

Research Article

Inflammatory Marker Changes in a Yearlong Randomized Exercise Intervention Trial among Postmenopausal Women

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Abstract

Chronic low-grade inflammation is a possible risk factor for cancer that may be modifiable with long-term exercise. Very few randomized controlled trials (RCT) have studied the isolated effects of exercise on low-grade inflammation exclusively in postmenopausal women. The Alberta Physical Activity and Breast Cancer Prevention Trial, a 2-armed RCT in healthy postmenopausal women, examined how 1 year of moderate to vigorous aerobic exercise, compared with usual inactivity, influenced circulating inflammatory markers. Baseline, 6-month, and 12-month serum was analyzed by direct chemiluminescent immunoassays to measure high sensitivity C-reactive protein (CRP) and ELISAs to measure interleukin 6 (IL-6) and TNF- α . Intention to treat analyses were conducted with linear mixed models. Statistically significant differences in CRP were observed over 12 months for exercisers versus controls (treatment effect ratio = 0.87, 95% CI = 0.79–0.96, $P = 0.005$), but not in IL-6 or TNF- α . A statistically significant trend ($P_{\text{trend}} = 0.021$) of decreasing CRP with increasing exercise adherence and stronger intervention effects on CRP in women with higher baseline physical fitness ($P_{\text{heterogeneity}} = 0.040$) was found. The intervention effect on CRP became statistically nonsignificant with adjustment for dietary fiber intake change and seemed to be mediated by fat loss. Low-grade inflammation may be lowered with exercise, but confounding by dietary intake occurred and should be considered in future studies. Further trials are needed to corroborate our findings about the optimal dose of exercise required to lower CRP levels and effect modification of CRP changes by levels of body fatness and fitness. *Cancer Prev Res*; 5(1); 98–108. ©2011 AACR.

Introduction

Chronic low-grade inflammation (1) is a risk factor for cardiovascular disease (2) and possibly other chronic diseases including cancer (3, 4). To date, most etiologic research surrounding preexisting, low-grade inflammation, and cancer incidence has focused on lung and colon cancers (5). Although the body of epidemiologic evidence relating inflammation specifically to postmenopausal breast cancer risk is more limited (6–8), the association is plausible given that postmenopausal breast cancer risk is increased with body fatness (9) and decreased with physical activity

(9, 10), which are 2 factors often related to low-grade inflammation (11). In addition, recent evidence suggests that inflammation may upregulate aromatase which could result in higher production of estrogens both in the breast tissue and in circulation (12).

Interleukin-6 (IL-6), TNF- α , and C-reactive protein (CRP) are biomarkers of inflammation that have been measured extensively in cardiovascular disease research but only more recently in relation to cancer (5, 7, 8). CRP is an acute phase protein, primarily hepatocyte derived, that is widely accepted as a sensitive and reliable biomarker of systemic inflammation (13, 14), whereas IL-6 and TNF- α are inflammation-responsive and proinflammatory cytokines, respectively, that influence CRP production (1, 14). Interleukin-6 upregulates CRP expression in the liver (1, 14) and TNF- α stimulates IL-6 production during low-grade inflammation (14–16). Interleukin-6 and TNF- α derive from numerous cell types in a variety of tissues (1, 17) including, most notably, adipose tissue (18, 19).

Exercise may be one lifestyle approach to reducing systemic, low-grade inflammation (15, 20) thereby lowering chronic disease risk. Indeed, findings from observational studies in adults generally show an anti-inflammatory role for physical activity (11, 16, 21). In developing a disease prevention strategy, however, it is important to understand in whom exercise is most beneficial, at what dose, and the underlying biologic mechanisms involved. Very few

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randomized controlled trials (RCT) of exercise, independent of any dietary intervention, have studied these questions exclusively in postmenopausal women (22–27), and findings were conflicting. Postmenopausal women represent a population subgroup that may respond differently to exercise given that female sex and older age have been associated with higher CRP levels (28) that may be partly related to a general increase in intraabdominal adiposity that occurs after menopause (29).

The Alberta Physical Activity and Breast Cancer Prevention (ALPHA) Trial was an RCT that examined how a 1 year aerobic exercise intervention, compared with a usual inactive lifestyle, influenced proposed biomarkers of postmenopausal breast cancer risk. Here, we describe the effect of our intervention on inflammatory biomarkers; namely, circulating CRP, IL-6, and TNF- α , which were secondary outcomes from the trial. The primary outcomes of the trial, endogenous sex hormone (30), and adiposity changes (31), have been previously reported.

Methods

The ALPHA Trial was approved by the research ethics boards of the former Alberta Cancer Board and the Universities of Calgary and Alberta. All participants provided signed informed consent. The study design and methods for the ALPHA Trial have been previously described (30). In brief, a 2-centered, 2-armed, yearlong, randomized controlled exercise intervention trial was conducted between 2003 and 2006 in Calgary and Edmonton, Alberta, Canada among 320 postmenopausal healthy women. This trial was designed as an efficacy trial to explore the effect of exercise on proposed anthropometric and blood biomarkers for postmenopausal breast cancer risk.

