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Association Between Physical Activity, Physical Performance, and Inflammatory Biomarkers in an Elderly Population: The InCHIANTI Study

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Background. Our aim was to determine the association between physical activity and physical performance, and inflammatory biomarkers in elderly persons.

Methods. One thousand four persons aged 65 years or more, participants in a cross-sectional population-based study, were included. Interviewers collected information on self-reported physical activity during the previous year. Moreover, 841 participants performed a 400-meter walking test to assess physical performance. Plasma concentrations of inflammatory biomarkers were determined.

Results. Compared to sedentary men, men practicing light and moderate-high physical activity had a significantly lower erythrocyte sedimentation rate (–0.33 and –0.40 mm/h; $p = .023$ and $p = .006$, respectively), fibrinogen level (–43 and –39 mg/dL; $p = .001$ and $p = .004$, respectively), and logarithm of C-reactive protein (CRP) (–0.43 and –0.73 mg/L; $p = .025$ and $p < .001$, respectively), whereas only those men practicing moderate-high physical activity had a significantly lower uric acid level (–0.57 mg/dL; $p = .023$), log(interleukin 6) levels (–0.33 pg/mL; $p = .014$), and log(tumor necrosis factor-α) (–0.31 pg/mL; $p = .030$). In women, those practicing light and moderate-high physical activity had significantly lower uric acid (–0.45 and –0.34 mg/dL; $p = .001$ and $p = .039$, respectively) and log(interleukin 6) levels (–0.18 and –0.30 pg/mL; $p = .043$ and $p = .004$, respectively); only those women practicing moderate-high physical activity had significantly lower log(CRP) (–0.31 mg/L; $p = .020$). In women, when the analysis was adjusted for body mass index, the association between physical activity and CRP was no longer significant. Similar findings were observed when we carried these analyses according to physical performance.

Conclusions. Current physical activity practice and performance are associated with inflammatory biomarkers. A significant beneficial association is already observed with light physical activity practice and intermediate performance.

PHYSICAL activity is an independent protective factor against coronary heart disease (CHD) (1,2). The basis for this knowledge rests on observational studies (3), and on the beneficial effect of physical activity on traditional cardiovascular risk factors (4). However, all together, the favorable effects on cardiovascular risk factors do not account for the full beneficial effect of physical activity on cardiovascular health, suggesting that part of the observed cardioprotective effects may by mediated by other still poorly characterized mechanisms.

There is evidence of an inverse association between physical activity (5–12) and physical fitness (13–16), and C-reactive protein (CRP), fibrinogen, and white blood count (WBC). These inflammatory biomarkers, and others (such as erythrocyte sedimentation rate [ESR], albumin, and specific cytokines), have been shown to be predictors of mortality, in particular cardiovascular mortality (17), and to be associated with higher incidence and prevalence of clinical manifestation of CHD (18–23). Unfortunately, data on the relation between physical activity and/or fitness and cytokines are scanty, especially on older persons, the population most affected by the burden of cardiovascular disease.

In contrast, the question of whether physical activity or physical fitness is more important in defining health benefits is still open (24). Physical activity is any bodily movement produced by skeletal muscles that results in an expenditure of energy, whereas physical fitness refers to the ability to perform physical activities and is determined by a combination of regular activity and genetically inherited ability (25). Usually physical fitness is indirectly measured by a standardized physical performance test.

Using data from a representative elderly population, we tested the hypothesis that both self-reported physical activity and physical performance, as an indirect measure of fitness, were associated with levels of proinflammatory and antiinflammatory cytokines and other biomarkers of inflammation.

Methods

InCHIANTI ("Invecchiare in Chianti," aging in the Chianti area) is a study of the factors contributing to the decline of

mobility in late life. The design of the study has been previously described in detail (26). In summary, InCHIANTI is a cross-sectional population-based study of persons living in two towns of the Chianti geographic area (Tuscany, Italy). The data collection started in September 1998 and was completed in March 2000.

Participants

In August 1998, 1270 persons aged 65 years or older were randomly selected from the population registry. Another 29 persons were selected randomly from those who were aged 90 years or older. Of the initial 1299 persons selected, 39 were not eligible for the study because they had already died or moved away from the area. Participation rate was very high at 91.6% (1154/1260). Participants who were not able to walk independently ($n = 50$) were excluded from this analysis. Finally, of these 1104 participants, 1004 had data on physical activity and at least one inflammatory biomarker (994 for fibrinogen, 1004 for interleukin 6 [IL-6] receptor), and 841 had data on physical performance and at least one inflammatory biomarker (833 for fibrinogen, 841 for uric acid). These figures represent 80% and 67% of the initial eligible population, respectively.

