# Inflammatory marker changes in postmenopausal women after a year-long exercise intervention comparing high versus moderate volumes

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## ABSTRACT

This randomized dose comparison trial examined if higher exercise volume decreased inflammatory biomarkers, associated with postmenopausal breast cancer risk, more than moderate exercise volume. The Breast Cancer and Exercise Trial in Alberta (BETA) was a two-center, two-armed randomized trial in 400 inactive, healthy, postmenopausal women, aged 50-74 years, with a body mass index of 22-40 kg/m$^2$. Participants were randomized to high (300 minutes/week) or moderate (150 minutes/week) volumes of aerobic exercise while maintaining usual diet. Fasting blood concentrations of C-reactive protein (CRP), interleukin-6 (IL-6), and tumour necrosis factor-alpha (TNF-α), were measured at baseline, six, and 12-months. Intention-to-treat analysis was performed using linear mixed models adjusted for baseline biomarker concentrations. Intention-to-treat analyses of 386 (97%) participants showed no statistically significant group differences for changes in biomarker levels at 6 and 12 months. Additionally, we did not observe any modification of this effect by baseline characteristics of participants. In post hoc analyses based on self-selected exercise level (measured in minutes/week) , CRP decreased by 22.45% for participants who exercised >246 minutes/week (highest quintile) and increased by 0.07% for those who exercised <110 minutes/week (lowest quintile, *P-trend*=0.04), adjusted for baseline covariates. When this analysis was restricted to include exercise time in the target heart rate zone only, statistically significant trends were observed for both CRP (*P*<0.01) and IL-6 (*P*=0.04). Prescribing 300 minutes/week of moderate-to-vigorous aerobic exercise did not improve inflammatory markers compared to 150 minutes/week in postmenopausal women. Decreases in CRP were observed with higher self-selected exercise volume .

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**INTRODUCTION**

Increased levels of pro-inflammatory biomarkers such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumour necrosis factor-$\alpha$ (TNF-$\alpha$) are associated with chronic diseases, such as coronary heart disease, diabetes and, more recently, cancer (1). Intra-abdominal adiposity increases generally in women post-menopause that can contribute to increased levels of adipocytokines, such as CRP, IL-6, and TNF-$\alpha$ (2, 3). Indeed, several recent case-control studies have demonstrated an association between breast cancer risk and increased levels of inflammatory cytokines (4, 5), predominantly in obese, postmenopausal women (6, 7), although these associations have not been consistently observed (8, 9). Of these three pro-inflammatory cytokines, CRP is the most studied as a risk factor for breast cancer in prospective studies. A newly published meta-analysis showed a modest significant increase in risk between the highest and lowest categories of circulating CRP (10), confirming the results of a previous meta-analysis of breast cancer risk with increased levels of both CRP and IL-6 (11).

CRP, IL-6 and TNF-$\alpha$ are characteristic of a low-grade chronic inflammatory state that is increased with physical inactivity or sedentary behaviour (12, 13). Increased physical activity has been shown to reduce chronic, low-grade inflammation and is therefore a promising lifestyle intervention for cancer prevention (14, 15). To date, there have been four randomized controlled trials (RCTs) in postmenopausal women that have examined the effect of physical activity on biomarkers for cancer prevention (16-19). Of these, three have examined the impact on inflammatory biomarkers and all found significant decreases in CRP levels with an exercise intervention (20-22). Additionally, several recent randomized and non-randomized controlled trials controlled trials have demonstrated a decrease in inflammatory biomarkers following an exercise intervention (23-27); however, not all of these results were independent of dietary

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interventions and some studies have shown no effect (28, 29). While there is substantial evidence supporting the role of physical activity in decreasing circulating levels of inflammatory biomarkers, the optimal dose of exercise has yet to be determined.

In our previous randomized controlled trial, the Alberta Physical Activity and Breast Cancer Prevention (ALPHA) Trial, we demonstrated that a one-year aerobic exercise intervention (prescribed 225 minutes per week) decreased circulating CRP, IL-6, and TNF-α levels compared to a usual inactive lifestyle defined as less than 90 minutes per week of physical activity (22). In an exploratory analysis, we also found that increasing exercise volume was associated with statistically significant linear trends of decreasing levels of these inflammatory markers. The Breast Cancer and Exercise Trial in Alberta (BETA) was designed to investigate the exploratory dose-response findings from the ALPHA Trial further to determine the effect of different volumes (150 versus 300 minutes per week) of aerobic exercise on circulating inflammatory biomarkers.  The primary outcome of this trial was changes in adiposity (30), where we observed that higher volumes of exercise were more effective in reducing total fat and other adiposity measures compared to lower volumes. The objective of the present study was to determine the effect of the high compared to the moderate volume exercise intervention on circulating levels of CRP, IL-6, and TNF-α, which were secondary outcomes in BETA.