Study participants and randomization

Women were identified through targeted letters of invitation sent through the Alberta Breast Screening Program, posters, and brochures through family physicians and 3 media campaigns. To be eligible for the trial, women had to be between 50 and 74 years of age, postmenopausal, cancer-free, inactive (defined as <90 min/wk of exercise or if between 90 and 120 min/wk having a VO_{2max} <34 mL/kg/min as assessed by a submaximal fitness test), no underlying comorbidities including being nondiabetic (as assessed by their physician and through a baseline blood screening), a body mass index [BMI = weight (kg)/height (m^2)] between 22 and 40, physically capable of undertaking a yearlong exercise intervention, no exogenous hormone or medication use that might affect estrogen metabolism, nonsmokers, low alcohol intake (≤ 2 drinks per day), not on a weight loss program or planning to commence one, and not planning any absences of 4 consecutive weeks or more within the year. Initial assessment for eligibility was done with a short telephone screening that was followed by physician approval, blood screening, a mammogram, and a submaximal fitness test. Once eligibility was determined a blocked, stratified randomization scheme was used; num-

bered sealed opaque envelopes were used to conceal allocation that was revealed by the Study Coordinator in Calgary at the time of randomization.

Exercise intervention

Women randomized to the exercise group were asked to undertake a yearlong, supervised intervention that consisted of 5 days per week of aerobic exercise of which 3 days were supervised by certified exercise trainers and 2 days were home-based, unsupervised sessions. Each session was at least 45 minutes of exercise at 70% to 80% heart rate reserve. The frequency, duration, and intensity of the intervention was gradually increased during the first 3 months and then maintained at full prescription for the final 9 months. Adherence was monitored with weekly exercise logs and heart rate monitors were worn to ensure that at least 50% of the sessions were done within the target heart rate zone. Several methods were used to ensure adherence to the exercise intervention that have been previously described (30).

Measurements and laboratory assays

Baseline and end of study measurements by self-administered questionnaires were taken to capture demographic, quality of life, medical, and lifestyle characteristics including dietary intake and physical activity. Physical fitness changes were assessed with a submaximal modified Balke treadmill protocol (32). Mammograms were taken at baseline and end of study as mammographic density was another outcome in our study. Fasting blood samples were collected at baseline, 6 months, and 12 months, and all bloods were processed and stored in $-86^{\circ}C$ freezers within 12 hours of collection. Blood assays were conducted at the Reproductive Endocrine Research Laboratory (University of Southern California, Los Angeles, CA). Each participant's samples from the 3 time points were included in a single batch but randomly ordered within batches that also included 2 pooled quality control samples. High sensitivity CRP was measured by solid-phase chemiluminescent immunometric assay on the Immulite 2000 analyzer (Siemens Healthcare Diagnostics). ELISAs were used to measure IL-6 and TNF- α (R&D). The sensitivities of the hsCRP, IL-6, and TNF- α assays are less than 0.01 mg/dL, 0.04 pg/mL, and 1.6 pg/mL, respectively. The intrabatch coefficients of variation (CV) for hsCRP, IL-6, and TNF- α were 4%, 9%, and 8%, respectively, and the interbatch CVs were 4%, 16%, and 12%, respectively.

Statistical analysis

An intent-to-treat analysis was used in this study to assess the intervention effect on exercisers versus controls using general linear models with inflammatory marker levels at 6 and 12 months as the outcome. Natural logarithm transformations of these biomarkers were used to correct for skewness in these data. The models included the main effects of intervention and time as well as their interaction term and were adjusted for baseline inflammatory marker values. The intervention effect was denoted as the treatment

effect ratio (TER) which is the ratio of adjusted geometric means of the biomarker effect for the exercise group over the control group calculated from the general linear models.

We also assessed possible confounding by unintended dietary change because some dietary components can exhibit pro- or anti-inflammatory properties (33–35). With guidance from review articles on inflammation and diet, we targeted the following variables for exploration as potential confounders: change in glycemic load, change in fruit and vegetable intake, change in intakes of total fiber, alcohol, fats (total, trans, saturated, polyunsaturated, and monounsaturated), and omega-3 fatty acids (docosahexaenoic acid, alpha-linoleic acid, and eicosapentaenoic acid).

We also conducted secondary analysis to examine possible mediation and moderation of the intervention effect with approaches described by Kraemer and colleagues (36) and Mackinnon and Fairchild (37). We have previously used these methods in a similar analysis of sex hormone changes in the ALPHA Trial (38).

We hypothesized that exercise-induced change in inflammatory marker levels was mediated by adiposity change that we assessed with variables for body weight, percent body fat, total body fat, and intraabdominal fat area. Our assessment of mediation used a 2-fold approach based on findings from the linear mixed models with both the intervention assignment and adiposity change predicting changes in inflammatory marker levels. First, we examined the change in TER pre- versus postadjustment for adiposity change over 6 and 12 months. If the adjustment attenuated TER, then we considered this finding to be suggestive of mediation (37). Second, we determined whether or not adiposity change had a main effect on inflammatory marker levels, adjusting for the intervention assignment. We considered this main effect in conjunction with the knowledge that (i) adiposity changes occurred during the intervention period and (ii) significantly greater changes in body fat were observed in exercisers versus controls (31), which are all proposed criteria for mediation (36).

In linear mixed models with inflammatory marker as the outcome, moderation (i.e., effect modification) was studied by determining the statistical significance of the interaction term ($P_{\text{heterogeneity}}$) between intervention group assignment and each baseline characteristic that was proposed as a moderator; namely, baseline physical fitness level, age, self-rated health, past year recreational physical activity, BMI, and baseline levels of CRP, IL-6, and TNF- α . Each model included independent variables for baseline levels of the inflammatory marker, intervention group assignment, time, and the hypothesized moderator. All potential moderators were treated as continuous variables. To help explain our findings from these analyses, intervention effects were also estimated within subgroups of each baseline characteristic. Subgroups were created by dichotomizing each variable at the median with 3 exceptions: self-rated health, measured using the SF-36 scale (39; range, 0–100), was defined as "low" (i.e., a score <82) or "high" (i.e., score \geq 82), BMI was categorized as normal weight (BMI < 25), overweight (BMI \geq 25 to <30), or obese (BMI \geq 30), and

baseline CRP was dichotomized with criteria described by Pearson and colleagues (13) that predict risk of cardiovascular disease and possibly cancer (8).

