

Exercise Training and Plasma C-Reactive Protein and Interleukin-6 in Elderly People

Barbara J. Nicklas, PhD,* Fang-Chi Hsu, PhD,[†] Tina J. Brinkley, PhD,* Timothy Church, MD,[‡] Bret H. Goodpaster, PhD,[§] Stephen B. Kritchevsky, PhD,* and Marco Pahor, MD^{||}

OBJECTIVES: To determine the effects of a long-term exercise intervention on two prominent biomarkers of inflammation (C-reactive protein (CRP) and interleukin-6 (IL-6)) in elderly men and women.

DESIGN: Single-blind, randomized, controlled trial: The Lifestyle Interventions and Independence for Elders (LIFE) Trial.

SETTING: The Cooper Institute, Dallas, Texas; Stanford University, Stanford, California; University of Pittsburgh, Pittsburgh, Pennsylvania; and Wake Forest University, Winston-Salem, North Carolina.

PARTICIPANTS: Four hundred twenty-four elderly (aged 70–89), nondisabled, community-dwelling men and women at risk for physical disability.

INTERVENTION: A 12-month moderate-intensity physical activity (PA) intervention and a successful aging (SA) health education intervention.

MEASUREMENTS: CRP and IL-6.

RESULTS: After adjustment for baseline IL-6, sex, clinic site, diabetes mellitus, treatment group, visit, and group-by-visit interaction, the PA intervention resulted in a lower ($P = .02$) IL-6 concentration than the SA intervention. Adjusted mean IL-6 at month 12 was 8.5% (0.21 pg/mL) higher in the SA than the PA group. There were no significant differences in CRP between the groups at 12 months ($P = .09$). Marginally significant interaction effects of the PA intervention according to baseline functional status ($P = .05$) and IL-6 (above vs below the median; $P = .06$)

were observed. There was a greater effect of the PA intervention on participants with lower functional status and those with a higher baseline IL-6.

CONCLUSION: Greater PA results in lower systemic concentrations of IL-6 in elderly individuals, and this benefit is most pronounced in individuals at the greatest risk for disability and subsequent loss of independence. *J Am Geriatr Soc* 56:2045–2052, 2008.

Key words: exercise training; inflammation; aging; interleukin-6; C-reactive protein

Chronic, low-grade inflammation is an independent predictor of several aging-related diseases, including coronary heart disease and stroke,^{1,2} diabetes mellitus,³ Alzheimer's disease,⁴ and osteoarthritis.⁵ In addition, inflammation predicts loss of function and onset of disability^{6–10} and mortality.⁸ Although several systemic biomarkers are indicative of an upregulated inflammatory state, C-reactive protein (CRP) and interleukin-6 (IL-6) show the most consistent association with disease and disability in older individuals.^{1,4,11} Moreover, circulating concentrations of CRP and IL-6 are higher in older persons,^{12–16} and there is especially strong evidence that IL-6 (which has been called a “cytokine for gerontologists”¹⁷) is high with advancing age, because there is a dramatic increase in the number of individuals aged 70 and older with high IL-6.¹⁵ Thus, given the widespread health risks of high CRP and IL-6, identification of successful therapies that reduce inflammation may be especially important in this age group.

Although use of certain pharmacological agents may reduce inflammation, side effects of these medications may limit their clinical application for the ongoing treatment of chronic inflammation.¹⁸ Alternatively, there is promising evidence that participation in regular physical activity (PA) lowers CRP and IL-6. Observational data in young and elderly persons show that greater PA is associated with lower CRP and IL-6 levels.^{19–25} In addition, several small or

From the *Section on Gerontology and Geriatric Medicine, J. Paul Sticht Center on Aging, Department of Internal Medicine; [†]Department of Biostatistical Sciences, Wake Forest University School of Medicine, Winston-Salem, North Carolina; [‡]Preventive Medicine Research Laboratory, Pennington Biomedical Research Center, Baton Rouge, Louisiana; [§]Department of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania; and ^{||}Department of Aging and Geriatric Research, University of Florida, Gainesville, Florida.

Presented in part at The Gerontological Society of America Annual Meeting, San Francisco, California, November 19, 2007.

Address correspondence to Barbara J. Nicklas, PhD, J. Paul Sticht Center on Aging, Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157. E-mail: bnicklas@wfubmc.edu

DOI: 10.1111/j.1532-5415.2008.01994.x

uncontrolled studies have shown an effect of aerobic exercise training on reducing CRP and IL-6 in middle-aged or older persons,^{26–34} although there is no randomized, controlled trial evidence of an effect of exercise training on CRP or IL-6 levels in older persons. Therefore, the purpose of this study was to determine whether a 12-month PA intervention would decrease systemic concentrations of CRP and IL-6 more than a no-exercise health education intervention in elderly men and women.

METHODS

Study Design

The findings are from an ancillary study to The Lifestyle Interventions and Independence for Elders Pilot (LIFE-P) Study, a four-site, single-blind, randomized, controlled clinical trial comparing a 12-month PA intervention with a successful aging (SA) intervention in 424 elderly, nondisabled, community-dwelling men and women at risk for physical disability. The study design and main findings on physical function of the LIFE-P Study have been published.^{35,36} The local institutional review boards at the clinic sites (Wake Forest University, Cooper Institute, University of Pittsburgh, and Stanford University) approved the study, and all study participants gave written informed consent to participate.