Laboratory Methods

Blood samples were taken in the morning after a fasting period of more than 8 hours. Serum and plasma were separated by low-speed centrifugation and stored at –80°C. WBC was determined using a hematology auto analyzer (SE 9000 DASIT; Sysmex, Kobe, Japan), and ESR was automatically determined by a DIESSE VES-Matic PC (Diagnostica Senese S.p.A., Monteriggioni, Italy). Albumin was measured by an agarose electrophoretic technique (Hydragel Protein(E) 15/30; Sebia, Issy-les-Moulineaux, France). The mean interassay coefficient of variation (CV) was 0.8%. Serum uric acid was determined by using commercial enzymatic tests (Roche Diagnostics, Mannheim, Germany) on a Roche Hitachi Modular P800 analyzer. The interassay CV was less than 2%. Plasma fibrinogen was automatically detected according to the Clauss method with an STA Fibrinogen kit (Diagnostica Stago Roche Diagnostics, Mannheim, Germany) and a Sta Stago Boehringer Mannheim analyzer.

Determination of CRP level was based on a high sensitivity enzyme-linked immunosorbent assay, a competitive immunoassay that uses purified protein and polyclonal anti-CRP antibodies. The interassay CV was ≈ 5.0%. The minimum detectable concentration was 0.03 mg/L. The average of two measures performed in each sample was used in the analysis.

A large panel of inflammatory cytokines, including several proinflammatory (interleukin 1 beta [IL-1β], IL-6, interleukin 18 [IL-18], tumor necrosis factor alpha [TNF-α]) and antiinflammatory (interleukin 1 receptor antagonist [IL-1ra], interleukin-10 [IL-10]) cytokines (27) was also determined. The quantitative measurement of serum levels of IL-6, soluble IL-6 receptors (sIL-6R), IL-10, IL-1β, IL-1ra, IL-18, and TNF-α was performed by enzyme-linked immunosorbent assays using commercial kits (BIOSOURCE International, Camarillo, CA). The lower detectable concentration was 0.10 pg/mL for IL-6, 8.00 pg/mL for sIL-6R, 1.00 pg/mL for IL-10, 0.01 pg/mL for IL-1β, 4.00 pg/mL for IL-1ra, 4.50 pg/mL for IL-18, and 0.09 pg/mL for TNF-α. The mean interassay CV for IL-6, sIL-6R, TNF-α, and IL-1β was 7.0%; it was 8.2% for IL-1ra, and 4.4% for IL-18.

Physical Activity Practice Assessment

Trained interviewers administered a structured questionnaire specifically developed for the study; the questionnaire required that the participant provide data on past and current physical activity. The details of the questionnaire have been previously reported (28). Briefly, data on current physical activity were collected by asking the following question: "Did you ever perform any sport or recreational physical activity, for at least three months, during the last year?" If the answer was affirmative, the interviewers asked the participant to specify the type of each physical activity, the number of months of practice, the number of times per month, and the number of minutes of practice each time. By combining these responses and available tables to assess the intensity of each physical activity, participants were classified as: a) inactive, including participants who were completely inactive and those who performed light intensity physical activity (i.e., walking, dancing; ≤4 Metabolic Equivalent Tax) less than 1 hour per week; b) light physical activity, including participants who performed light intensity physical activity 2–4 hours per week; c) moderate–high physical activity, including participants who performed at least light physical activity 5 hours per week or more and those who performed moderate physical activity (i.e., gymnastics, swimming; >4 Metabolic Equivalent Tax) 1–2 hours per week or more. Information about former (when participants were 20–40 and 40–60 years old) physical activity practice was recorded in the same way.

Physical Performance Evaluation

An objective assessment of physical function and performance was carried out by trained physical therapists (26). The time to walk 400 meters as fast as possible is highly correlated with maximum oxygen consumption (VO_2max) in elderly people ($r > 0.75$) (29), and it is used in this analysis as a performance-based measure of physical fitness (30). Time was measured by using an optoelectronic system connected to a digital chronometer and a printer (Chronoprinter Tag-Heuer CR501; Zingerle Sports Timing, Bolzano, Italy). Eight hundred forty-one participants performed this test. Three groups according to tertile distribution were defined in each different age (65–74 y, 75–84 y, and ≥85 y) and sex strata: low, intermediate, and high performance. Those participants who performed the test and were not able to complete the 400 meters ($n = 47$) were included in the low performance group.

Other Variables

The participants were invited to the study clinic for a comprehensive evaluation of health status and anthropometrical measures conducted using standardized methods. Body mass index (BMI) was calculated as weight in kilograms divided by height (in meters squared). Presence of major chronic diseases (cardiovascular disease, CHD, stroke, peripheral artery disease), cardiovascular risk factors, and current inflammatory process (infections, bronchitis, arthritis) were ascertained by trained geriatricians according to standard algorithms that used information on medical

history, drug treatments, signs and symptoms, medical documents, and hospital discharge records (31). Smoking habits were classified as follows: never smoked, former smoker, or current smoker. Intakes of alcohol, vitamin C, vitamin E, and β-carotene were estimated using a detailed food frequency questionnaire developed and validated in the context of the European Prospective Investigation into Cancer and nutrition (EPIC) (32).