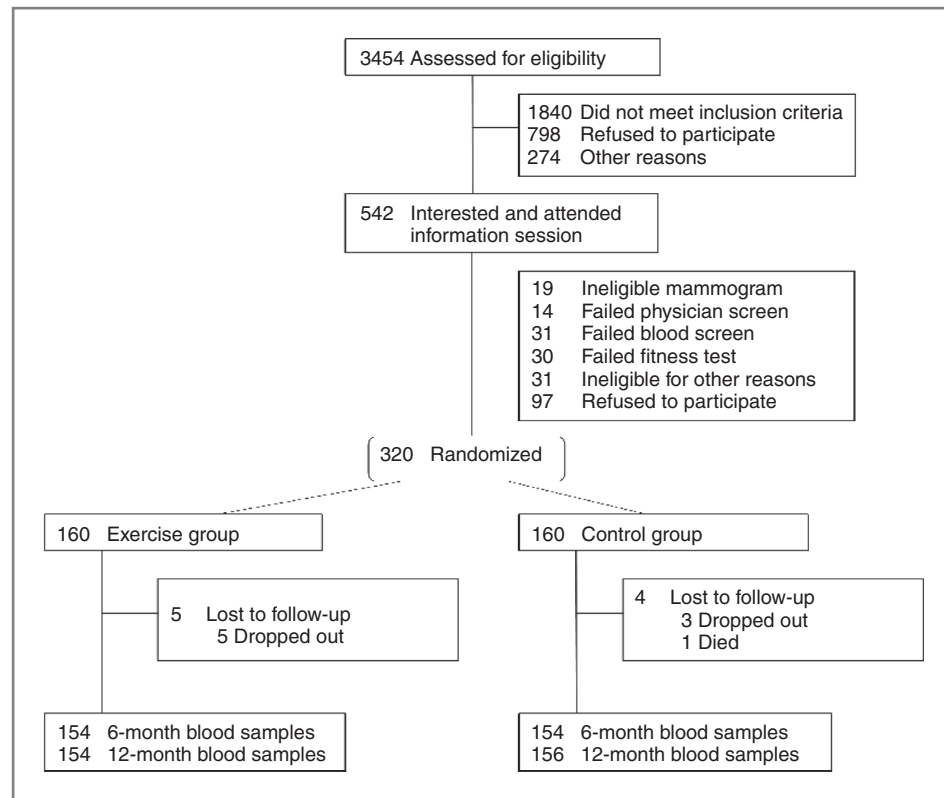
We examined correlations between inflammatory marker changes and body weight and body composition changes by Spearman rank correlation coefficient (r_s). We also examined how the change in each inflammatory marker correlated with changes in other inflammatory markers. Finally, in all analyses, we excluded the top 1% of CRP values to account for possible acute inflammation at the time of blood sampling. All analyses were conducted with SAS software (version 9.1; SAS Institute).

Results

A total of 3,454 women expressed an interest in the trial and after initial telephone screening 527 attended an information session where they provided informed consent (Fig. 1). Of these women, 327 passed through all of the eligibility screens successfully and 320 women were randomized. We had 12-month blood samples for 154 women in the exercise group and 156 controls that were included in these analyses. Baseline characteristics for the 2 groups were similar (Table 1). As expected, our study population was mainly overweight (20% were normal weight, 80% were overweight or obese, with a BMI range of 20.4–43.9) with a mean BMI of 29 for both groups. Participants on average had a very low alcohol intake (<0.5 alcoholic drinks per day), were relatively unfit ($VO_{2\text{max}}$ around 27 mL/kg/min for both groups) and had low levels of weekly physical activity (11 MET-h/wk of exercise or sports activities over the past year). Few women were regular users of nonsteroidal anti-inflammatory drugs (NSAID) or statins at baseline, with approximately 13.2% of the study population reporting use of NSAIDs and 13.4% statins. Baseline CRP levels were relatively low, with a median value around 1.3 mg/L (range: 0.11–14.50 mg/L, 8 exercisers and 9 controls had CRP values >10 mg/L). CRP levels between 3 and 10 mg/L are generally considered minor elevations in CRP or "low-grade inflammation" whereas levels more than 10 mg/L are considered clinically significant inflammatory states (1, 28).

The exercise intervention had a significant effect on lowering CRP levels over 12 months (Table 2). When comparing the change in exercisers versus controls, we observed a TER of 0.87 (95% CI = 0.79–0.96) indicating a greater decrease in CRP levels in the exercise group. Excluding regular users of NSAIDs or statin medications from this model did not alter the TER or its statistical significance. No statistically significant effects of exercise on IL-6 or TNF- α were observed. We then tested for potential confounding of the intervention effect on CRP by adjusting the model for change in total dietary fiber intake. The intervention effect was attenuated and became statistically nonsignificant (TER = 0.90, 95% CI = 0.80–1.02). This attenuation can be explained because among the controls there was a significant average decrease in total fiber intake over the 12-month intervention period (mean = -1.9 g/d, 95% CI = -3.2 to -0.6) that did not occur in

Figure 1. Recruitment, randomization, and follow-up of participants in the Alberta Physical Activity and Breast Cancer Prevention Trial. [Here, the top 1% of CRP measures (10 of 938) was excluded from analyses.]



exercisers (mean = 0.5 g/d, 95% CI = -0.4 to 1.3). Furthermore, among the controls, CRP changes were significantly correlated with total fiber intake ($r_s = -0.19$, $P = 0.02$) suggesting that in general women who decreased fiber intake during the intervention period experienced increases in CRP levels. For no other dietary variables was the CRP model adjusted because, unlike fiber intake, no other dietary change differed significantly between the exercise and control groups and, at the same time, was significantly related to CRP changes in our study population thus meeting all criteria for confounding.