Study Participants

Detailed inclusion and exclusion criteria and a flow diagram of specific numbers of individuals screened and reasons for exclusion have been published.³⁶ Briefly, the major inclusion criteria were age 70 to 89, low functional performance based on a Short Physical Performance Battery (SPPB) score of less than 10 (on a scale of 0 (worst) to 12 (best)), sedentary lifestyle, ability to complete a 400-m walk test within 15 minutes without sitting and without using an assistive device, completion of a behavioral run-in that required tracking and logging of healthy behaviors, and willingness to be randomized to either treatment group. The major exclusion criteria were living in a nursing home; self-reported inability to walk 1 mile; significant cognitive impairment; severe hearing or visual impairment; and severe cardiac, pulmonary, neurological, orthopedic, renal, or psychiatric disease.

A total of 3,141 persons were screened over the telephone, and 566 completed two screening clinic visits, with a total of 424 (106% of study goal) participants randomized (PA = 213; SA = 211). All of the 424 randomized participants consented to the baseline blood draw, and a sufficient blood sample was successfully collected from 369 participants (87%). Blood samples were available from 345 participants at the 6-month follow-up (6-month retention rate of 93%) and from 335 participants at the 12-month follow-up (12-month retention rate of 91%). Of the 79 participants with missing 6-month data, two had died, 22 withdrew consent or dropped from the study, and 55 did not have a blood sample drawn because of technical difficulties. Of the 89 participants with missing 12-month data, four had died, 25 withdrew consent or dropped from the study, and 60 did not have a blood sample drawn because of technical difficulties.

Interventions

The PA intervention consisted of a combination of aerobic, strength, balance, and flexibility exercises and was divided into three phases. For the first 2 months (adoption phase), three center-based exercise sessions (40–60 minutes) per week were conducted in a supervised setting. During the next 4 months (transition phase), the number of center-based sessions was reduced (2 times/week), and home-based exercises (≥ 3 times/week) were started. The subsequent maintenance phase (Week 25 to trial end) consisted of the home-based intervention, optional one to two times per week center-based sessions, and monthly telephone contacts.

The PA intervention included group-based behavioral counseling sessions (1 time/week for the first 10 weeks) that focused on PA participation. The intervention focused on walking as the primary mode of exercise, and the goal was to engage in walking for at least 150 min/wk. A brief warm-up preceded each session, and a brief cool-down period followed. Participants also completed lower extremity strengthening exercises followed by lower extremity stretching exercises. The intensity of training was gradually increased over the first 2 to 3 weeks. Perceived exertion was used to regulate the intensity of exercise. Participants were asked to walk at a target intensity of 12 to 13 (somewhat hard), and they were discouraged from exercising at levels of 15 or higher (hard) or 11 or less (fairly light). Strengthening exercises were performed at a perceived exertion of 15 to 16.

A SA health education intervention was used as the active control. Participants met in groups weekly for the first 26 weeks and monthly for the remaining weeks. Sessions included health topics relevant to older adults such as nutrition, medications, foot care, and recommended preventive health care. At the end of each session, a short instructor-led intervention (5–10 minutes) of gentle upper extremity stretching was delivered. Phone calls were made after each missed session to encourage regular participation, and participants received a monthly newsletter.

Measurements

CRP and IL-6

Blood samples were collected from LIFE Study participants in the early morning (between 7 and 9 a.m.) after a 12-hour fast at the baseline and 6- and 12-month assessment visits. The 6- and 12-month blood samples were collected at least 24 hours after the last acute bout of exercise training, and blood sampling was postponed (1–2 weeks after recovery of symptoms) in the event of an acute respiratory, urinary tract, or other infection. All blood was collected, processed, divided into aliquots, and stored locally at -80°C until shipment to the Biological Specimen Repository at Wake Forest University, where samples were placed for long-term storage at -80°C until analysis.

Plasma CRP was determined using an automated immunoanalyzer (IMMULITE, Diagnostics Products Corporation, Los Angeles, CA). This assay has a sensitivity of 0.1 mg/L, with a calibration range up to 250 mg/L. In the biogerontology laboratory at Wake Forest University School of Medicine, the interassay and intra-assay coefficients of variation (CV) for the CRP assay are 6.7% and

3.5%, respectively. Five samples (two baseline and one 6- and two 12-month time points) were below the lower limit of detection for CRP and were not included in the analyses. Plasma IL-6 was determined using the Quantikine high-sensitivity enzyme-linked immunosorbent assay kit from R&D Systems (Minneapolis, MN). This assay has a sensitivity of 0.10 pg/mL with a detection range of 0 to 10.0 pg/mL. The interassay and intra-assay CVs for IL-6 are 9.8% and 3.0%, respectively. IL-6 was not detectable for one sample (6-month timepoint). All samples were measured in duplicate, and the average of the two values was used for data analyses. Duplicate samples that did not provide a CV of less than 15% were reanalyzed, and all values were averaged for data analyses.

Short Physical Performance Battery

The SPPB is based on a timed short-distance walk, repeated chair stands, and balance test.³⁷ Each of the performance measures is assigned a score ranging from 0 to 4, with 4 indicating the highest level of performance and 0 the inability to complete the test. The categories computed for walking speed and chair stands are derived from cutpoints based on quartiles of time to perform each task assessed in the Established Populations for Epidemiologic Study of the Elderly (EPSE).³⁷ A summary score ranging from 0 (worst) to 12 (best) is calculated by summing all scores.

