Published in final edited form as:
Med Sci Sports Exerc. 2010 December ; 42(12): 2189–2196. doi:10.1249/MSS.0b013e3181e3ac80.

Long-Term Physical Activity and Inflammatory Biomarkers in Older Adults

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Abstract

Purpose—To determine the effects of a 12-month physical activity intervention on inflammatory biomarkers in elderly men and women.

Methods—424 elderly (aged 70–89 years), nondisabled, community-dwelling men and women at risk for physical disability were enrolled in a multicenter, single-blind, randomized controlled-trial. Participants were randomized to participate in either a 12-month moderate-intensity physical activity (PA) intervention or a successful aging (SA) health education intervention. Biomarkers of inflammation (IL-6sR, IL-1sRII, sTNFRI, sTNFRII, IL-8, IL-15, adiponectin, IL-1ra, IL-2sRα, and TNF-α) were measured at baseline, 6 and 12 months.

Results—A baseline blood sample was successfully collected from 368 participants. After adjustment for gender, clinic site, diabetes status, and baseline outcome measure, IL-8 was the only inflammatory biomarker affected by the PA intervention (p=0.03). The adjusted mean IL-8 at month 12 was 9.9% (0.87 pg/mL) lower in the PA compared to the SA group. Secondary interaction analyses between baseline biomarker status and treatment showed one significant interaction (p=0.02) such that the PA intervention reduced IL-15 concentrations in participants with a baseline IL-15 above the median value of 1.67 pg/mL. However, these associations were no longer significant after consideration for multiple comparisons.

Conclusions—Overall, this study does not provide definitive evidence for an effect of regular exercise for altering systemic concentrations of the measured inflammatory biomarkers in older adults.

Keywords

exercise; aging; inflammation; cytokines; soluble receptors

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Introduction

Inflammation, the body's complex biological reaction to damaging stimuli, is a necessary response of the adaptive immune system. This response is typically acute, resulting in increases in pro-inflammatory cytokines and acute phase proteins that are rapidly released into the circulation. However, a prolonged inflammatory state has detrimental health effects and predisposes to a wide variety of chronic diseases, especially those that are more prevalent with advanced age, such as cardiovascular disease and diabetes (19). Chronic inflammation is also a strong predictor of both disability and mortality in the elderly—even in the absence of clinical disease (16,30). Moreover, higher concentrations of pro-inflammatory cytokines and acute phase reactants are often seen in older adults, compared to middle-aged or younger adults (10,34). This observation, coupled with the disproportionate adverse consequences of a prolonged inflammatory state in the elderly, points to the inflammation pathway as a potential target for interventions to reduce aging-related disease and disability. However, at present, there are no known definitive therapies for treating chronic inflammation in the elderly.

While anti-inflammatory medications will reduce inflammation acutely, their clinical application for the on-going treatment of chronic inflammation is limited, indicating the need to identify non-pharmacologic treatments. Notably, regular physical activity (PA) is associated with lower risk of aging-related chronic disease and disability, even in those who begin to exercise later in life (31). However, the mechanism responsible for this protective adaptation is not completely understood. Numerous studies report the beneficial effects of habitual PA on more traditional disease risk factors such as hypertension, insulin insensitivity, altered lipid profiles, and obesity (29), but less is known about its effect on inflammation. Since a single bout of exercise induces an inflammatory response that is similar to that induced by infection or trauma (28), it is questionable whether or not long-term physical activity may be effective for reducing chronic inflammation, especially in the elderly.

Data from numerous smaller studies suggest that regular PA has the potential to reduce circulating levels of several inflammatory biomarkers (24). Yet to date, there are very limited data from randomized, controlled trials to definitively conclude that long-term regular exercise training reduces chronic inflammation. We previously showed, in elderly men and women, that 12 months of moderate-intensity physical activity lowers systemic concentrations of interleukin-6 (IL-6), but not C reactive protein (CRP), relative to a non-exercise control intervention (25). However, due to the complexity of the immune system and the inter-relatedness of inflammatory biomarkers (23), it is unlikely that a single biomarker reflects all health risk. Therefore, the purpose of this study was to expand our previous research by determining whether this 12-month exercise intervention would affect multiple biomarkers of inflammation. Specifically, we chose to focus on adiponectin (a protein with anti-inflammatory properties), and on the cytokines tumor necrosis factor alpha (TNF-α), IL-8, and IL-15, as well as various cytokine receptors (IL-6sR, IL-1ra, IL-1sRII, sTNFRI, sTNFRII, and IL-2 sRα) which, because of the short half-life of many cytokines, may be more representative of the inflammatory response as a whole (1).