Ethics

The local ethics committee approved the protocol. All participants received a description of the study procedures and objectives, and all gave their informed consent including specific permission to use the biological samples for research purposes.

Statistical Analysis

The chi-square test was used to compare proportions between groups. Analysis of variance, for normally distributed variables, and the Kruskal-Wallis test were used to compare continuous variables between groups.

The association between physical activity and physical performance, and inflammatory biomarkers was assessed by multiple linear regression analysis. Some continuous variables (CRP, IL-6, sIL-6R, IL-10, IL-1β, IL-1ra, IL-18, and TNF-α) were highly skewed and were log-transformed to meet the assumptions of multiple linear regression. This linear regression was not appropriate to evaluate the association between physical activity practice or performance, and IL-10. Thus, logistic regression analysis was used to determine the association between physical activity and performance, and IL-10. For this purpose, the level of IL-10 was coded as below versus above the minimum detectable level (1.00 pg/mL).

A fixed set of covariates that were clinically relevant or statistically associated with physical activity or performance and were further associated with inflammatory biomarkers (both at an alpha level of 0.10) were included in the linear regression models. BMI might be considered a confounder variable but also a factor in the causal pathway of the association between physical activity and lower inflammation. To explore this possibility, two multiple linear regression models were defined, one excluding BMI (Model 1) and one including BMI (Model 2). All the analyses were stratified by sex, and a p value less than .05 was considered to be statistically significant.

Results

Information about relevant clinical, anthropometrical, and behavioral characteristics of the participants and inflammatory biomarkers distribution stratified by sex is presented in Table 1. Participants with missing data for physical activity or the outcome variables ($n = 100$) were older (79 vs 75 years), and presented a higher proportion of inactive people (34% vs 20%) than did those participants whose data were included in the analysis ($n = 1004$). Participants with missing data for physical performance or the outcome variables ($n = 263$) were older (81 vs 74 years), and presented a higher prevalence of inactive people (47% vs 13%) and chronic cardiovascular diseases (28% vs 11%) than did those participants whose data were included in the analysis ($n = 841$).

Table 1. Characteristics of the Participants in the Study

	Men ($N = 440$)	Women ($N = 564$)
Age, y*	74.6 (6.8)	75.9 (7.4)
Body mass index, kg/m^2*	27.1 (3.3)	27.7 (4.5)
Smoking status, %		
Never smokers	29.1	82.6
Former smokers	54.1	10.1
Current smokers	16.8	7.3
Systolic blood pressure, mmHg*	148.0 (18.7)	151.7 (19.8)
Hypertension, %	44.9	58.4
Diabetes, %	9.9	8.7
Prevalent cardiovascular disease, %	19.6	8.7
Prevalent inflammatory process, %	27.0	28.0
Physical activity, %		
Inactive	12.3	25.5
Light	36.4	49.1
Moderate–high	51.4	25.4
Time to walk 400 m, min*‡	5.35 (1.39)	6.09 (1.37)
White blood count, K/μL*	6.37 (1.65)	5.94 (1.53)
Erythrocyte sedimentation rate, mm/h*	2.49 (0.86)	2.93 (0.72)
Albumin, mg/dL*	423 (29)	417 (28)
Uric acid, mg/dL*	5.60 (1.46)	4.86 (1.34)
Fibrinogen, mg/dL*	348 (79)	365 (71)
C-reactive protein, mg/L†	2.95 (0.46–18.05)	2.50 (0.57–16.20)
Interleukin-6, pg/mL†	1.56 (0.49–8.13)	1.35 (0.39–5.93)
Soluble interleukin-6 receptor, ng/mL†	91 (38–213)	94 (35–199)
Interleukin-10, pg/mL†	4.84 (1.18–832.85)	8.88 (1.35–1927.50)
Interleukin-1β, pg/mL†	0.12 (0.02–0.42)	0.12 (0.03–0.40)
Interleukin-1 receptor antagonist, pg/mL†	133 (57–300)	131 (60–300)
Interleukin-18, pg/mL†	423 (241–723)	349 (205–640)
Tumor necrosis factor-α, pg/mL†	4.98 (0.92–15.52)	5.22 (0.90–13.82)

Notes: *Continuous variables are presented as mean (standard deviation).
†Continuous variables are presented as median (percentile 5–percentile 95).
‡Data from 362 men and 432 women who completed the 400-meter walking test.

Data on inflammatory biomarker levels according to sex and physical activity practice are presented in Table 2. Physical activity was inversely associated with WBC, ESR, fibrinogen, CRP, IL-6, and IL-1ra, and was positively associated with albumin in men and women. Moreover, physical activity was inversely associated with uric acid, sIL-6R, and IL-18 in women and with TNF-α in men.