## MATERIALS AND METHODS

### Study Population

Detailed methods of BETA have been previously described elsewhere (31). Briefly, the trial was a two-centre, two-armed, year-long randomized controlled exercise intervention trial in 400 healthy, postmenopausal women conducted between 2010-2013. The study protocol was

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approved by the Alberta Cancer Research Ethics Committee, the Conjoint Health Research

Ethics Board of the University of Calgary and the Health Research Ethics Board of the

University of Alberta. Eligibility criteria included: 1) a resident of Calgary or Edmonton, 2) 50-

74 years of age, 3) postmenopausal, 4) no hormone replacement therapy within the 12 months

prior to enrolment, 5) body mass index (BMI) between 22-40 kg/m$^2$, 5) drinkers of ≤14

alcoholic drinks per week, 6) non-smoker, 7) inactive, 8) able to do unrestricted or progressive

physical activity as assessed by physician screening, 9) levels in the normal ranges of

cholesterol, fasting blood glucose (<7 mmol/L), thyroid stimulating hormone and alanine

aminotransferase, 10) cancer-free and 11) not on a weight loss program or planning to

commence one. Inactivity was defined as <90 minutes per week of exercise or if between 90 and

120 minutes per week, having a VO$_{2max}$ <34.5 ml/kg/min as assessed by a submaximal fitness

test.


**Exercise Intervention**

Women were randomized within each centre to either a moderate or high volume aerobic

exercise intervention of 150 minutes per week (n=200) or 300 minutes per week (n=200),

respectively, based on Health Canada's physical activity guidelines (32, 33) and those from the

American Cancer Society (34, 35). Exercise sessions took place five times/week at 65-75% heart

rate reserve, with three days weekly supervised by certified exercise trainers and two days of

home-based unsupervised sessions. Exercise adherence was monitored using weekly exercise

logs and usual diet was maintained. Heart rate monitors were worn to ensure that at least 50% of

exercise sessions were completed within the target heart rate zone. Methods to ensure adherence

to exercise interventions have been previously described (17, 31).

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**Biomarker Assays**

Blood samples were collected from each participant at baseline (60mL), 6 and 12 months (40mL) post-randomization. Blood draws were performed after a minimum 10-hour fast and complete abstinence from exercise and alcohol for 24 hours. High-sensitivity CRP assays were conducted at the Reproductive Endocrine Research Laboratory (University of Southern California, Los Angeles, CA). Hs-CRP (henceforth referred to as CRP) was quantified using solid-phase chemiluminescent immunometric assay on an Immulite 2000 analyzer (Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA), which had a sensitivity of less than 0.01 mg/dL and an intrabatch coefficient of variation (CV) of 8% and an interbatch CV of 9%. The remaining inflammatory biomarkers of interest were assayed at Eve Technologies (Calgary, AB, Canada) using the Bio-Plex™ 200 system (Bio-Rad Laboratories, Inc., Hercules, CA, USA). The cytokine assay consisted of IL-6 and TNF-α, with sensitivities ranging from 0.05-0.48 pg/mL. The intrabatch CV was 9% for both IL-6 and TNF-α and the interbatch CV was 14% for IL-6 and 11% for TNF-α. Individual analyte values and other assay details are available through Eve Technologies.

**Statistical Analysis**

For all analyses, the natural logarithm transformation was applied to inflammatory biomarker levels because of the skewed distributions of these measurements, and results are presented after back-transformation. To account for possible acute inflammation at time of blood sampling, participants with extremely high inflammatory biomarker concentrations were excluded from the analyses: the threshold concentration for exclusion was 30 mg/L for CRP,

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thereby excluding four participants, and 20 pg/mL for IL-6, excluding two participants. There were no excluded participants for the TNF-α analysis since no extreme outliers were identified. In addition, participants with missing blood samples at any time point were removed from the analysis (n=2).