Methods

Study Design

This study was conducted as an ancillary study to The Lifestyle Interventions and Independence for Elders Pilot (LIFE-P) trial, 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 (27,33) as well as IL-6 and CRP outcome data (primary inflammatory biomarkers of interest) (25), are published.

The local institutional review boards at the clinical 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. The consolidated standards of reporting trials (CONSORT) guidelines were followed.

Study Participants

Detailed randomization, inclusion and exclusion criteria, and a flow diagram of specific numbers of individuals screened and reasons for exclusion are published (27,33)). Briefly, the major inclusion criteria were age of 70–89 years, 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-meter 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 one mile; significant cognitive impairment (Mini-Mental State Examination (MSSE) Score < 21); severe hearing or visual impairment; and severe cardiac, pulmonary, neurological, orthopedic, renal, or psychiatric disease.

Interventions

Interventions have been described in detail elsewhere (33). Briefly, 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), 3 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 1 to 2 times per week center-based sessions, and monthly telephone contacts.

Additionally, 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 minutes/week. A brief warm-up proceeded 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 quantified using the Borg scale and 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

Participants were enrolled between April 2004 and February 2005. Baseline assessments included a personal interview, anthropometric measures, physical exam, electrocardiogram, and a physician evaluation. Follow-up visits in the clinic occurred at 6- and 12-months.

Prevalence of clinical conditions was determined using self-reported physician-diagnosed disease information.

Short Physical Performance Battery (SPPB)—A global measure of physical function was performed to characterize functional status of the participants. The SPPB is based on a timed short-distance walk, repeated chair stands, and balance test (15). 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 cut-points based on quartiles of time to perform each task assessed in the Established Populations for Epidemiologic Study of the Elderly (EPESE). A summary score ranging from 0 (worst) to 12 (best) is calculated by summing all scores.

Inflammatory Biomarkers—All blood samples were collected from LIFE Study participants in the early morning (between 7 and 9 AM) 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, and blood sampling was postponed (1–2 weeks after recovery of all 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 later analysis.

All of the 424 randomized participants consented to the baseline blood draw, and a sufficient blood sample was successfully collected from 368 (87%) participants. Blood samples were available from 345 participants (81% of randomized participants) at the 6-month follow-up and from 334 participants (79%) at the 12-month follow-up. Of the 79 participants with missing 6-month data, 2 had died, 22 withdrew consent or dropped from the study, and 55 did not have a blood sample drawn due to technical difficulties. Of the 90 participants with missing 12-month data 4 had died, 25 withdrew consent or dropped from the study, and 61 did not have a blood sample drawn due to technical difficulties.

All biomarker assays were run using Quantikine enzyme-linked immunosorbant kits from R&D systems (Minneapolis, MN), with the exception of IL-8 and IL-15 which were run using the QuantiGlo chemiluminescent enzyme-linked immusoborbent assay kits from R&D systems (Minneapolis, MN), and CRP which was determined using an automated immunoanalyzer (IMMULITE, Diagnostics Products Corporation, Los Angeles, CA). Sensitivities, detection and reference ranges, and inter- and intra-assay coefficients of variation (CV) for each biomarker assessed are presented in Table 1. 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 30% for TNF-α, 25% for sTNFRI, sTNFRII, IL-2sRα, IL-6sR, IL-1sRII, IL-8, and IL-15, and 20% for adiponectin, IL-6 and CRP, were reanalyzed. All values were averaged for data analyses.