We examined whether the effect of the exercise intervention on the inflammatory biomarker changes was altered by level of adherence to the exercise program by categorizing the women in the exercise group into 3 levels of adherence (Table 3). For CRP, we observed a statistically significant trend ($P = 0.021$) with increasing adherence suggesting that higher doses of exercise may reduce this inflammatory marker to a greater extent.

We subsequently investigated mediation of CRP changes by decreased body weight or body fat (Table 4). Mediation of IL-6 and TNF- α changes was not studied because no intervention effect was observed for these markers. The intervention effect on CRP changes essentially disappeared with adjustment for weight and body fat changes, which was suggestive of mediation. In addition, all measures of adiposity change had main effects on CRP levels, adjusting for the intervention assignment (P for mediator < 0.001). When exercise and control groups were combined, CRP changes

correlated significantly with changes in body weight, percent body fat, total body fat, and intraabdominal fat area ($P < 0.0001$; $r_s = 0.33, 0.28, 0.34, \text{ and } 0.33$, respectively).

In statistical tests for moderation (Table 5), 2 significant moderating effects were detected with respect to baseline physical fitness and BMI. It seemed that the intervention effect on CRP changes was modified by baseline physical fitness whereby women with higher $VO_{2\max}$ levels at baseline experienced a stronger intervention effect than women with lower baseline fitness ($P_{\text{heterogeneity}} = 0.040$). Baseline BMI also modified the effect of the exercise intervention for both IL-6 ($P_{\text{heterogeneity}} = 0.053$; borderline significance) and TNF- α ($P_{\text{heterogeneity}} = 0.030$). To characterize significant interactions, we examined intervention effects within subgroups of the baseline characteristics that were proposed as moderators. The TERs for IL-6 decreased with increasing BMI whereas for TNF- α an opposite trend was found. With respect to CRP, we found that the subgroup with baseline CRP levels of 3 mg/L or more experienced more intervention effects (TER = 0.78, 95% CI = 0.60–1.01) than those with lower baseline CRP levels (TER = 0.90, 95% CI = 0.79–1.02) but neither effect was statistically significant, nor was there any evidence for moderation ($P_{\text{heterogeneity}} = 0.354$) when baseline CRP was treated as a continuous variable.

Discussion

In a yearlong exercise intervention in postmenopausal women, CRP levels decreased significantly in exercisers

Table 1. Baseline characteristics of study participants, Alberta Physical Activity and Breast Cancer Prevention Trial, $n = 320$

Baseline characteristic	Exercisers ($n = 160$)	Controls ($n = 160$)
	Mean \pm SD	Mean \pm SD
Age (y)	61.2 \pm 5.4	60.6 \pm 5.7
Body composition measurements		
BMI (kg/m ²)	29.1 \pm 4.5	29.2 \pm 4.3
Intraabdominal fat area (cm ²)	101.4 \pm 55.4	103.2 \pm 56.0
Total body fat (kg)	30.9 \pm 8.2	31.3 \pm 8.6
Percent body fat	42.2 \pm 4.9	42.4 \pm 5.7
Alcohol intake (g/d)	4.4 \pm 5.9	5.0 \pm 7.6
Total energy intake (kcal/d)	1,551.2 \pm 598.7	1,527.3 \pm 535.0
Protein intake (g/d)	62.3 \pm 26.7	61.6 \pm 23.1
Total carbohydrate intake (g/d)	196.6 \pm 72.8	204.0 \pm 79.3
Total fat intake (g/d)	59.0 \pm 33.2	53.0 \pm 24.1
Total dietary fiber intake (g/d)	19.6 \pm 9.1	20.5 \pm 9.7
Total glycemic load	92.2 \pm 35.7	94.1 \pm 38.0
Past year total physical activity (MET-h/wk)		
Total physical activity	114.2 \pm 57.6	129.1 \pm 77.9
Occupational activity	50.4 \pm 49.1	52.2 \pm 57.9
Household activity ^a	52.9 \pm 34.3	63.9 \pm 53.5
Recreation activity	10.2 \pm 11.8	12.1 \pm 13.6
Maximal oxygen consumption (mL/kg/min)	27.1 \pm 6.2	26.8 \pm 6.0
	n (%)	n (%)
Full-time employment	82 (55)	79 (51)
Education beyond high school	112 (70)	102 (64)
Married/common-law	113 (71)	125 (78)
White/Caucasian	144 (91)	145 (91)
Ever used hormone therapy	75 (47)	71 (44)
Regular NSAID user ^c	18 (11)	24 (15)
Regular statin user ^c	25 (16)	18 (11)
	Median (IQR)	Median (IQR)
CRP ^b (mg/L)	1.3 (0.6–3.0)	1.2 (0.7–2.6)
IL-6 (pg/mL)	1.5 (1.1–2.0)	1.4 (1.1–2.2)
TNF- α (pg/mL)	1.4 (1.2–1.8)	1.4 (1.2–1.8)

Abbreviation: IQR, interquartile range.

^aThere were no statistically significant differences at baseline between exercisers and controls for these variables except for household activity, P value = 0.030.