Physical performance was inversely associated with ESR and IL-6 both in men and women. Moreover, physical performance was inversely associated with CRP in men, whereas it was inversely associated with fibrinogen and IL-1ra, and positively associated with IL-1β, in women (Table 3).

Multiple linear regression analysis was performed to determine the multivariate-adjusted magnitude of the association between inflammatory biomarkers and physical activity and performance. The statistically significant associations between physical activity or performance and inflammatory biomarkers observed in men are presented in Table 4. Light and moderate–high physical activity practices were associat-

Table 2. Circulating Inflammatory Biomarker Levels According to Physical Activity Practice in Men and Women

	Inactive	Light	Moderate–High	*p* Value
Men	(*N* = 54)	(*N* = 160)	(*N* = 226)	
WBC, K/μL*	6.90 (1.88)	6.52 (1.54)	6.15 (1.63)	.004
ESR, mm/h*	2.93 (0.87)	2.47 (0.84)	2.39 (0.84)	<.001
Albumin, mg/dL*	409 (32)	425 (33)	426 (25)	.001
Uric acid, mg/dL*	5.99 (2.19)	5.65 (1.51)	5.48 (1.18)	.054
Fibrinogen, mg/dL*	394 (105)	343 (66)	341 (76)	<.001
CRP, mg/L†	5.94 (1.03–100.68)	3.10 (0.46–18.44)	2.06 (0.43–13.76)	<.001
IL-6, pg/mL†	2.43 (0.80–11.96)	1.70 (0.49–10.51)	1.37 (0.44–6.67)	<.001
SIL-6R, ng/mL†	90 (35–188)	95 (44–217)	90 (32–213)	.577
IL-10, pg/mL†	6.21 (1.38–1263.88)	4.06 (1.12–416.18)	5.27 (1.18–1006.84)	.356
IL-1β, pg/mL†	0.10 (0.02–0.33)	0.12 (0.02–0.42)	0.12 (0.02–0.48)	.476
IL-1ra, pg/mL†	165 (47–729)	137 (61–404)	129 (55–258)	.047
IL-18, pg/mL†	455 (230–713)	431 (248–714)	415 (240–738)	.443
TNF-α, pg/mL†	6.63 (1.19–22.89)	5.54 (0.92–15.86)	4.52 (0.80–12.82)	.004
Women	(*N* = 144)	(*N* = 277)	(*N* = 143)	
WBC, K/μL	6.31 (1.67)	5.80 (1.46)	5.82 (1.47)	.003
ESR, mm/h	3.08 (0.79)	2.84 (0.67)	2.97 (0.71)	.003
Albumin, mg/dL	410 (33)	420 (25)	419 (25)	.003
Uric acid, mg/dL	5.38 (1.64)	4.68 (1.20)	4.69 (1.12)	<.001
Fibrinogen, mg/dL	385 (73)	359 (68)	356 (72)	<.001
CRP, mg/L	3.00 (0.65–25.74)	2.39 (0.58–14.00)	2.25 (0.45–15.88)	.014
IL-6, pg/mL	1.71 (0.41–7.09)	1.31 (0.38–5.29)	1.08 (0.37–3.89)	<.001
sIL-6R, ng/mL	104 (32–210)	92 (37–181)	94 (33–235)	.037
IL-10, pg/mL	5.90 (1.18–1895.72)	8.97 (1.36–2129.13)	9.66 (1.42–1837.97)	.500
IL-1β, pg/mL	0.12 (0.02–0.41)	0.12 (0.03–0.41)	0.12 (0.04–0.42)	.924
IL-1ra, pg/mL	144 (77–306)	128 (59–309)	127 (50–294)	.018
IL-18, pg/mL	376 (205–634)	345 (199–663)	339 (209–648)	.049
TNF-α, pg/mL	5.54 (1.44–14.79)	5.20 (0.68–12.06)	4.82 (0.96–17.69)	.121

Notes: *Continuous variables are presented as mean (standard deviation). Analysis of variance test.

†Continuous variables are presented as median (percentile 5–percentile 95). Kruskal–Wallis test.

WBC = white blood count; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; IL-6 = interleukin 6; sIL-6R = soluble interleukin 6 receptor; IL-10 = interleukin 10; IL-1β = interleukin 1 beta; IL-1ra = interleukin 1 receptor antagonist; IL-18 = interleukin 18; TNF-α = tumor necrosis factor alpha.

ed with lower ESR, fibrinogen, and CRP (Table 4, Model 1). The magnitude of the coefficients estimating the association of light and moderate-high physical activity compared to a sedentary state was similar for the models predicting these three inflammatory biomarkers. Only moderate-high physical activity practice was significantly associated with lower levels of uric acid, IL-6, and TNF-α. Similarly, compared to low physical performance, intermediate and high physical performance were inversely associated with ESR and CRP. High physical performance was also associated with a lower level of IL-6. When the analyses were further adjusted for BMI (Table 4, Model 2), the magnitude of the coefficients for physical activity and performance were only slightly reduced, and most of them remained significantly associated with lower levels of inflammatory biomarkers. In these models, BMI was directly associated with levels of uric acid and CRP, but it was not associated with ESR, fibrinogen, IL-6, or TNF-α. In contrast, neither physical activity nor physical performance was associated with WBC, albumin, sIL-6R, IL-1β, IL-1ra, or IL-18.