Statistical Analysis

All statistical analyses were performed using SAS software, version 9.2 (SAS Institute, Inc., Cary, NC) and a probability level of <0.05 was adopted throughout. Sample means and standard deviations were computed for the continuous descriptive characteristics, and count and proportions were calculated for the discrete descriptive characteristics according to intervention groups. Estimation of missing data was done using maximum likelihood techniques (8). Means between groups were compared using independent t-tests to assess the balance achieved via randomization for the continuous descriptive characteristics (after transformation to approximate the normality assumption if necessary) and using chi-squared

tests for the discrete descriptive characteristics. Relationships among all baseline inflammatory biomarkers were assessed using Spearman correlation coefficients.

For the primary statistical analysis, in order to minimize the heterogeneity of variance and best approximate the conditional normality assumption, sTNFR1, sTNFR2, IL-8, IL-15, adiponectin, IL-1ra, IL-2sRα, TNF-α were log-transformed. IL-6sR and IL-1sRII were normally distributed and therefore not transformed. CPR and IL-6 data were previously reported (24); and, although presented in the tables for completeness, these data were not included in the primary statistical analysis for this paper. Raw values for each intervention group at each time point are reported as means and standard deviations. Differences in mean values of each biomarker between treatment groups were estimated using repeated measures analysis of covariance with baseline outcome measure, sex (stratifying variable for randomization), clinic site, diabetes status, 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. Between group differences in biomarker changes over time, adjusted for baseline value, are reported as least squares mean and 95% confidence interval. Overall comparisons between groups across follow-up visits were obtained using a contrast to compare average effects across both follow-up visits; and, a Bonferroni correction method was used to correct for the problem of multiple comparisons. Lastly, interactions between baseline biomarker status ($<$ median vs. $\geq$ median) and intervention group were also examined.

Results

Baseline Characteristics and Relationships between Inflammatory Biomarkers

Baseline characteristics of the study sample are shown in Table 2. The two treatment groups were similar with regard to all baseline characteristics except prevalence of diabetes, which was greater in the PA group ($p<0.01$). Additionally, no differences were noted between groups at baseline with regard to any inflammatory biomarker (all $p>0.40$). We examined the degree of inter-relatedness between biomarkers and these descriptive data are presented as Spearman correlation coefficients in Table 3. The strongest relationships were seen between the soluble receptors. Furthermore, all significant correlations between biomarkers were positive, except for the correlation between adiponectin and IL-1ra, and the correlation between IL-15 and TNF-α, which were negative.

Effects of PA Intervention on Inflammatory Biomarkers

Adherence to the PA and SA interventions was previously reported (27). Briefly, in the PA group, attendance during the adoption and transition phases averaged 71% and 61%, respectively. During the maintenance phase, participants engaged in an average of 3.7 walking sessions per week and walked an average of 138±149 minutes per week (median 119 min/wk, IQR 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 ($p=0.98$) and significantly higher in the PA group during follow-up ($p<0.01$ at 6 and 12 months) (27). There were no changes in body weight as a result of either intervention. Likewise, in the subset of participants with measures of body composition (32), there were no changes in fat mass or lean mass in either group.

Table 4 shows the unadjusted mean and standard deviation of the individual biomarkers for each time point by treatment group. The between group differences in 6- and 12-month changes from baseline (adjusted for baseline value) are also shown in Table 4 as least squares means and 95% confidence intervals (CI). IL-6, IL-8 and sTNFRI were the only biomarkers that decreased more at 12 months in the PA versus SA group. Linear regression modeling, adjusting

for baseline outcome measure, sex, clinical site, diabetes mellitus, intervention assignment, visit, and an intervention by visit interaction, showed that the PA intervention resulted in significantly lower levels of IL-8 than the SA intervention (p=0.03). Adjusted mean IL-8 at 12-months was 9.9% (0.87 pg/mL) higher for the SA group than the PA group. Marginally significant effects of the PA intervention were also seen for IL-1sRII (p=0.06) and sTNFR1 (p=0.06). IL-1sRII values were significantly higher in the PA group at 6 months (SA = 9919 ±158 pg/mL vs. PA = 10419±161 pg/mL; p=0.03), however by 12 months, values between groups were not significantly different (SA = 9900±175 pg/mL vs. PA = 10188±176 pg/mL; p=0.25), rendering the overall ANCOVA model not significant. sTNFRI tended to be lower in the PA group at 6-months (SA = 1693±30 pg/mL vs. PA = 1592±30 pg/mL; p=0.05) and at 12 months (SA = 1740±43 pg/mL vs. PA = 1639±43 pg/mL; p=0.17). However, after adjustment for multiple comparisons, there were no significant effects of the PA intervention on any inflammatory biomarker.

