other chronic diseases.

In this work, we observed a consistent inverse association of leisure-time physical activity with several inflammatory markers related to cardiovascular disease. In addition, even moderate amounts of physical activity can have a profound and favorable effect on cardiovascular health. These findings have clinical as well as public health significance, since the moderate intensity and amount of physical activity are well tolerated by most middle-aged and older individuals and have a relatively low risk [3]. We are in agreement with the reports by Ford [18] and King et al. [19] on about 14,000 adult participants in the National Health and Nutrition Examination Survey III (1988–1994). In these studies, the time devoted to physical activity was inversely associated with CRP levels as well as with both plasma fibrinogen concentration and white blood cell count, after adjusting for several potential confounders. Similarly, Abramson and Vaccarino [10] reported that physical activity was independently associated with a lower odds of having elevated inflammation levels (CRP and WBC) among apparently healthy US adults 40 years and older, independent of several confounding factors. An inverse relationship between plasma fibrinogen levels and leisure-time physical activity has also reported by several others [20–22]. In contrast, Pischon et al. [23] reported that the association between physical activity and inflammatory markers was lost after adjusting for body mass index and leptin. Although we cannot explain the different results in the previous study, several factors need to be addressed, including the small number of subjects enrolled and the arbitrary classification of fitness levels.

Activation markers of coagulation and fibrinolysis are increased in individuals at risk of coronary artery disease and other thrombotic disorders [24]. The observed association between elevated plasma fibrinogen and coronary risk may also reflect, in part, an ongoing inflammatory process, because fibrinogen is an acute-phase reactant. Fibrinogen is also related to venous tromboembolism, suggesting that physical activity might have a protective effect against both arterial and venous thrombosis by reducing fibrinogen levels.

## *Limitations*

Occupational physical activity was not taken into account in the present study. Another limitation is that leisure-time physical activities have been related to a healthier lifestyle habits and consequently to a better health status. For example, adoption of a healthier dietary pattern or reduced smoking habits may be more common among individuals who were devoted to leisure-time exercise. Although we took into account dietary and smoking habits of the participants, the influence of this potential confounder cannot be entirely excluded.

## *Conclusion*

Our findings emphasize the importance of even moderate physical activity in the primary prevention of coronary heart disease through the reduction of inflammatory indices. Despite the known limitations of the cross-sectional design, our findings have significant public health impact, since moderate levels of physical activity can be well tolerated by most people with minimal risk for injury. Thus, physical activity, along with other lifestyle modifications, can become effective preventive ways in the reduction of the inflammation process. Public health policy should focus on informing the community about the crucial importance of physical activity that impedes inflammation, coagulation, and consequently the development of cardiovascular disease.

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