Body Composition

Total body fat mass and lean mass were measured using dual X-ray absorptiometry at baseline and 12-month follow-up in a subset ($n = 222$) of the LIFE participants (3 sites—Wake Forest University, Cooper Institute, and University of Pittsburgh).

Statistical Analyses

Statistical analyses were performed using SAS software, version 9.1 (SAS Institute, Inc., Cary, NC). The sample means and standard deviations were computed for the continuous descriptive characteristics, and the count and proportions were calculated for the discrete descriptive characteristics according to intervention groups. To minimize the heterogeneity of variance and best approximate the conditional normality assumption, CRP and IL-6 were log-transformed for the primary statistical analyses. Comparisons of 12-month changes in log-transformed CRP and log-transformed IL-6 between intervention groups were performed using the two-sample *t*-test. Raw values and log-transformed values for each intervention group at each time point were reported as means \pm standard deviations. Differences in mean CRP and IL-6 between intervention groups were estimated using repeated-measures analysis of covariance with the baseline measure, sex (stratifying variable for randomization), clinic site, diabetes mellitus, intervention assignment, visit, and an intervention-by-visit interaction included in the model. Hypothesis tests for intervention effects at the 6- and 12-month assessment visits were performed using contrasts of the 6- and 12-month intervention means. Overall comparisons between groups for CRP and IL-6 across follow-up visits were obtained using a contrast to compare average effects across both follow-up visits. In addition, an interaction between baseline SPPB and intervention group was

also tested for by additional adjustment for the main effect of SPPB and interaction effect of SPPB and intervention group in the model; the analysis was then further stratified according to SPPB score (≤ 7 vs > 7). The same analysis was repeated to test for an interaction between baseline IL-6 group ($<$ median vs \geq median) and intervention group. The analysis stratified according to baseline IL-6 was also performed. No sex interaction was found, so no subgroup analysis according to gender was performed.

RESULTS

Baseline Characteristics and Relationships

The two treatment groups had similar baseline characteristics, except for a slightly higher prevalence of diabetes mellitus in the PA group (Table 1). In addition, there were no differences in baseline CRP or IL-6 concentrations between treatment groups (Table 2). In all participants, there was a significant positive pair-wise correlation between CRP and IL-6 (correlation coefficient (r) = 0.39, $P < .001$). In addition, IL-6 was positively related to age ($r = 0.13$, $P = .02$) and body mass index (BMI) ($r = 0.18$, $P < .001$), whereas CRP was related to BMI ($r = 0.10$, $P = .05$) but not age ($r = -0.01$, $P = .81$). IL-6 was higher in men than women (3.60 ± 3.93 vs 3.27 ± 4.06 pg/mL; $P = .046$), and there were no racial or ethnic differences in CRP or IL-6. In addition, there was no relationship between

Table 1. Baseline Descriptive Characteristics According to Treatment Group

Characteristic	Physical Activity (n = 183)	Successful Aging (n = 186)
Age, mean \pm SD	76.4 \pm 4.1	77.0 \pm 4.4
Female, n (%)	126 (68.9)	125 (67.2)
White, n (%)	141 (77.1)	141 (75.8)
Body mass index, kg/m ² , mean \pm SD	30.7 \pm 6.0	29.8 \pm 5.5
Total fat mass, kg, mean \pm SD*	30.3 \pm 9.0	29.5 \pm 9.5
Total lean mass, kg, mean \pm SD*	47.9 \pm 10.9	46.6 \pm 10.7
Smoking, n (%)		
Never	148 (80.9)	157 (84.4)
Former	28 (15.3)	25 (13.4)
Current	7 (3.8)	4 (2.15)
Mini-Mental State Examination score, mean \pm SD	27.0 \pm 2.3	27.5 \pm 2.1
Prevalent comorbidities, n (%)		
Hypertension	127 (69.8)	129 (69.4)
Diabetes mellitus	52 (28.4)	32 (17.2) [†]
Cancer	28 (15.3)	32 (17.3)
Myocardial infarction	22 (12.1)	12 (6.5)
Stroke	8 (4.4)	12 (6.5)
Congestive heart failure	11 (6.1)	12 (6.5)
Chronic obstructive pulmonary disorder	26 (14.4)	27 (14.6)
Short Physical Performance Battery score, mean \pm SD	7.61 \pm 1.45	7.46 \pm 1.41

* $n = 114$ for physical activity and $n = 108$ for successful aging.

[†] $P = .01$ between groups.

SD = standard deviation.

Table 2. Unadjusted Actual Values and Log-Transformed Values of Plasma C-Reactive Protein (CRP) and Interleukin-6 (IL-6) Concentrations According to Treatment Group at Baseline and 6 and 12 Months

Biomarker	Physical Activity			Successful Aging		
	Mean \pm SD	Median (IQR)	n	Mean \pm SD	Median (IQR)	n
CRP, mg/L						
Baseline	5.78 \pm 11.53	1.97 (4.47)	182	4.38 \pm 5.29	2.66 (4.13)	185
6 months	3.57 \pm 4.15	2.01 (3.77)	173	4.85 \pm 8.96	2.23 (4.68)	171
12 months	4.21 \pm 5.53	2.25 (3.48)	172	4.08 \pm 4.89	2.43 (3.94)	161
Δ CRP (12 months to baseline) [†]	-1.87 \pm 12.25		153	-0.37 \pm 5.82		153
IL-6, pg/mL						
Baseline	3.39 \pm 4.03	2.46 (1.92)	183	3.36 \pm 4.01	2.45 (2.27)	186
6 months	3.26 \pm 3.59	2.50 (2.06)	173	3.75 \pm 5.15	2.67 (2.15)	171
12 months	2.97 \pm 1.91	2.51 (1.92)	173	3.59 \pm 4.65	2.49 (1.96)	162
Δ IL-6 (12 months to baseline) [†]	-0.53 \pm 4.19		155	0.42 \pm 3.27		155

[†] Change between groups $P = .17$ for CRP and $P = .03$ for IL-6.