^bTop 1% of CRP measures were excluded from analyses resulting in the exclusion of 3 controls and 1 exerciser; resultant sample sizes for CRP were $n = 159$ for exercisers and $n = 157$ for controls.

^cRegular use defined as at least 3 times weekly for at least 1 month during the past year.

relative to controls, however, no significant intervention effects on circulating IL-6 or TNF- α were observed. Our analyses suggest that (i) the significant intervention effect on CRP levels may be partly explained by decreased dietary fiber intake in the control group that may have increased CRP levels in controls (33–35) and (ii) decreases in CRP levels were mediated primarily by fat loss. Secondary analyses implied that intervention effects on CRP levels were stronger with increasing exercise adherence, and that intervention effects on CRP levels were stronger in women who were more physically fit at baseline. Weaker evidence sug-

gested that effects on IL-6 were stronger in women with higher baseline BMI and that TNF- α levels may also be moderated by baseline BMI.

To our knowledge, 5 comparable RCTs have described the isolated effect of long-term exercise on circulating CRP, IL-6, or TNF- α levels exclusively in cancer-free postmenopausal women (22–27). These 5 studies were 6 (22, 27) or 12 months (23–26) in duration involving mainly aerobic exercise. All 5 RCTs examined CRP changes whereas 2 RCTs also measured IL-6 and/or TNF- α levels (22, 25). With respect to CRP, only one of the 5 RCTs reported a statistically

Table 2. Inflammatory biomarker concentrations for exercisers and controls 6 and 12 months from baseline

	Baseline	6 months	12 months	Treatment effect ratio of exercise/control (95% CI)^b	Between-group P
	Geometric mean (95% CI)^a	Geometric mean (95% CI)	Geometric mean (95% CI)		
CRP ^a (mg/L)					
Exercisers ^c	1.4 (1.2–1.6)	1.2 (1.1–1.4)	1.1 (1.0–1.3)	0.87 (0.79–0.96)	0.005
Controls ^d	1.3 (1.1–1.5)	1.3 (1.1–1.5)	1.3 (1.1–1.5)		
IL-6 (pg/mL)					
Exercisers	1.5 (1.4–1.6)	1.5 (1.4–1.6)	1.5 (1.4–1.7)	0.99 (0.92–1.07)	0.785
Controls	1.6 (1.4–1.7)	1.5 (1.4–1.7)	1.6 (1.4–1.7)		
TNF- α (pg/mL)					
Exercisers	1.5 (1.4–1.6)	1.5 (1.4–1.6)	1.4 (1.3–1.5)	1.00 (0.97–1.04)	0.912
Controls	1.4 (1.4–1.5)	1.4 (1.4–1.5)	1.4 (1.3–1.4)		

^aTop 1% of CRP measures (10 of 938) were excluded from analyses; 3 controls and 1 exerciser were excluded.

^bThe TER was calculated from a general linear model for each biomarker, estimating a parameter with anti-logarithm corresponding to the ratio of adjusted geometric means for the exercise intervention group over the control group; this ratio was assumed to be common at 6 months and 12 months postrandomization. A ratio less than 1.0 indicates lower inflammatory marker levels in exercisers relative to controls at 6 and 12 months; a ratio greater than 1.0 indicates a higher inflammatory marker levels in exercisers; and a ratio equal to 1.0 indicates no difference between exercisers and controls.

^cExercise group: *n*, baseline = 160, 6 months = 154, 12 months = 154.

^dControl group: *n*, baseline = 160, 6 months = 154, 12 months = 156.

significant intervention effect after 12 months of exercise at 60% to 75% maximal heart rate for 45 minutes or more per day, 5 days per week (25), a prescription similar to that in the ALPHA Trial. The other 4 trials prescribed less intense and/or less frequent exercise. In a meta-analysis by Kelley and Kelley (40) of 5 aerobic exercise RCTs, 4 weeks or longer in 323 adult men and women, a statistically significant decrease in CRP levels was not observed. It has been speculated, however, that exercising 3 to 4 days per week for 40 to 80 minutes per day at an intensity of 70% to 80% VO_{2max} can lower CRP levels within 2 months (41). Therefore, our suggestive finding that exercise reduced CRP levels may be partly attributable to the higher intensity and duration of the exercise that was prescribed in the ALPHA Trial. Our secondary analysis of exercise adherence similarly implied that higher exercise dose may be more effective for decreasing circulating CRP levels, with the greatest decreases occurring in women who exercised at least 150 minutes per week. A comparable RCT in postmenopausal women also showed a dose-response relation between exercise duration and CRP changes (25) but the Dose Response to Exercise in Women (DREW) Trial, which was an RCT designed specifically to test the effect of exercise dose on physiologic outcomes, did not show a dose-response trend with CRP changes in 421 postmenopausal women (27). Women prescribed the highest level of exercise in the DREW Trial exercised, on average, 192 minutes (3.1 sessions) per week with an intensity goal of only 50% VO_{2max} . Our secondary analysis also showed, interestingly, that intervention effects on CRP levels became stronger in women who were more physically fit at baseline. The reason for this finding is unknown but

could relate perhaps to these fitter women exercising with greater intensity. We did not find any linear association between exercise adherence and baseline fitness levels.