Results on significant associations between physical activity or performance and inflammatory biomarkers in women are presented in Table 5. Light physical activity practice was inversely associated with uric acid, fibrinogen, and IL-6; moderate-high physical activity practice was inversely associated with uric acid, CRP, and IL-6 (Table 5, Model 1). Both intermediate and high performance were inversely associated, and with a similar magnitude, with ESR. In addition, intermediate performance was inversely associated with IL-6, and high physical performance was associated with higher levels of IL-1β and with lower levels of fibrinogen, CRP, and IL-1ra. When the analyses were further adjusted for BMI (Table 5, Model 2), the association between physical activity and performance, and CRP and IL-1ra were not further statistically significant, suggesting that changes in BMI could be a critical step in the casual pathway for these associations. In these models, BMI was directly associated with ESR, uric acid, fibrinogen, CRP, and IL-6, but it was not associated with IL-1β and IL-1ra. In contrast, neither physical activity nor physical performance were associated with WBC, albumin, sIL-6R, IL-18, or TNF-α. We did not observe significant associations between IL-10, below or above the detectable threshold, and physical practice or performance.

We also examined the associations between current or past physical activity practices and circulating levels of inflammatory biomarkers. Only current physical activity practice was significantly associated with a lower level of these biomarkers (Figure 1). Past light or moderate-high physical activity in participants who become currently inactive was associated with the same level of inflammatory biomarkers as in those who were inactive and remain currently inactive.

Discussion

Using data obtained in an epidemiological study performed in a population-based sample, we demonstrated

Table 3. Circulating Inflammatory Biomarker Levels According to Physical Performance, as a Measure of Physical Fitness, in Men and Women

	Low	Intermediate	High	*p* Value
Men	(*N* = 121)	(*N* = 127)	(*N* = 124)	
WBC, K/μL*	6.63 (1.86)	6.23 (1.62)	6.17 (1.38)	.061
ESR, mm/h*	2.62 (0.77)	2.37 (0.85)	2.30 (0.84)	.006
Albumin, mg/dL*	425 (25)	424 (29)	427 (28)	.675
Uric acid, mg/dL*	5.71 (1.49)	5.50 (1.37)	5.46 (1.05)	.297
Fibrinogen, mg/dL*	355 (88)	335 (72)	341 (71)	.115
CRP, mg/L†	1.19 (1.13)	0.86 (1.12)	0.70 (1.04)	.002
IL-6, pg/mL†	0.56 (0.76)	0.39 (0.80)	0.20 (0.83)	.002
SIL-6R, ng/mL†	4.50 (0.56)	4.52 (0.46)	4.56 (0.59)	.721
IL-10, pg/mL†	2.05 (1.94)	2.16 (2.04)	2.30 (1.88)	.779
IL-1β, pg/mL†	−2.16 (0.81)	−2.00 (0.82)	−2.14 (0.72)	.257
IL-1ra, pg/mL†	4.97 (0.47)	4.82 (0.67)	4.82 (0.51)	.056
IL-18, pg/mL†	382 (149–1226)	382 (149–1226)	382 (149–1226)	.940
TNF-α, pg/mL†	1.42 (0.83)	1.52 (0.76)	1.47 (0.83)	.613
Women	(*N* = 156)	(*N* = 157)	(*N* = 156)	
WBC, K/micrL	5.86 (1.57)	5.85 (1.28)	5.82 (1.49)	.968
ESR, mm/h	3.02 (0.75)	2.83 (0.59)	2.84 (0.69)	.025
Albumin, mg/dL	418 (25)	420 (25)	420 (26)	.713
Uric acid, mg/dL	4.84 (1.19)	4.67 (1.18)	4.70 (1.19)	.375
Fibrinogen, mg/dL	374 (78)	358 (67)	353 (62)	.021
CRP, mg/L	2.82 (0.60–17.12)	2.34 (0.61–12.73)	2.21 (0.47–11.17)	.064
IL-6, pg/mL	1.47 (0.48–4.63)	1.07 (0.35–5.21)	1.21 (0.30–6.59)	.004
sIL-6R, ng/mL	94 (31–173)	96 (38–212)	92 (35–219)	.571
IL-10, pg/mL	9.15 (1.36–1319.29)	7.07 (1.18–2167.80)	8.16 (1.34–2148.68)	.652
IL-1β, pg/mL	0.12 (0.02–0.38)	0.12 (0.02–0.30)	0.14 (0.03–0.44)	.017
IL-1ra, pg/mL	144 (68–314)	127 (61–255)	117 (48–285)	.006
IL-18, pg/mL	353 (201–705)	328 (193–626)	330 (205–578)	.096
TNF-α, pg/mL	5.46 (0.71–15.52)	4.66 (0.66–13.78)	4.82 (1.18–12.06)	.678

Notes: *Continuous variables are presented as mean (standard deviation). Analysis of variance test.