SD = standard deviation; IQR = interquartile range.

baseline functional status (SPPB score) and CRP ($r = -0.02$, $P = .63$) or IL-6 ($r = -0.09$, $P = .09$).

Effects of PA Intervention on CRP and IL-6

Adherence to the PA and SA interventions was previously reported.³⁶ In the PA group, attendance during the adoption and transition phases averaged 71% and 61%, respectively, and during the maintenance phase, participants engaged in an average of 3.7 walking sessions per week and walked an average of 138 \pm 149 minutes per week (median 119 min/wk, interquartile range 123 min/wk). Attendance at the SA group sessions averaged 70% for Weeks 1 to 26 and 73% for Weeks 27 to 52. The estimated calories expended engaging in moderate PA was similar in the two groups at baseline and significantly higher in the PA group during follow-up.³⁶ There were no changes in body weight as a result of either intervention (PA: baseline = 82.6 \pm 18.1 kg, 6 months = 83.7 \pm 17.7 kg, 12 months = 83.6 \pm 18.3 kg; SA: baseline = 81.8 \pm 17.9 kg, 6 months = 82.0 \pm 18.1 kg, 12 months = 81.1 \pm 16.9 kg). Likewise, there were no changes in body composition and no effect of PA on total body fat mass (PA: baseline = 30.3 \pm 9.0 kg, 12 months = 29.9 \pm 9.1 kg; SA: baseline = 29.5 \pm 9.5 kg, 12 months = 29.0 \pm 9.5 kg; $P = .20$) or lean mass (PA: baseline = 47.9 \pm 10.9 kg, 12 months = 47.6 \pm 10.8 kg; SA: baseline = 46.6 \pm 10.7 kg, 12 months = 46.4 \pm 10.7 kg; $P = .68$) in the subset of participants ($n = 222$) with measures of body composition.

Table 2 shows the unadjusted means (actual and log values) for CRP and IL-6 in each treatment group at baseline and at each follow-up assessment. On average, the PA intervention resulted in a 32% reduction in CRP and a 16% reduction in IL-6 by the end of the 12 months, whereas the SA intervention resulted in an 8% reduction in CRP and a 13% increase in IL-6. Unadjusted overall changes (12-month minus baseline) in CRP were not significantly different between treatment groups, but changes in IL-6 were significantly different between groups ($P = .03$; Table 2).

After adjustment for baseline IL-6, sex, clinic site, diabetes mellitus, treatment group, visit, and group-by-visit

interaction, the PA intervention resulted in a lower ($P = .02$) IL-6 concentration than the SA intervention (Figure 1). Adjusted mean IL-6 at 12 months was 8.5% (0.21 pg/mL) higher in the SA than in the PA group, although there were no significant differences in CRP concentrations between the groups at 12 months ($P = .09$).

Subgroup Analyses

Further analyses (using the same covariates as above in the main model) were performed to determine whether the effects of the PA intervention on IL-6 concentrations were similar in men and women, in those with higher (SPPB > 7) and lower (SPPB \leq 7) overall physical function at baseline, and in those with higher and lower baseline IL-6 (according to median IL-6 value: 2.46 pg/mL). There was no significant interaction of sex ($P = .65$) for the effects of PA on IL-6, but

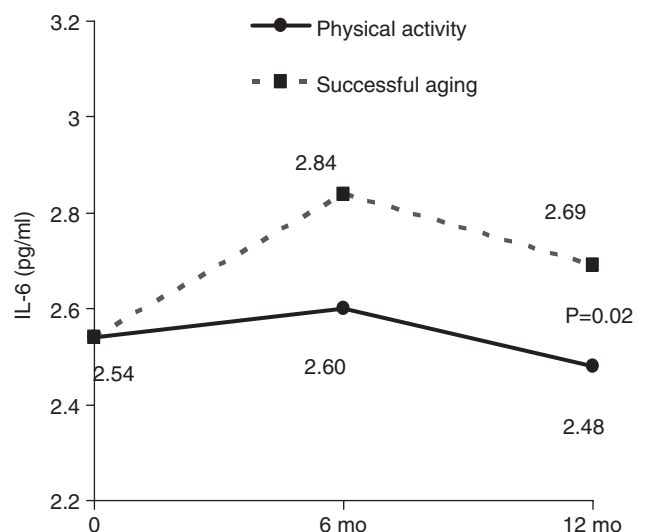


Figure 1. Adjusted interleukin-6 (IL-6) means for each treatment group estimated from repeated-measures analysis of covariance adjusted for baseline IL-6, sex, clinic site, diabetes mellitus, treatment group, visit, and treatment-by-visit interaction. On average, the physical activity group had lower IL-6 levels over time than the successful aging group.