It is unclear whether or not baseline CRP levels moderate the effect of exercise on this biomarker. Some trials have shown exercise to decrease CRP levels only in subgroups with higher CRP levels at baseline (using a cut point of 3.0 mg/L; ref. 42), or shown baseline CRP level to be a significant predictor of exercise-induced CRP changes (24), whereas others have not (26, 43). We found no compelling evidence of moderation by baseline CRP levels in the ALPHA Trial, although the median baseline CRP level in our study was relatively low (28) partly because of our exclusion criteria (e.g., we excluded women who were HRT users, smokers, or with major comorbidities). Significant moderation might have been found in a more diverse study population, perhaps including a higher proportion of participants with baseline CRP levels above 3 mg/L. Most likely, such moderation of an exercise effect would depend on the cause of elevated CRP levels at baseline, for example, smoking, HRT use, obesity, and so on (28), but only trials designed specifically to explore these potential moderating factors could determine this.

Although there is convincing evidence that obesity creates an inflammatory state (44) and that weight loss decreases circulating CRP levels in adults (45, 46), controversy surrounds the role of exercise that may occur independently of weight loss; it is postulated that the relative contributions from "fitness" versus "fatness" on inflammatory markers may depend on gender, age, and disease status (47). In this group of disease-free postmenopausal women, the effect of our intervention on CRP levels seemed to have been

Table 3. Inflammatory biomarker concentrations at baseline and 12 months in controls and exercisers stratified by adherence level

	Baseline	12 Months	Ratio 12 months/ baseline (95% CI) ^c	Percent change ^d	<i>P</i> ^e	<i>P</i> _{trend} ^f
	Geometric mean (95% CI)	Geometric mean (95% CI)				
CRP ^b (mg/L)						
Controls ^a	1.3 (1.1–1.5)	1.3 (1.1–1.5)	0.99 (0.89–1.11)	–0.6	Ref	0.021
<150 min/wk ^a	1.3 (1.0–1.7)	1.2 (0.9–1.5)	0.92 (0.74–1.14)	–8.2	0.489	
150–225 min/wk ^a	1.5 (1.2–2.0)	1.3 (1.0–1.6)	0.82 (0.68–1.00)	–17.7	0.146	
>225 min/wk ^a	1.2 (0.9–1.6)	1.1 (0.7–1.3)	0.82 (0.72–0.94)	–17.8	0.036	
IL-6 (pg/mL)						
Controls	1.6 (1.4–1.7)	1.6 (1.4–1.7)	1.01 (0.93–1.10)	1.1	Ref	0.633
<150 min/wk	1.4 (1.1–1.7)	1.6 (1.2–2.0)	1.11 (0.91–1.36)	11.4	0.479	
150–225 min/wk	1.5 (1.4–1.7)	1.5 (1.3–1.7)	0.97 (0.86–1.11)	–2.6	0.572	
>225 min/wk	1.4 (1.2–1.7)	1.5 (1.2–1.8)	1.02 (0.85–.21)	1.5	0.813	
TNF- α (pg/mL)						
Controls	1.4 (1.4–1.5)	1.4 (1.3–1.4)	0.94 (0.91–0.97)	–6.3	Ref	0.910
<150 min/wk	1.6 (1.4–1.8)	1.4 (1.2–1.5)	0.87 (0.78–0.97)	–13.0	0.142	
150–225 min/wk	1.5 (1.4–1.7)	1.5 (1.3–1.6)	0.94 (0.88–1.01)	–5.7	0.535	
>225 min/wk	1.5 (1.4–1.6)	1.3 (1.2–1.5)	0.91 (0.86–0.97)	–8.6	0.487	

^a*n* = 156, 40, 67, and 47 for controls and 3 exercise adherence levels of 150 or less, 150 to 225, more than 225 min/wk, respectively.

^bTop 1% of CRP measures were excluded from analyses; resulting sample sizes were *n* = 153, 38, 65, and 46, respectively—in total 8 less than before.

^cRatio of geometric means at 12 months to geometric means at baseline.

^dPercentage biomarker change at 12 months from baseline for that level or group.

^e*P* values for biomarker change at 12 months from baseline between controls and that level of exercise adherence, adjusted for the baseline value.

^fTrend test for biomarker change at 12 months from baseline across controls and 3 adherence groups, adjusted for the baseline value.

mediated almost entirely by changes in body composition. In linear mixed models of CRP change, the TERs were attenuated to almost null after adjusting for change in total body fat, percent body fat, or intraabdominal fat area. Two other RCTs in postmenopausal women (25, 27) also revealed adiposity-related CRP changes, whereas another comparable RCT showed CRP decreases that were unrelated to weight loss (26). Conflicting reports may be due to the extent of fat loss in these trials. In the ALPHA Trial exercisers lost, on average, 2.3 kg of body weight and 2.4 kg and 2.0% of body fat (31). In the second RCT, a significant intervention effect on CRP levels was found only in the subgroup who lost more than 2.0% body fat (25), whereas in the DREW Trial, the mean change in CRP, adjusted for baseline CRP and intervention group, was significantly more in women who lost the most weight (>2.6 kg) during the trial than the other subgroups (27). In the fourth RCT of postmenopausal women, in which CRP decreased independently of weight loss (suggesting the involvement of a fat-independent mechanism), an average of only 1.3 kg of body fat was lost in the exercise group (26). Among the proposed mechanisms relating CRP changes to exercise (46–48), loss of body fat predominates and, for women in the ALPHA Trial, seems the most plausible. The infiltration of inflammatory cells into adipose tissue ultimately increases circu-

lating CRP levels (46) by producing TNF- α and IL-6 (18, 44). Conversely with fat loss, circulating levels of TNF- α and IL-6 might be expected to decrease. Thus, it was somewhat surprising in the ALPHA Trial that IL-6 and TNF- α levels were unchanged with exercise.