Further analyses (using the same covariates as above in the main model) were performed to determine whether any effect of the PA intervention on inflammatory biomarker concentration was contingent on baseline biomarker level. Stratification of each baseline biomarker into less than the median value or greater than or equal to the median value yielded only one significant result, with the PA intervention reducing IL-15 only in those participants with higher IL-15 at baseline (p=0.02).

Discussion

Overall, the findings from this randomized, controlled trial do not provide definitive evidence that a one-year PA intervention is successful at mediating systemic biomarkers of inflammation in older adults at risk for disability. Although the exercise intervention did lower systemic concentrations of IL-8, and reduce IL-15 in individuals with elevated IL-15 at baseline, these associations were no longer significant after adjustment for multiple comparisons. Additionally, correlation analyses performed in this study agree with previously published results (36) suggesting that inflammatory cytokines and their receptors work in tandem, and that levels are inter-correlated.

Due to the inverse relationship that exists between muscle mass, muscle strength, and other measures of physical function with inflammation in the elderly (4,38), as well as the role of inflammation in predisposing to various chronic diseases (3,18), identification of successful interventions to attenuate inflammation is a major goal of studies on healthy human aging. Although our study results do not strongly support the notion that long-term exercise can affect the panel of inflammatory biomarkers measured in this study, adoption of regular exercise does have many other health benefits for older adults (2,22,37). Indeed, the primary aim of the LIFE-P trial was to examine the effect of a structured PA intervention on physical functioning in the elderly, with published results (27) showing improved physical performance (as measured by the SPPB and 400-meter walk speed) in the PA group. Moreover, we previously demonstrated that the LIFE PA intervention reduced circulating levels of IL-6, likely the strongest systemic biomarker of inflammation in an aging population, especially in those with functional limitations and elevated IL-6 at baseline (25). Thus, findings from this study do not refute the general recommendation for exercise in older adults.

When comparing the results of this study to that of prior related research, many discrepancies exist. Evidence from epidemiologic studies in older adults show that greater levels of physical activity or fitness are associated with lower circulating levels of several inflammatory biomarkers, including IL-6, TNF-α, and CRP (5,38); although, these correlations do not prove a causal mechanism. Data from several uncontrolled exercise training studies also contradict the present findings, at least with regard to certain inflammatory biomarkers. For instance, in

patients with chronic heart failure, 12 weeks of aerobic exercise reduced TNF-α concentrations (20), 6 weeks of cycle ergometry reduced sTNFRII concentrations (21), and 16 weeks of combined aerobic and resistance exercise training decreased both TNF receptors (but not TNF-α itself) (6). Importantly, all of these studies had a small number of participants, were conducted in populations with elevated inflammatory markers (i.e. patients with congestive heart failure or obesity), and had relatively short durations. At the time of this writing, only a few randomized, controlled trials have been published that report the effects of a structured exercise intervention on inflammatory biomarkers. In agreement with our findings, 12 weeks of high-intensity progressive resistance strength training did not affect IL-1, IL-2, TNF-α, or IL-6 in healthy elderly individuals (32). Similarly, in frail, elderly, nursing home residents, 32-weeks of exercise did not induce changes in soluble receptors of cytokine activity (neopterin and sTNFRII) in the serum (17).