there was marginal statistical evidence for an interaction with baseline functional status ($P = .05$) and IL-6 (above vs below the median; $P = .06$). There was a much greater effect of the PA intervention in participants with lower functional status (SPPB ≤ 7 ; Figure 2) and in those with higher baseline IL-6 (IL-6 ≥ 2.46 pg/mL; Figure 3). There was no observed effect of the PA intervention in persons with a higher SPPB or a lower IL-6. Because SPPB was marginally ($P = .09$) related to IL-6 at baseline (e.g., persons with lower function tended to have higher IL-6 levels), both interaction terms (treatment by SPPB score and treatment by median IL-6) were included in the same model to ascertain whether these interactions were independent of one another. The analyses showed that both interaction terms remained marginally significant ($P = .06$ and $.06$, respectively). In addition, mean baseline IL-6 values were similar between the SPPB groups (3.35 ± 2.67 pg/mL and 3.39 ± 4.76 pg/mL), indicating that the effects of baseline functional status on the differential IL-6 response to the PA intervention were probably not due to differences in baseline IL-6.

DISCUSSION

These findings provide randomized controlled trial evidence that a 1-year PA intervention results in lower systemic concentrations of IL-6 in elderly individuals at risk for disability, although the subgroup of participants with lower functional status (SPPB score ≤ 7) and those with higher baseline IL-6 drove the effect of the exercise intervention on IL-6, because there was no observed effect in persons with a higher SPPB or a lower baseline IL-6. There was no interaction of sex for the effects of PA on IL-6, so similar responses were observed in men and women. Thus, regular PA—even in the absence of weight loss—is an effective therapy for reducing systemic concentrations of IL-6, an important biological predictor of risk for disability and mortality.^{6–10} Furthermore, this benefit of regular PA is most beneficial in older individuals at the greatest risk for disability and subsequent loss of independence.

It is well known that a single bout of strenuous exercise acutely increases systemic IL-6 levels, as well as concentrations of other cytokines and acute phase reactants,³⁸ but

because the observation of a reduction in systemic IL-6 with long-term exercise training is consistent with some previously published data from smaller and uncontrolled studies of a shorter duration,^{28,31,34} it appears that chronic muscle contractions performed regularly decrease systemic IL-6 concentrations. Additionally, the current findings extend those of previous studies in several ways. First, the data provide evidence from a randomized controlled design that causally links the observed lower IL-6 to the greater PA. In addition, the intervention was of sufficient length (12 months) but did not change body weight, indicating that exercise training does not need to result in weight loss to have an effect on IL-6. Finally, it was found that the effect of the greater PA on IL-6 was much more pronounced in the subset of persons with higher baseline IL-6 and in those with worse physical function. There was a mean increase in IL-6 levels in the SA group, especially in those with lower function at baseline, suggesting that PA may result in lower IL-6 by preventing an age-related increase. As seen in other published studies,^{6,14–16} concentrations of IL-6 were positively related to age at baseline in the individuals enrolled in this study.

The mechanism by which chronic exercise alters IL-6 concentrations in the circulation must be through an inhibitory effect on IL-6 production or a stimulatory effect on IL-6 clearance. Adipose tissue is a significant source of circulating IL-6, and individuals with more fat have higher levels of IL-6.³⁹ In the present study, IL-6 was directly related to BMI at baseline, but the intervention did not cause weight loss—or changes in body composition (measured in a subset of LIFE participants)—making it unlikely that the observed reduction in IL-6 could be solely attributed to a loss of body fat. In addition, although data are limited, it does not appear that exercise in the absence of fat loss influences production or release of IL-6 by adipose tissue *per se*.^{40,41} Nevertheless, data are beginning to show that chronic exercise may decrease proinflammatory cytokine production from peripheral mononuclear cells.^{42,43}

Although there was a trend for the PA intervention to lower CRP levels, a statistically significant treatment effect was not found for CRP in the entire sample or in subgroups

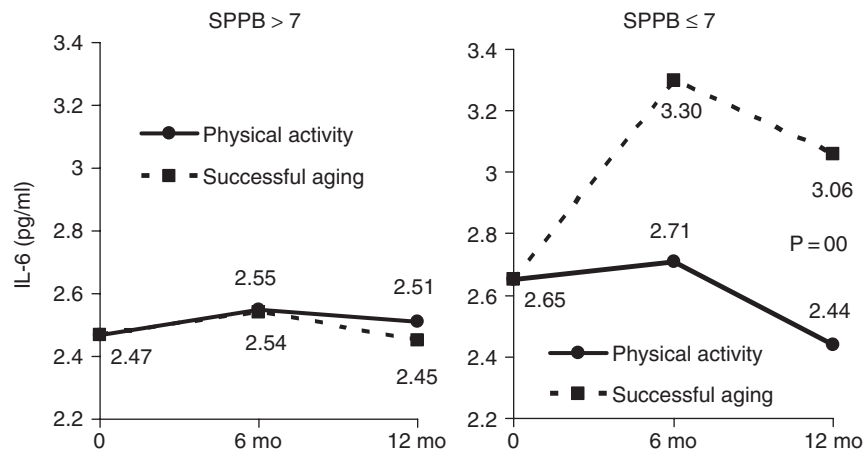


Figure 2. Adjusted interleukin-6 (IL-6) means for each treatment group stratified by baseline functional status (Short Physical Performance Battery score). Means are estimated from repeated-measures analysis of covariance adjusted for baseline IL-6, sex, clinic site, diabetes mellitus, treatment group, visit, and treatment-by-visit interaction. P for interaction = $.05$.