Another mechanistic pathway to consider when examining the role of exercise in breast cancer etiology is the impact of estrogen on inflammation. The role of estrogens in inflammation is complex with both pro- and anti-inflammatory roles depending upon several factors such as the target organs involved, the expression of estrogen receptors, intracellular metabolism of estrogens that all lead to biologically active metabolites with different anti- and proinflammatory functions (49). In postmenopausal women, estrogen typically represses inflammatory response, and a decrease in estrogen levels through exercise could potentially cause an increase in systemic inflammation (50). In the ALPHA Trial, we observed a decrease in estradiol and free estradiol levels but there was no corresponding increase in CRP suggesting that endogenous estrogens may not have had a strong influence on low-level inflammation in this study.

Of other comparable RCTs in postmenopausal women, only the DREW Trial examined changes in both IL-6 and TNF- α levels and as with our study, found no significant

Table 4. Exercise intervention effects on CRP levels before and after adjustment for body composition changes

Before adjustment		After adjustment	
Treatment effect ratio of exercise/control (95% CI) ^a	Hypothesized mediator	Treatment effect ratio of exercise/control (95% CI) ^a	<i>P</i> _{mediator} ^b
0.87 (0.79–0.96)	Change in weight	0.95 (0.84–1.07)	<0.001
	Change in percent body fat	0.97 (0.86–1.10)	<0.001
	Change in total body fat	0.96 (0.85–1.09)	<0.001
	Change in intraabdominal fat area	0.97 (0.86–1.10)	<0.001

NOTE: Top 1% of CRP measures were excluded from analyses.

^aThe TER was calculated from a general linear model estimating a parameter with antilogarithm corresponding to the ratio of adjusted geometric means for the exercise intervention group over the control group; this ratio was assumed to be common at 6 months and 12 months postrandomization. A ratio less than 1.00 indicates lower CRP levels in exercisers relative to controls at 6 and 12 months; a ratio more than 1.00 indicates a higher CRP levels in exercisers; and a ratio equal to 1.00 indicates no difference between exercisers and controls. The model after adjustment has one more covariate compared with the model before adjustment: change in hypothesized mediator at 6 and 12 months.

^b*P* value for the association between mediator and outcome after adjustment for intervention assignment.

changes in these markers in exercise or control groups (22). Furthermore, in another comparable RCT (25), exercise did not seem to alter IL-6 levels. Yet in a smaller RCT of obese postmenopausal women ($n = 35$) with no control group (51), those assigned to 6 months of a combined hypocaloric diet and exercise intervention experienced significant decreases in levels of IL-6, CRP, and soluble receptors for IL-6 and TNF- α (sTNFR1), whereas women assigned to a diet-only intervention did not, implying the biomarker changes were driven by exercise. Neither group experienced changes in TNF- α or sTNFR2 levels.

It is unclear why exercise-induced changes in IL-6 and TNF- α levels were not apparent in the ALPHA Trial or in other trials; however, several possible reasons exist. The first possible reason relates to fat loss. Previous research suggests that approximately 25% of circulating IL-6 derives from adipose tissue (19) and in our trial, IL-6 changes correlated significantly with all measures of adiposity change. Thus, it is possible that the exercise-induced fat loss experienced in the ALPHA Trial was insufficient to observe a significant decrease in circulating IL-6 levels. In addition, our tests for moderation, albeit of borderline statistical significance, suggested that IL-6 decreases were greater in women with higher baseline BMI (Table 5) which in turn correlated significantly with body fat changes during the trial (data not shown). In contrast, we found less evidence of moderation and no correlation between circulating TNF- α and adiposity changes. In a study comparing lean versus overweight and obese men and women, Kern and colleagues (18) found that obesity was related to the secretion of TNF- α from adipose tissue but not to plasma TNF- α , whereas plasma IL-6 levels more strongly related to obesity than to IL-6 secretion from adipose tissue. Therefore, in ALPHA Trial participants, the possibility remains that exercise caused local changes in TNF- α production (e.g., in adipose

tissue) that were not reflected in our measurement of circulating TNF- α , possibly on account of its short half-life (52). We did not measure changes in the more stable TNF soluble receptors 1 and 2 which might have better shown the effects of exercise on the biological activity of TNF- α (53).

Our study offers several strengths relative to other RCTs in postmenopausal women that compared exercise with a control group (22–27). Second only to the DREW trial ($n = 421$; ref. 27), we examined one of the largest group of postmenopausal women, but unlike the former study, we excluded HRT users (45% were HRT users at baseline in the DREW Trial) and included normal weight women as well as women who were overweight and obese. In addition, aerobic exercise in the DREW trial was prescribed at lower intensity (50% peak VO_2 (27) versus 70% to 80% heart rate reserve in the ALPHA Trial). The exercise prescription in the ALPHA Trial was relatively intense, which may be a requirement for reducing low-grade inflammation (41), and was supervised for 3 of the 5 prescribed days of exercise per week. Furthermore, we employed sophisticated measures of body fat changes that enhanced our examination of fat loss as a potential mediator of exercise-induced inflammatory marker changes.