An intention-to-treat (ITT) analysis using linear mixed models was conducted to determine the intervention effect on inflammatory biomarker levels measured at six and 12 months between moderate and high volume exercise groups. Models for each biomarker were adjusted for baseline values of the biomarker and included the main effects of intervention and time, their interaction term, and a random intercept of subjects accounting for within-subject correlation of each biomarker. The models were used to determine the treatment effect ratio (TER) for the intervention effect, which is the ratio of adjusted geometric means of the biomarker level for the high volume over the moderate volume exercise group. Note that a TER that is greater than 1.0 indicates that the high volume exercise group has the higher adjusted geometric mean of the biomarker level (i.e., stronger inflammatory state) than the moderate volume exercise group. Potential confounding was assessed by examining the change in the β-coefficient with and without the potential confounder in the model. We confirmed that baseline differences between the two randomization groups in dietary intake, cholesterol levels, arthritis and use of non-steroidal anti-inflammatory drugs did not confound our inference on intervention effects.

Potential moderation (effect modification) of the intervention main effect was hypothesized *a priori*, as previously done in other analyses from the ALPHA Trial (22, 36). To assess moderation, the statistical significance of the interaction term ($P_{\text{heterogeneity}}$) between intervention group assignment and each proposed moderator at baseline was evaluated.

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Moderation was determined using the same models as in the ITT analysis with the addition of the hypothesized moderator. Potential moderators were assessed as continuous variables and the models included baseline levels of fitness, age, past year recreational physical activity, BMI, body fat percentage, CRP, IL-6 and TNF-α. In interpreting the relevance of the findings of the moderation analyses, intervention effects were further estimated between subgroups of each baseline characteristic that was deemed to be of interest *a priori*. Subgroups were divided at the median for each variable, with the exception two variables. BMI was divided into clinically meaningful categories of normal weight ($<25$ kg/m$^2$), overweight ($\geq25$ to $<30$ kg/m$^2$) and obese ($\geq30$ kg/m$^2$). Baseline CRP was dichotomized using criteria from Pearson *et al*.(37), with which risk of cardiovascular disease and potentially cancer can be predicted.

In addition to the ITT analysis, an analysis by self-selected exercise volume was also evaluated. Participants were divided based on quintiles of mean minutes of exercise completed per week, as well as by the mean minutes per week spent in their target heart rate zone. TERs were calculated within each exercise volume quintile. A linear trend test was used to test for a linear association between exercise volume quintile and change in inflammatory biomarker from baseline to 12 months, based on a linear model predicting change at 12 months from baseline, where volume quintiles were treated as a continuous variable. All analyses were conducted using SAS software (version 9.2; SAS Institute).

**RESULTS**

Flow of participants through BETA has been reported elsewhere (30). In brief, there were 863 women who met the inclusion criteria. Of these, 400 women participated in the study and were randomized to either the high or the moderate volume exercise groups (Supplementary

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Figure S1). Overall, 14 women did not complete the study, leaving a study population of 195 women in the high volume exercise group and 191 women in the moderate group (97% retention rate). Blood samples at 12 months post-randomization were obtained for each of these women and were included in the statistical analyses. Baseline characteristics were very similar between randomization groups (Table 1). There were no statistically significant differences between groups, with the exception of baseline CRP values, which were slightly higher in the moderate volume exercise group (*P*=0.04).

In the ITT analysis, there were no significant differences between exercise intervention groups for all three biomarkers (Table 2). In terms of the intervention effect, the TERs for all three biomarkers were all greater than or equal to the null value of 1.0, although not statistically significantly so, indicating that changes favored the moderate volume exercise intervention compared to the high volume exercise intervention. No confounders were identified in our assessment for potential confounding based on the *a priori* criteria described in the methods section.

When assessing moderation, we did not identify any significant moderators, although we did observe trends with CRP and TNF-α when stratifying by physical fitness, age, BMI and body fat percentage (Table 3). In general, we observed that the TERs were higher and at times approaching statistical significance, in participants with higher BMI ($>30$ kg/m$^2$), body fat percentage ($>40.3\%$) and age at baseline ($>60$ years), as well as lower physical fitness (VO$_2$ max$<27.2$ mL/kg/min) at baseline.

Lastly, we performed an analysis stratified by self-selected exercise volume of all study participants who completed the trial, based on quintiles of mean minutes per week of exercise (Table 4), as well as mean minutes per week of exercise in their target heart rate zones (Table 5).