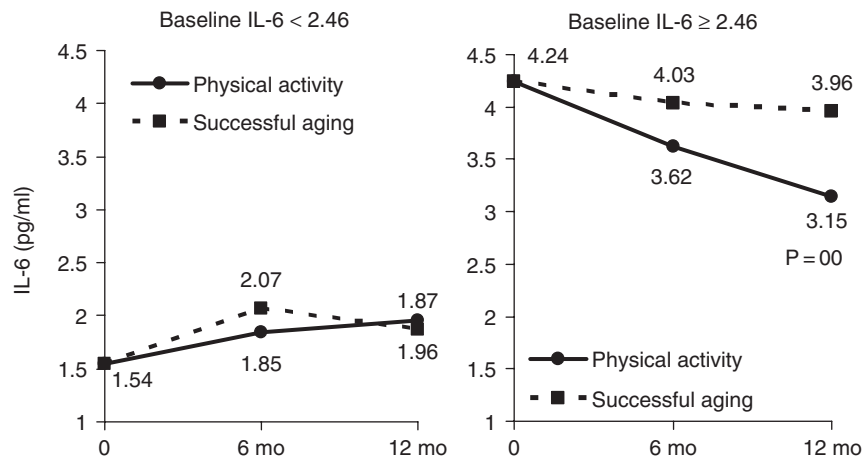


Figure 3. Adjusted interleukin-6 (IL-6) means for each treatment group stratified according to baseline IL-6 (median IL-6). Means are estimated from repeated-measures analysis of covariance adjusted for baseline IL-6, sex, clinic site, diabetes mellitus, treatment group, visit, and treatment-by-visit interaction. P for interaction = .06.

of individuals with higher CRP or lower physical function at baseline. On average, the PA intervention reduced CRP nearly 2.0 mg/L, although this reduction was not different from in the control group. Using this effect size, post hoc power analyses indicate that statistical power with the present sample size was 27% and that, to reach 80% power with the same effect size, 643 participants would need to be studied in each intervention group. Despite a large body of cross-sectional evidence showing that a higher volume of PA is associated with a lower CRP concentration,^{19–25} not all prior intervention studies show an effect of increasing PA for reducing CRP.^{27,30,32,34,44,45} However, these studies were conducted with smaller sample sizes ($N = 16–140$) than the current study. Previously published intervention studies showing that exercise training reduced CRP did not compare individuals randomized to exercise or a nonexercise control group,^{26,28,29,46–48} or the intervention also resulted in slight to moderate decreases in body weight or fat.^{26,33,47–49} Thus, exercise training interventions that result in even a slight amount of weight reduction are beneficial for reducing CRP levels, whereas it appears that increasing PA alone has a small, often undetectable, effect on CRP.

Although the findings of the current study indicate that increasing PA can be advocated as an effective therapy for reducing systemic IL-6, whether this reduction resulted in an improvement in risk factors for adverse health conditions associated with inflammation was not tested. A high blood concentration of IL-6 can be indicative of several aging-related diseases but is an especially strong risk factor for subsequent cardiovascular disease^{1,2} and disability^{6–10} in older persons. Although there is currently no established IL-6 cutpoint used to identify greater disease or disability risk, one study suggested that the higher risk of mobility disability associated with IL-6 was nonlinear, with the risk rising rapidly beyond a concentration of 2.5 pg/mL; individuals above this level were approximately 62% more likely to develop disability over the next 4 years.⁷ Average baseline IL-6 in the individuals enrolled in the LIFE Trial was 3.38 pg/mL, suggesting that, overall, they were at high risk for development of disability. Furthermore, the mean decrease in IL-6 in all individuals in the PA intervention

group was 0.53 pg/mL ($\sim 16\%$), to an average of 2.97 pg/mL. Unfortunately, there are no available data regarding whether this magnitude of decline in IL-6 is associated with a lower risk of subsequent disability or other aging-related adverse health conditions. Thus, longitudinal studies are needed to determine whether there is a delay in the onset of physical disability or a reduction in disease incidence associated with this reduction in IL-6 seen with regular exercise.

These findings should be interpreted in light of certain aspects of the study and potential limitations. First, the entire sample was aged 70 and older, and the effects of the intervention may not directly translate to another age group, and they may not be observed in all older persons. Moreover, because the subset of individuals with lower physical function drove the observed IL-6 response to PA, this effect may have been underestimated, because missing blood samples may have disproportionately come from these impaired individuals. In addition, the PA intervention in the LIFE Study used a combination of aerobic (mainly walking) and light lower extremity resistance exercise. This intervention does not make it possible to determine whether one type of training has greater antiinflammatory effects than another, nor does it provide information regarding possible dose-response effects of increasing the exercise intensity or the overall caloric expenditure of PA. Despite these caveats, this study points to the benefit of regular PA—even in the absence of weight loss—as an effective therapy for reducing systemic concentrations of IL-6 in elderly people, especially in those with the greatest risk for disability.