†Continuous variables are presented as median (percentile 5–percentile 95). Kruskal–Wallis test.

WBC = white blood count; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; IL-6 = interleukin 6; sIL-6R = soluble interleukin 6 receptor; IL-10 = interleukin 10; IL-1β = interleukin 1 beta; IL-1ra = interleukin 1 receptor antagonist; IL-18 = interleukin 18; TNF-α = tumor necrosis factor alpha.

that physical activity and performance are associated with lower circulating levels of proinflammatory biomarkers in older men and women. Specifically, we found consistent associations between physical activity and performance, lower ESR, and lower plasma levels of fibrinogen, CRP, and IL-6. Our data confirm previous research showing that physical activity (13–20) and fitness (21–24) are inversely associated with inflammatory biomarkers such as CRP, WBC, and fibrinogen. Moreover, our study provides original contributions to the knowledge on this topic.

First, whereas most of the available evidence for an association between physical activity and lower inflammation is based on self-reported information on physical activity practice, we found that physical performance in the 400-meter walking test, which might be considered a proxy measure of fitness, was also associated with lower inflammation.

Second, most of the studies assessing the association between physical fitness and inflammatory biomarkers have been carried out in a young or middle-aged population. In our study, we also demonstrated that physical fitness is significantly associated with lower plasma levels of proinflammatory markers in the elderly population.

Third, we demonstrated that the association between physical activity and performance and inflammatory biomarkers is already observed when comparing light physical activity versus a sedentary state, or intermediate versus low performance level. We also found that current rather than past level of physical activity was associated with lower levels of inflammatory biomarkers.

Finally, in this study we tested the association between physical activity and performance and a large panel of inflammatory markers, including several proinflammatory (IL-1β, IL-6, IL-18, and TNF-α) and antiinflammatory (IL-1ra, IL-10) cytokines (27). It has been suggested that studying only proinflammatory markers may be misleading because it does not consider the potential effect of counteractive mechanisms. However, we found no clear evidence that physical activity is associated with parallel decline in antiinflammatory cytokines, especially IL-10 and IL-1ra. These findings suggest that physical activity selectively readjusts the signaling network of cytokines toward lower levels of inflammation.

One of the strengths of this study is that we are adjusting our results for dietary antioxidant intake which has been associated with lower inflammation. In our study, IL-6 was inversely associated with vitamin C ($r = -0.123$), β-carotene ($r = -0.146$), and vitamin E ($r = -0.103$) intake. It is also known that active people have a more healthy diet. In our study, more active participants presented a higher intake of these nutrients. Thus, diet may be considered a confounder. However, the results of our diet-adjusted analysis support a diet-independent association between physical activity and performance and lower levels of proinflammatory biomarkers.

Table 4. Multiple Linear Regression Coefficients (Standard Error) of the Association Between Physical Activity Practice, Physical Performance, and Inflammatory Biomarkers in Men

		Physical Activity			Physical Performance	
	N	Light vs Inactive	Moderate–High vs Inactive	*N*	Intermediate vs Low	High vs Low
Model 1						
ESR, mm/h	425	−0.33 (0.15)*	−0.40 (0.15)†	367	−0.23 (0.11)*	−0.29 (0.11)†
Uric acid, mg/dL	427	−0.39 (0.25)	−0.57 (0.25)*	369	−0.14 (0.17)	−0.21 (0.17)
Fibrinogen, mg/dL	421	−43 (13)†	−39 (13)†	363	−18 (10)	−9 (10)
Log CRP, mg/L	423	−0.43 (0.19)*	−0.73 (0.19)†	366	−0.31 (0.14)*	−0.39 (0.14)†
Log IL-6, pg/mL	426	−0.18 (0.14)	−0.33 (0.14)*	367	−0.11 (0.10)	−0.27 (0.10)†
Log TNF-α, pg/mL	427	−0.17 (0.14)	−0.31 (0.14)*	367	0.13 (0.11)	0.05 (0.11)
Model 2						
ESR, mm/h	414	−0.21 (0.15)	−0.30 (0.15)*	367	−0.23 (0.11)*	−0.32 (0.11)†
Uric acid, mg/dL	416	−0.36 (0.26)	−0.48 (0.26)	369	−0.08 (0.17)	−0.10 (0.17)
Fibrinogen, mg/dL	410	−38 (14)†	−34 (14)†	363	−18 (10)	−11 (10)
Log CRP, mg/L	410	−0.38 (0.20)	−0.59 (0.20)†	366	−0.28 (0.14)*	−0.32 (0.14)*
Log IL-6, pg/mL	413	−0.12 (0.15)	−0.28 (0.14)*	367	−0.11 (0.10)	−0.27 (0.10)†
Log TNF-α, pg/mL	414	−0.13 (0.15)	−0.27 (0.15)	367	0.13 (0.11)	0.08 (0.11)