Given the inconsistencies between epidemiologic and randomized, controlled trial data, it has been recently suggested that the reduction in body weight, specifically body fatness, could be a potential confounding mechanism through which physical activity may reduce systemic inflammation. The cytokines IL-6, TNF-α, TNF-α receptors, IL-8, and IL-1ra are elevated in obese people, and are reduced with weight loss achieved through dietary restriction (26). In a recent epidemiologic study by Elosua et al. (7), authors report that intermediate and higher levels of self-reported physical activity and physical performance (as assessed by a 400-meter walk test) were inversely associated with IL-6, CRP, and IL-1ra. However, after adjustment for BMI, the association between physical activity and CRP and IL-1ra were not statistically significant, suggesting that only exercise interventions that reduce body weight may be effective in lowering systemic inflammation. Results from the Cardiovascular Health Study showed that greater physical activity was significantly associated with a lower inflammatory state, as well as lower BMI and waist to hip ratio (11). This suggests that central obesity is connected with an elevated inflammatory state, and that lesser degrees of central obesity associated with exercise could also be linked to inflammation. Finally, a large randomized, controlled trial showed that a two-year diet and exercise counseling intervention that reduced BMI by 4.2 kg/m^2 also reduced serum concentrations of CRP, IL-6 and IL-18, and increased levels of adiponectin (9). In our study, body weight and composition were unchanged by the intervention. Therefore, it may be that exercise interventions are effective for improving chronic inflammation only if there is concomitant weight loss.

The current findings extend those of previous studies in several ways. First, the data provide evidence from a randomized, controlled study which is the definitive research design for examining effects of a treatment. Second, to our knowledge, this is the first large scale exercise trial to include such a diverse panel of inflammatory markers, including several pro-and anti-inflammatory cytokines and their receptors. Each biomarker was chosen specifically for its known stimulation of the inflammatory response, as well as age-related increased expression (10,12,14,35). Finally, the study design controlled for seasonal, post-prandial, and diurnal variation in measured biomarkers, and the assay variability was acceptable.

Despite the strengths of this study, some limitations are worthy of note. First, cytokine expression is very variable, and given the precision of our estimates, a larger sample size may have yielded different results. Second, although the PA intervention was able to improve physical functioning in the elderly, attenuated adherence rates during the adoption and transition phases of the PA intervention may have compromised the ability to detect a significant effect of the intervention on the inflammatory biomarkers. Third, systemic measures were only obtained at one time during the day at each session, and no information was collected on local inflammation. In a recent study by Gielen and associates (13), authors reported that exercise training did not reduce serum inflammatory markers in male patients with congestive heart failure, but did reduce TNF-α, IL-6, and IL-1β gene expression in local skeletal muscle.

This suggests that exercise may elicit local anti-inflammatory effects that may not be evident in the systemic circulation, but could be very important to clinical outcomes such as sarcopenia. Lastly, results from this study can only be generalized to populations of similar demographics, including baseline inflammatory status.

Given that there is no known treatment for age-related inflammation, exploration in this area of study is still warranted. Future research should aim to determine whether type, intensity, and duration of exercise are important to intervention success. Researchers should also be careful to note study details, such as the specific parameters being studied, body weight status, and baseline inflammatory status, as variations in such characteristics may yield conflicting results and inherent confusion in the literature. Moreover, it is important to recognize that although elevated inflammatory biomarkers are associated with poorer health outcomes, inflammation remains an essential component of immune defense. Even IL-6, the cytokine most strongly associated with advancing age, morbidity, and mortality, possesses both pro- (39) and anti- (40) inflammatory properties. Thus, more data are needed to fully understand the role of inflammation in disease and aging.

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. The results of the present study do not constitute endorsement by ACSM.

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Table 1

Relevant Assay Details for Each Biomarker.