ACKNOWLEDGMENTS

The LIFE-P Study was funded by a grant from the National Institutes of Health (NIH), National Institute on Aging (NIA) (U01 AG22376) and supported in part by the Intramural Research Program, NIA, NIH. The ancillary study was supported in part by the Wake Forest University Claude D. Pepper Older Americans Independence Center (P30 AG21332) and by NIH Grant 1R01 AG027529 to Dr. Nicklas.

Conflict of Interest: The editor in chief has reviewed the conflict of interest checklist provided by the authors and has

determined that the authors have no financial or any other kind of personal conflicts with this manuscript.

Author Contributions: BJN: acquisition of data, study concept and design, analysis and interpretation of data, preparation of manuscript. FCH: study concept and design, analysis and interpretation of data, preparation of manuscript. TJB: acquisition of data, analysis and interpretation of data, preparation of manuscript. TC: acquisition of data, study concept and design, analysis and interpretation of data, preparation of manuscript. BHG, SBK, and MP: acquisition of data, study concept and design, preparation of manuscript.

Sponsor's Role: None.

REFERENCES

- Kritchevsky SB, Cesari M, Pahor M. Inflammatory markers and cardiovascular health in older adults. *Cardiovasc Res* 2005;66:265–275.
- Cesari M, Penninx BW, Newman AB et al. Inflammatory markers and onset of cardiovascular events: Results from the Health ABC Study. *Circulation* 2003;108:2317–2322.
- Schmidt MI, Duncan BB, Sharrett AR et al. Markers of inflammation and prediction of diabetes mellitus in adults (Atherosclerosis Risk in Communities Study): A cohort study. *Lancet* 1999;353:1649–1652.
- Dziedzic T. Systemic inflammatory markers and risk of dementia. *Am J Alzheimers Dis Other Dement* 2006;21:258–262.
- Sharif M, Shepstone L, Elson CJ et al. Increased serum C reactive protein may reflect events that precede radiographic progression in osteoarthritis of the knee. *Ann Rheum Dis* 2000;59:71–74.
- Cohen HJ, Pieper CF, Harris T et al. The association of plasma IL-6 levels with functional disability in community-dwelling elderly. *J Gerontol A Biol Sci Med Sci* 1997;52A:M201–M208.
- Ferrucci L, Harris TB, Guralnik JM et al. Serum IL-6 level and the development of disability in older persons. *J Am Geriatr Soc* 1999;47:639–646.
- Harris TB, Ferrucci L, Tracy RP et al. Associations of elevated interleukin-6 and C-reactive protein levels with mortality in the elderly. *Am J Med* 1999;106:506–512.
- Taaffe DR, Harris TB, Ferrucci L et al. Cross-sectional and prospective relationships of interleukin-6 and C-reactive protein with physical performance in elderly persons: MacArthur Studies of Successful Aging. *J Gerontol A Biol Sci Med Sci* 2000;55A:M709–M715.
- Penninx BW, Kritchevsky SB, Newman AB et al. Inflammatory markers and incident mobility limitation in the elderly. *J Am Geriatr Soc* 2004;52:1105–1113.
- Maggio M, Guralnik JM, Longo DL et al. Interleukin-6 in aging and chronic disease: A magnificent pathway. *J Gerontol A Biol Sci Med Sci* 2006;61A:575–584.
- Grimble RF. Inflammatory response in the elderly. *Curr Opin Clin Nutr Metab Care* 2003;6:21–29.
- Wener MH, Daum PR, McQuillan GM. The influence of age, sex, and race on the upper reference limit of serum C-reactive protein concentration. *J Rheumatol* 2000;27:2351–2359.
- Ferrucci L, Corsi A, Lauretani F et al. The origins of age-related pro-inflammatory state. *Blood* 2005;105:2294–2299.
- Giuliani N, Sansoni P, Girasole G et al. Serum interleukin-6, soluble interleukin-6 receptor and soluble gp130 exhibit different patterns of age- and menopause-related changes. *Exp Gerontol* 2001;36:547–557.
- Forsey RJ, Thompson JM, Ernerudh J et al. Plasma cytokine profiles in elderly humans. *Mech Ageing Dev* 2003;124:487–493.
- Ersler WB. Interleukin-6: A cytokine for gerontologists. *J Am Geriatr Soc* 1993;41:176–181.
- Canvin JM, el Gabalawy HS. Anti-inflammatory therapy. *Phys Med Rehabil Clin N Am* 1999;10:301–317.
- Gefken D, Cushman M, Burke G et al. Association between physical activity and markers of inflammation in a healthy elderly population. *Am J Epidemiol* 2001;153:242–250.
- Wannamethee SG, Lowe GD, Whincup PH et al. Physical activity and hemostatic and inflammatory variables in elderly men. *Circulation* 2002;105:1785–1790.
- 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.
- Church TS, Barlow CE, Earnest CP et al. Associations between cardiorespiratory fitness and C-reactive protein in men. *Arterioscler Thromb Vasc Biol* 2002;22:1869–1876.
- King DE, Carek P, Mainous AG III et al. Inflammatory markers and exercise: Differences related to exercise type. *Med Sci Sports Exerc* 2003;35:575–581.
- Reuben DB, Judd-Hamilton L, Harris TB et al. The associations between physical activity and inflammatory markers in high-functioning older persons: MacArthur Studies of Successful Aging. *J Am Geriatr Soc* 2003;51:1125–1130.