Notes: Model 1 was adjusted for age, smoking status, hypertension, current inflammatory process, prevalent cardiovascular disease, and intake of vitamin C, vitamin E, and β-carotene. Model 2 was further adjusted for body mass index.

*$p < .05$.

†$p < .01$.

ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; IL-6 = interleukin 6; TNF-α = tumor necrosis factor alpha.

The mechanism by which regular physical activity is associated with lower levels of inflammatory biomarkers is uncertain. An interesting hypothesis is that regular physical activity may forestall inflammation by reducing obesity and the percentage of visceral fat, and improving peripheral insulin receptor sensitivity (33). In fact, obesity (34) and peripheral insulin resistance (35) are directly associated with systemic inflammation. Noteworthy, in women but not in men, the association between physical activity or performance, and CRP and IL-1ra, was no longer statistically significant when BMI was included in the models, suggesting that physical activity may reduce CRP and IL-1ra through its effects on BMI.

The free radical theory of aging offers another potential explanation for our findings (36). According to this theory, reactive oxygen species generated in normal metabolic processes may cause important cell and tissue oxidative damage. In unfit individuals, subliminal injuries to myocytes due in part to reactive oxygen species and in part to unusual muscle stretching determine an inflammatory response. There

Table 5. Multiple Linear Regression Coefficients (Standard Error) of the Association Between Physical Activity Practice, Physical Performance, and Inflammatory Biomarkers in Women

		Physical Activity			Physical Performance	
	N	Light vs Inactive	Moderate–High vs Inactive	*N*	Intermediate vs Low	High vs Low
Model 1						
ESR, mm/h	535	−0.15 (0.08)	0.02 (0.09)	458	−0.20 (0.08)*	−0.16 (0.08)*
Uric acid, mg/dL	540	−0.45 (0.14)†	−0.34 (0.16)*	460	−0.17 (0.14)	−0.08 (0.13)
Fibrinogen, mg/dL	538	−16 (8)*	−15 (9)	458	−14 (8)	−17 (8)*
Log CRP, mg/L	531	−0.20 (0.11)	−0.31 (0.13)*	454	−0.16 (0.11)	−0.25 (0.11)*
Log IL-6, pg/mL	541	−0.18 (0.09)*	−0.30 (0.10)†	460	−0.25 (0.09)†	−0.16 (0.09)
Log IL-1β, pg/mL	522	0.02 (0.08)	0.04 (0.10)	441	−0.03 (0.08)	0.25 (0.08)†
Log IL-1ra, pg/mL	541	−0.11 (0.06)	−0.07 (0.07)	460	−0.12 (0.06)	−0.17 (0.06)†
Model 2						
ESR, mm/h	522	−0.11 (0.08)	0.06 (0.09)	458	−0.18 (0.08)*	−0.13 (0.08)†
Uric acid, mg/dL	525	−0.33 (0.13)†	−0.17 (0.15)	460	−0.01 (0.13)	0.13 (0.13)
Fibrinogen, mg/dL	523	−13 (8)	−11 (9)	458	−11 (8)	−13 (8)
Log CRP, mg/L	516	−0.10 (0.11)	−0.13 (0.13)	454	−0.01 (0.11)	−0.06 (0.11)
Log IL-6, pg/mL	525	−0.15 (0.09)	−0.25 (0.10)†	460	−0.20 (0.09)*	−0.09 (0.09)
Log IL-1β, pg/mL	506	0.03 (0.08)	0.04 (0.10)	441	−0.03 (0.09)	0.25 (0.09)†
Log IL-1ra, pg/mL	525	−0.09 (0.06)	−0.02 (0.07)	460	−0.05 (0.06)	−0.09 (0.06)

Notes: Model 1 was adjusted for age, smoking status, hypertension, current inflammatory process, prevalent cardiovascular disease, and intake of vitamin C, vitamin E, and β-carotene. Model 2 was further adjusted for body mass index.

*$p < .05$.

†$p < .01$.

ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; IL-6 = interleukin 6; IL-1β = interleukin 1 beta; IL-1ra = interleukin 1 receptor antagonist.