Biomarker	Sensitivity	Standard Range	Inter-Assay Variability (%)	Intra-Assay Variability (%)	Reference* Range
CRP (mg/L)	0.1	0–250	6.7	3.5	1.4 – 11.0
IL-6 (pg/mL)	0.1	0–10	9.8	3.0	3.12 – 12.5
IL-6sR (pg/mL)	6.5	31.2 – 2000	12.6	2.4	17,000 – 46,000
IL-1sRII (pg/mL)	<10	31.2 – 2000	14.8	5.5	6000 – 18000
sTNFRI (pg/mL)	<3.0	7.8 – 500	11.7	3.0	484 – 1407
sTNFRII (pg/mL)	0.6	7.8 – 500	8.4	5.3	829 – 2262
IL-8 (pg/mL)	0.03	1.6 – 5000	12.1	4.2	1.75 – 7.74
IL-15 (pg/mL)	0.11	1.03 – 750	10.9	5.1	0.98 – 3.23
Adiponectin (μg/ml)	0.25	3.9 – 250	13.9	7.1	1.20 – 19.97
IL-1ra (pg/mL)	6.26	31.2 – 2000	10.4	2.6	105 – 1062
IL-2sRα (pg/mL)	< 10	78 – 5000	9.6	2.7	410 – 2623
TNF-α (pg/mL)	0.11	0.5 – 32	15.6	5.2	0 – 2.14

All visits from one sample were run on the same plate.

* Values obtained from manufacturer kit insert, n<100 per biomarker.

Table 2

Baseline Descriptive Characteristics According to Treatment Group.

Characteristics	Physical Activity (n=182)	Successful Aging (n=186)
Age (years)	76.4±4.1	77.0±4.4
Female, n (%)	126 (69.2)	125 (67.2)
White, n (%)	140 (76.9)	141 (75.8)
Body Mass Index, kg/m^2	30.7±6.0	29.8±5.5
Smoking, n (%)		
#x02003;Never	147 (80.8)	157 (84.4)
Former	28 (15.4)	25 (13.4)
Current	7 (3.9)	4 (2.15)
Mini-Mental State Examination Score	27.0 ± 2.3	27.5 ± 2.1
Prevalent Comorbidities, n (%)		
Hypertension	126 (69.6)	129 (69.4)
Diabetes mellitus	52 (28.6)	32 (17.2)*
Cancer	28 (15.4)	32 (17.2)
Myocardial infarction	21 (11.6)	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	7.60 ± 1.46	7.46 ± 1.41

* $p < 0.01$ between groups; data are presented as means ± SD or %

Table 3

Spearman Correlation Analysis Among Inflammatory Biomarkers

	CRP	IL-6	IL-6sR	IL-1srII	sTNFRI	sTNFRII	IL-8	IL-15	Adiponectin	IL-1ra	IL-2sRα	TNF-α
CRP	1	0.39†	0.04	0.05	0.17	0.17	−0.08	0.08	−0.09	0.16§	0.12*	0.00
IL-6		1	0.04	0.05	0.30†	0.25†	0.08	0.08	−0.03	0.21†	0.07	0.13*
IL-6sR			1	0.10*	0.20†	0.16§	0.07	−0.06	0.09	0.10	0.23†	0.02
IL-1srII				1	−0.02	−0.04	0.04	−0.00	−0.01	0.03	0.00	0.12*
sTNFRI					1	0.73†	0.13*	0.17§	−0.03	0.26†	0.55†	0.16§
sTNFRII						1	0.15§	0.19†	0.00	0.29†	0.58†	0.21†
IL-8							1	−0.04	0.04	0.05	0.12*	0.14§
IL-15								1	−0.00	0.08	0.04	−0.12*
Adiponectin									1	−0.26†	0.12*	0.01
IL-1ra										1	0.13§	0.11*
IL-2sRα											1	0.17§
TNF-α												1

Spearman correlation coefficients (r) presented;

*indicates p<0.05;

§indicates p<0.01;

†indicates p<0.001

Table 4

Plasma Cytokine Concentrations According to Treatment Group at Baseline, 6 and 12 months, as well as the Between Group Difference in Change.