- Kasapis C, Thompson PD. The effects of physical activity on serum C-reactive protein and inflammatory markers: A systematic review. *J Am Coll Cardiol* 2005;45:1563–1569.
- Milani RV, Lavie CJ, Mehra MR. Reduction in C-reactive protein through cardiac rehabilitation and exercise training. *J Am Coll Cardiol* 2004;43:1056–1061.
- Hammett CJ, Oxenham HC, Baldi JC et al. Effect of six months' exercise training on C-reactive protein levels in healthy elderly subjects. *J Am Coll Cardiol* 2004;44:2411–2413.
- Goldhammer E, Tanchilevitch A, Maor I et al. Exercise training modulates cytokines activity in coronary heart disease patients. *Int J Cardiol* 2005;100:93–99.
- Lakka TA, Lakka HM, Rankinen T et al. Effect of exercise training on plasma levels of C-reactive protein in healthy adults: The HERITAGE Family Study. *Eur Heart J* 2005;26:2018–2025.
- Fairey AS, Courneya KS, Field CJ et al. Effect of exercise training on C-reactive protein in postmenopausal breast cancer survivors: A randomized controlled trial. *Brain Behav Immun* 2005;19:381–388.
- Kohut ML, McCann DA, Russell DW et al. Aerobic exercise, but not flexibility/resistance exercise, reduces serum IL-18, CRP, and IL-6 independent of beta-blockers, BMI, and psychosocial factors in older adults. *Brain Behav Immun* 2006;20:201–209.
- Zoppini G, Targher G, Zamboni C et al. Effects of moderate-intensity exercise training on plasma biomarkers of inflammation and endothelial dysfunction in older patients with type 2 diabetes. *Nutr Metab Cardiovasc Dis* 2006;16:543–549.
- Oberbach A, Tonjes A, Kloting N et al. Effect of a 4 week physical training program on plasma concentrations of inflammatory markers in patients with abnormal glucose tolerance. *Eur J Endocrinol* 2006;154:577–585.
- Dekker MJ, Lee S, Hudson R et al. An exercise intervention without weight loss decreases circulating interleukin-6 in lean and obese men with and without type 2 diabetes mellitus. *Metabolism* 2007;56:332–338.
- Rejeski WJ, Fielding RA, Blair SN et al. The Lifestyle Interventions and Independence For Elders (LIFE) pilot study: Design and methods. *Contemp Clin Trials* 2005;26:141–154.
- Pahor M, Blair SN, Espeland M et al. Effects of a physical activity intervention on measures of physical performance: Results of the Lifestyle Interventions and Independence For Elders Pilot (LIFE-P) study. *J Gerontol A Biol Sci Med Sci* 2006;61A:1157–1165.
- Guralnik JM, Ferrucci L, Pieper CF et al. Lower extremity function and subsequent disability: Consistency across studies, predictive models, and value of gait speed alone compared with the short physical performance battery. *J Gerontol A Biol Sci Med Sci* 2000;55A:M221–M231.
- Pedersen BK, Steensberg A, Schjerling P. Exercise and interleukin-6. *Curr Opin Hematol* 2001;8:137–141.
- Mohamed-Ali V, Goodrick S, Rawesh A et al. Subcutaneous adipose tissue releases interleukin-6, but not tumor necrosis factor-alpha, in vivo. *J Clin Endocrinol Metab* 1997;82:4196–4200.
- Polak J, Klimcakova E, Moro C et al. Effect of aerobic training on plasma levels and subcutaneous abdominal adipose tissue gene expression of adiponectin, leptin, interleukin 6, and tumor necrosis factor alpha in obese women. *Metabolism* 2006;55:1375–1381.
- Klimcakova E, Polak J, Moro C et al. Dynamic strength training improves insulin sensitivity without altering plasma levels and gene expression of adipokines in subcutaneous adipose tissue in obese men. *J Clin Endocrinol Metab* 2006;91:5107–5112.
- Smith JK, Dykes R, Douglas JE et al. Long-term exercise and atherogenic activity of blood mononuclear cells in persons at risk of developing ischemic heart disease. *JAMA* 1999;281:1722–1727.
- Sloan RP, Shapiro PA, Demeersman RE et al. Aerobic exercise attenuates inducible TNF production in humans. *J Appl Physiol* 2007;103:1007–1011.
- Marcell TJ, McAuley KA, Traustadottir T et al. Exercise training is not associated with improved levels of C-reactive protein or adiponectin. *Metabolism* 2005;54:533–541.
- Rauramaa R, Halonen P, Vaisanen SB et al. 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.

46. Mattusch F, Dufaux B, Heine O et al. Reduction of the plasma concentration of C-reactive protein following nine months of endurance training. *Int J Sports Med* 2000;21:21–24.
47. Okita K, Nishijima H, Murakami T et al. Can exercise training with weight loss lower serum C-reactive protein levels? *Arterioscler Thromb Vasc Biol* 2004;24:1868–1873.
48. Obisesan TO, Leeuwenburgh C, Phillips T et al. C-reactive protein genotypes affect baseline, but not exercise training-induced changes, in C-reactive protein levels. *Arterioscler Thromb Vasc Biol* 2004;24:1874–1879.
49. Giannopoulou I, Fernhall B, Carhart R et al. Effects of diet and/or exercise on the adipocytokine and inflammatory cytokine levels of postmenopausal women with type 2 diabetes. *Metabolism* 2005;54:866–875.