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In the analysis of mean minutes per week, we observed the highest percent changes for CRP and IL-6 in the third and fifth quintiles of exercise volume; CRP differences were statistically significantly different than the lowest adherence quintile. The highest percent changes for TNF-α occurred in the 1st and 3rd quintiles. Overall, there is a linear trend in mean minutes per week and the reduction in CRP levels (*P*=0.04), indicating a stronger association with increased exercise time. This trend was not found for IL-6 or TNF-α.

When considering the amount of time spent in the target heart rate zone, an even stronger trend was found across all quintiles of exercise time and reduction of CRP levels ($P_{trend}$<0.01). A linear trend was also observed for the reduction in IL-6 levels with increased exercise time spent in the target heart rate zone ($P_{trend}$=0.04), despite non-statistically significant differences between the change in the four higher quintiles compared to the lowest, referent quintile. No trends or differences between exercise volume quintiles were observed for TNF-α.

**DISCUSSION**

In this year-long randomized dose comparison trial of 300 versus 150 minutes per week of aerobic exercise in postmenopausal women, we found no evidence of differential effects on inflammatory biomarkers related to breast cancer risk. Effect modification was not found by physical fitness (measured by VO$_2$ max), age, past year recreational activity, BMI, body fat percentage or baseline levels of CRP, IL-6 and TNF-α. In secondary analyses based on self-selected exercise volume levels, we found that there was a linear trend associated with increased reductions in CRP levels with increased exercise time in the target heart rate zone.

While baseline characteristics between randomization groups were similar, we observed a significant difference in baseline CRP values. Specifically, baseline CRP levels in both groups

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were low, overall, with median values of 1.90 mg/L in the moderate exercise group and 1.56 mg/L in the high group. These levels are expected for a healthy population. CRP values between 3 and 10 mg/L are considered as low-grade inflammation and levels above 10 mg/L are considered clinically inflammatory states (38, 39).

Interestingly, although we did not observe significant differences between groups in our ITT analysis, the point estimates of the TERs suggested that the moderate volume exercise program may be more effective in reducing levels of CRP, IL-6 and TNF-α. However, there were some differences in baseline levels of inflammatory biomarkers between randomization groups and, in particular the high volume group had significantly lower CRP values at baseline. While it is possible that a lower volume of exercise could be more effective in reducing inflammatory biomarkers, it is also possible a minimum threshold of CRP levels may exist in postmenopausal women, thereby making it more difficult for participants in the high volume group with lower CRP levels at baseline to reduce CRP levels further.

There has been one previous study, known as the Dose-Response to Exercise in postmenopausal Women (DREW) that examined the effect of physical activity dose-response on inflammatory biomarkers in postmenopausal women for cardiopulmonary health. The DREW Trial found no direct effect of any amount of exercise on levels of CRP, IL-6 of TNF-α (40-42). However, three previous RCTs of exercise interventions in postmenopausal women found that an exercise or exercise and diet intervention significantly reduced levels of CRP compared to non-exercise controls: this effect was predominantly mediated by changes in adiposity (20-22). Baseline BMI was a moderator in one study as the effectiveness of the exercise intervention was only evident in obese women (BMI>30 kg/m$^2$) at baseline (21). Adipose tissue has been well-

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studied as a source of pro-inflammatory cytokines, thus larger decreases in adiposity can lead to decreased levels of circulating cytokines (43, 44).

In our analysis of potential moderation in the present study, we did not find any statistically significant interactions between the intervention effects and the potential moderators examined. There were, however, trends in the data, as we found that the moderate volume exercise group had greater decreases in CRP and IL-6 when the analysis was restricted to those participants who were, at baseline, below the median physical fitness (VO$_{2max}$<27.2 mL/kg/min), above the median body fat percentage (≥40.3%), older than 60 years of age, or obese (BMI>30 kg/m$^2$). It is also noteworthy that these subgroups of women started with higher baseline values of CRP and IL-6, regardless of randomization group (Supplementary Figures S2 and S3), indicating that women who are older, less fit or more obese have higher levels of chronic inflammation and may benefit more from a moderate volume exercise intervention compared to a high volume. In terms of treatment effects, we speculate that the high volume exercise prescription in older, less physically fit, or more obese women could potentially be causing more inflammation, thus making the moderate volume exercise prescription more effective in reducing levels of CRP and IL-6. Analyses by subgroups of potential moderators were not performed for inflammatory markers in the DREW study (40-42), and thus there are no similar studies with which to compare our results.