Biomarker	Baseline X ±SD	6 Months X ±SD	12 Months X ±SD
CRP (mg/L)			
Physical Activity	5.63±11.4	3.57±4.15	4.23±5.54
Successful Aging	4.38±5.29	4.85±8.96	4.08±4.89
Between Group Difference in Change; LS mean (95% CI)		1.70 (0.14, 3.25)	0.00 (−1.18, 1.17)
IL-6 (pg/mL)			
Physical Activity	3.38±4.04	3.26±3.59	2.98±1.91*
Successful Aging	3.36±4.01	3.75±5.15	3.59±4.65
Between Group Difference in Change; LS mean (95% CI)		0.80 (−0.08, 1.68)	0.81 (0.10, 1.51)
IL6sR (pg/mL)			
Physical Activity	36849±13720	36692±15446	35371±13238
Successful Aging	36772±14315	37920±14180	36338±12675
Between Group Difference in Change; LS mean (95% CI)		585 (−1531, 2701)	−138 (−2066, 1789)
IL-1sRII (pg/mL)			
Physical Activity	10262±3580	10334±3429	9971±3348
Successful Aging	10231±3482	9833±2912	9812±2936
Between Group Difference in Change; LS mean (95% CI)		−605 (−1049, −160)	−361 (−854, 132)
sTNFRI (pg/mL)			
Physical Activity	1626±1034	1644±1069	1620±903*
Successful Aging	1654±1104	1639±895	1752±1256
Between Group Difference in Change; LS mean (95% CI)		106 (21, 191)	103 (−20, 225)
sTNFRII (pg/mL)			
Physical Activity	2990±1045	3032±1234	2950±995
Successful Aging	3029±1208	2979±1044	3098±1217
Between Group Difference in Change; LS mean (95% CI)		−5 (−161, 152)	141 (2, 280)
IL-8 (pg/mL)			
Physical Activity	7.50±4.73	7.96±7.80	7.77±4.67*
Successful Aging	7.73±10.37	8.33±13.44	8.81±12.15
Between Group Difference in Change; LS mean (95% CI)		0.32 (−0.61, 1.26)	0.8 (0.06, 1.55)
IL-15 (pg/mL)			
Physical Activity	1.77±0.56	1.72±0.40	1.72±0.42
Successful Aging	1.76±0.42	1.74±0.45	1.80±0.54
Between Group Difference in Change; LS mean (95% CI)		0.05 (−0.02, 0.11)	0.08 (0, 0.16)
Adiponectin (μg/mL)			

Biomarker	Baseline X ±SD	6 Months X ±SD	12 Months X ±SD
Physical Activity	11.27±7.77	12.32±10.19	11.25±8.03
Successful Aging	12.12±8.93	12.45±10.24	12.76±10.21
Between Group Difference in Change; LS mean (95% CI)		−0.23 (−1.57, 1.10)	1.05 (−0.16, 2.26)
IL-1ra (pg/mL)			
Physical Activity	366±287	334±204	359±249
Successful Aging	349±295	389±425	350±373
Between Group Difference in Change; LS mean (95% CI)		66 (7, 126)	7 (−46, 60)
IL-2sRα (pg/mL)			
Physical Activity	1060±456	1105±509	1076±501
Successful Aging	1088±621	1084±511	1110±601
Between Group Difference in Change; LS mean (95% CI)		23 (−35, 81)	48 (−19, 114)
TNF-α (pg/mL)			
Physical Activity	2.68±4.26	2.60±3.93	2.43±3.54
Successful Aging	2.58±3.35	2.62±4.46	2.68±4.26
Between Group Difference in Change; LS mean (95% CI)		0.23 (−0.45, 0.90)	0.31 (−0.26, 0.89)

All biomarker group X ±SD values are unadjusted. Between group difference in change are reported as change from baseline (month 6 – baseline; month 12 - baseline), between groups (SA – PA), and are adjusted for the baseline value. N for PA group by time-point: 182 at baseline, 173 at 6 months, and 172 at 12 months for all biomarkers except for IL-8 (n=170) and IL-15 and adiponectin (n=171) at 12 months. N for SA group by time-point: 186 at baseline, 172 at 6 months, and 162 at 12 months for all biomarkers except for CRP at all time-points (n=185, 171, 161, respectively), IL-6 (n=171) at 6 months, and sTNFRI (n=161) and sTNFRII (n=160) at 12 months. All missing data were due to insufficient quantity of sample (n=6) or values below the lower limit of detection (n=4).

* indicates unadjusted statistical significance ($p<0.05$).