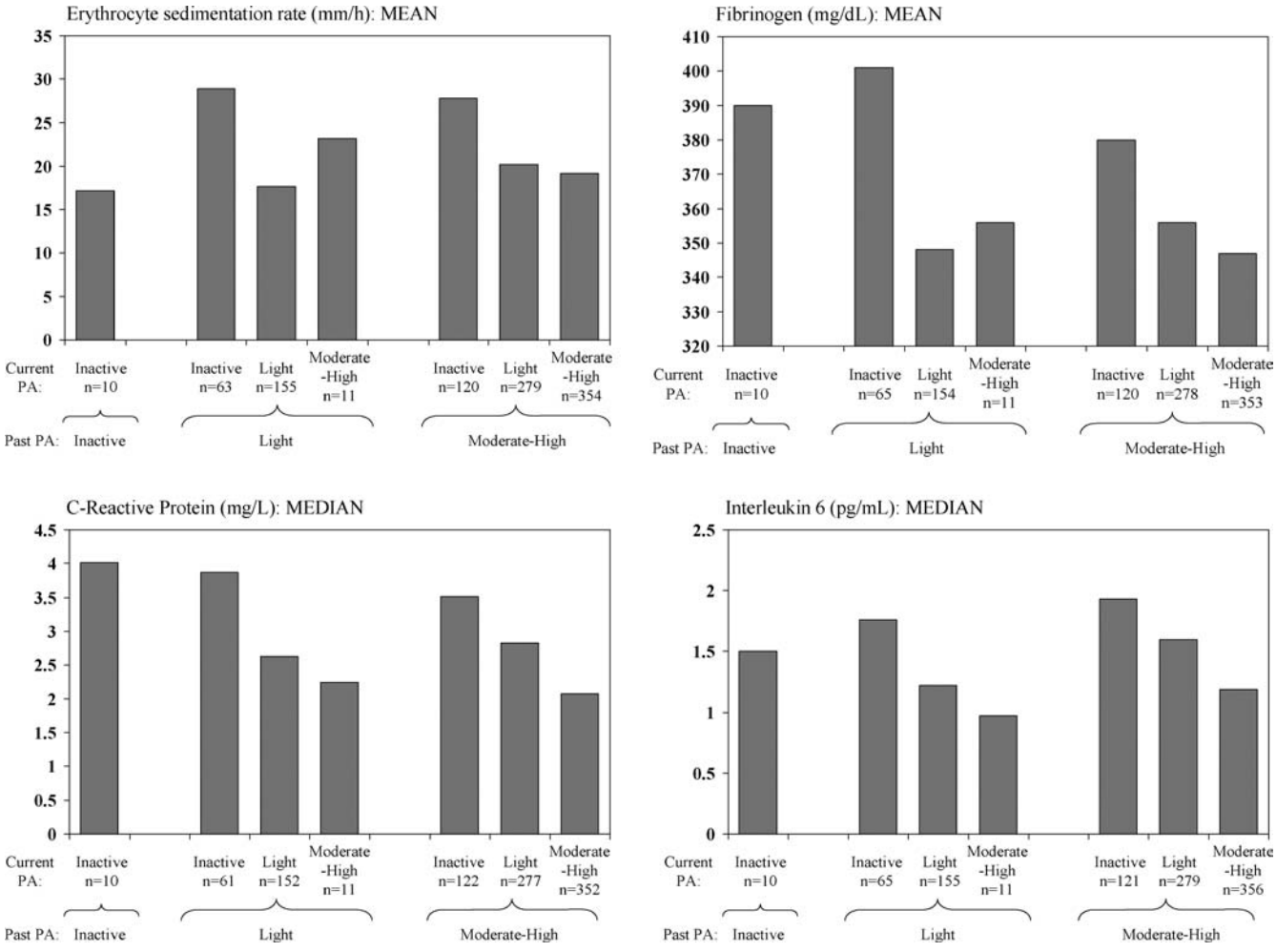

Figure 1. Erythrocyte sedimentation rate, fibrinogen, C-reactive protein, and interleukin-6 mean or median, according to current and past physical activity practice.

is evidence, both from animal and human studies, that long-term exercise implies an increment in the mechanical resistance of myocytes to stretching, and in the endogenous antioxidant enzyme activity (37), therefore preventing excessive and self-sustained local inflammatory reaction.

The most important limitation of our study is its cross-sectional nature. The direction of the causal pathway between physical activity and lower level of inflammation remains unclear. However, some experimental studies have shown that physical activity can prospectively reduce CRP levels, other inflammatory markers (38–40), and the mononuclear cell production of atherogenic cytokines (41). Another limitation is that the participants with missing data for physical activity and/or fitness or the outcome variables were older and more inactive than were those participants whose data were included in the analyses. Nevertheless, we do not think that these differences could significantly affect the validity of the observed results.

In our study, we demonstrated that current physical activity practice and performance are associated with inflammatory biomarkers. A significant beneficial association is already observed with light physical activity practice and intermediate performance. These findings support public health recommendations suggesting that significant benefit could be already achieved with light to moderate physical activity and that "it is never too late" to become physically active.

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