In terms of limitations, we examined only a small subset of inflammatory markers in blood, and our study did not consider polymorphisms in the genes encoding CRP, IL-6, or TNF- α which could modify individual changes in these markers subsequent to long-term exercise. In addition our findings may not be generalizable to all women because the ALPHA Trial focused on healthy, predominantly white women who were nonsmokers and nonusers of HRT. The baseline CRP levels in our trial were relatively low, predicting "average" risk for cardiovascular disease (13) and possibly cancer (8) whereas women with higher levels of

Table 5. Exercise intervention effects on inflammatory biomarkers, stratified by potential moderators

Potential moderator ^a		TER ^d (95% CI)		
Baseline level	n ^c	CRP	IL-6	TNF- α
Physical fitness (VO ₂ max)				
<27.5 mL/kg/min	82/80	0.98 (0.83–1.16)	1.03 (0.92–1.14)	0.99 (0.93–1.05)
>27.5	77/79	0.77 (0.66–0.91) <i>P</i> ^e = 0.040	0.95 (0.84–1.08) <i>P</i> ^e = 0.373	1.01 (0.95–1.07) <i>P</i> ^e = 0.439
Age, y				
≤60	73/81	0.85 (0.71–1.01)	0.94 (0.83–1.06)	0.98 (0.93–1.03)
>60	87/78	0.90 (0.77–1.05) <i>P</i> ^e = 0.615	1.03 (0.92–1.15) <i>P</i> ^e = 0.256	1.02 (0.95–1.09) <i>P</i> ^e = 0.476
Self-rated health ^b				
Low	88/76	0.94 (0.80–1.11)	0.93 (0.82–1.05)	1.00 (0.93–1.06)
High	71/81	0.79 (0.67–0.92) <i>P</i> ^e = 0.119	1.05 (0.93–1.17) <i>P</i> ^e = 0.153	1.00 (0.95–1.06) <i>P</i> ^e = 0.905
Past year recreational activity				
<7 MET-h/wk	87/74	0.81 (0.69–0.96)	0.93 (0.83–1.04)	1.03 (0.97–1.09)
≥7	73/85	0.94 (0.80–1.11) <i>P</i> ^e = 0.227	1.04 (0.92–1.17) <i>P</i> ^e = 0.187	0.97 (0.92–1.04) <i>P</i> ^e = 0.193
BMI				
≤25 kg/m ²	34/30	0.88 (0.70–1.11)	1.16 (0.94–1.44)	0.93 (0.81–1.08)
>25–≤30	63/67	0.91 (0.76–1.10)	1.02 (0.91–1.14)	1.01 (0.95–1.06)
>30	63/63	0.84 (0.69–1.03) <i>P</i> ^e = 0.735	0.87 (0.76–1.00) <i>P</i> ^e = 0.053	1.03 (0.98–1.09) <i>P</i> ^e = 0.030
CRP				
<3.0 mg/L	119/125	0.90 (0.79–1.02)		
≥3.0	40/32	0.78 (0.60–1.01) <i>P</i> ^e = 0.354		
IL-6				
<1.45 pg/mL	77/85		1.08 (0.98–1.19)	
≥1.45	83/75		0.90 (0.78–1.03) <i>P</i> ^e = 0.061	
TNF- α				
<1.4 pg/mL	78/83			1.03 (0.98–1.08)
≥1.4	82/77			0.97 (0.90–1.04) <i>P</i> ^e = 0.163

NOTE: Top 1% of CRP measures were excluded from analyses.

^aLevel of potential moderator at baseline.

^bSelf-rated health measured by self-administered questionnaire using SF-36 scale (range, 0–100) where low was a score of $x < 82$ and high was $x \geq 82$.

^cNumber of exercisers/number of controls.

^dThe TER was defined as the geometric mean ratio, estimated from least square means, for the difference in treatment effect between exercisers and controls averaged across the entire study period, and then back log transformed. A ratio less than 1.00 indicates lower inflammatory marker levels in exercisers relative to controls at 6 and 12 months; a ratio more than 1.00 indicates higher inflammatory marker levels in exercisers; and a ratio equal to 1.00 indicates no difference between exercisers and controls.

^eStatistical significance of the interaction term between intervention group and the potential moderator. Note that all moderators were treated as continuous variables when calculating this *P* value for heterogeneity.

low-grade inflammation might experience a different level of benefit from exercise.

In conclusion, our findings suggest that CRP levels can be lowered with long-term, moderate to vigorous aerobic exercise in postmenopausal women with low CRP levels

at baseline, although decreased dietary fiber intake in the control group may have confounded our results. Our evidence that exercise-induced CRP changes were mediated by fat loss implies that other weight loss interventions will also be effective for lowering CRP levels, as has

already been shown in the literature (45, 46), although concurrent roles for fat-independent mediators remain plausible. The decrease in cancer risk that might result from the CRP changes experienced in the ALPHA trial is unknown. The Rotterdam Study was a prospective cohort study of cancer risk in 7,017 men and women age 55 years or more that were followed for 10.2 years on average (8). That study estimated a 1.3% increase in cancer risk (colorectal, breast, lung, and prostate) for every 10% increase in CRP levels. In the ALPHA Trial, CRP levels were lowered by an average of 21.4% in the exercise group. Extrapolating from the Rotterdam Study, we estimate that the ALPHA Trial exercise intervention would have decreased cancer risk by 2.8% with perhaps greater risk reductions for specific cancer sites (e.g., lung; refs. 8, 54). Currently no long-term RCTs in exclusively postmenopausal women have shown that exercise alone alters IL-6 or TNF- α levels significantly. Although it is possible that exercise has no impact on these inflammatory markers in postmenopausal women, greater insight might be gained through future study of the soluble receptors for IL-6 and TNF- α that influence the activities of these cytokines. Further trials are needed to corroborate our findings about the optimal dose of exercise that is required to induce CRP changes and effect modification of CRP changes by baseline physical fitness and IL-6 and TNF- α changes by baseline BMI. Our results further imply that dietary confounding should be considered in

future epidemiologic studies of exercise and low-grade inflammation.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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