In considering the overall effect of exercise time, there was indeed a significant trend of decreasing CRP levels with increasing exercise time. In these analyses stratified by self-selected exercise level, we observed a mild bi-modal effect, with the strongest percent decreases in CRP values in the third and fifth quintiles of exercise time. The reason for this bimodal pattern is unclear. Our secondary analyses also revealed that the amount of time spent in the target heart

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rate zone is potentially more important than the total exercise time in inducing changes in

inflammatory biomarkers, since we observed an even stronger association between exercise time

and CRP levels and also observed a significant trend effect with IL-6 in these analyses than in

the analyses of total exercise time. Hence, exercise intensity, in addition to dose, is relevant

when determining the impact of physical activity on inflammatory biomarkers in relation to

breast cancer prevention. Limited research has examined the role of exercise intensity on

changes in inflammatory biomarkers, although some observational studies have found that higher

exercise intensity is associated with reduced levels of CRP (45-48), IL-6 (45) and TNF-α (45).

One RCT in young adults found that higher intensity exercise reduced circulating TNF-α levels

more effectively than lower doses (49), however, this finding has not been consistently

demonstrated in RCTs for TNF-α or other inflammatory biomarkers (50, 51). Results from our

study suggest that longer periods of vigorous exercise could be more beneficial in reducing

chronic inflammation although more research in this area is necessary to corroborate this finding.

In this study of inflammatory biomarkers, the strongest associations of exercise were with

CRP which is known to be a very sensitive and objective systemic marker for inflammation and

the acute phase response to tissue damage, infection and malignant neoplasia, where

concentrations of circulating CRP can increase up to 10,000 fold in response to stimulus (52). It

is also one of the most studied biomarkers, particularly with respect to cardiovascular disease

(53-55). Recent studies have shown the potential of IL-6 as a myokine (a cytokine secreted from

skeletal muscle that can have anti-inflammatory effects), despite IL-6 being known as a pro-

inflammatory cytokine when secreted from other tissues or in the blood. As a myokine, an

increase in circulating IL-6 can trigger an increase in other anti-inflammatory cytokines such as

interleukin-10 (IL-10) and interleukin-1 receptor antagonist (IL-1ra), leading to an overall anti-

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inflammatory effect (56). While this increase in IL-6 has been observed predominantly after an acute bout of higher intensity exercise, the anti-inflammatory effect of IL-6 could be a possible mechanism by which physical activity reduces chronic inflammation. This situation could possibly explain why anti-inflammatory effects were strongest in those with the highest levels of high intensity exercise in our analysis of time in target heart rate zone.

To our knowledge, BETA is the first randomized controlled trial to examine the impact of aerobic exercise volume on biomarkers for breast cancer prevention. Overall, we did not observe significant differences between the high and moderate volume exercise groups. In secondary analyses based on self-selected exercise volume, we found that there was a stronger reduction of CRP and IL-6 with increased exercise time. Further research based on exercise intensity and exercise volume is necessary to support our conclusions.

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## ACKNOWLEDGEMENTS

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# REFERENCES

1. Grivennikov SI, Greten FR, Karin M. Immunity, Inflammation, and Cancer. Cell. 2010;140:883-99.

2. Lee CG, Carr MC, Murdoch SJ, Mitchell E, Woods NF, Wener MH, et al. Adipokines, inflammation, and visceral adiposity across the menopausal transition: a prospective study. J Clin Endocrinol Metab. 2009;94:1104-10.

3. Neilson HK, Conroy SM, Friedenreich CM. The Influence of Energetic Factors on Biomarkers of Postmenopausal Breast Cancer Risk. Curr Nutr Rep. 2014;3:22-34.

4. Ollberding NJ, Kim Y, Shvetsov YB, Wilkens LR, Franke AA, Cooney RV, et al. Prediagnostic Leptin, Adiponectin, C-Reactive Protein, and the Risk of Postmenopausal Breast Cancer. Cancer Prev Res. 2013;6:188-95.

5. Erdei E, Kang H, Meisner A, White K, Pickett G, Baca C, et al. Polymorphisms in cytokine genes and serum cytokine levels among New Mexican women with and without breast cancer. Cytokine. 2010;51:18-24.

6. Dossus L, Jimenez-Corona A, Romieu I, Boutron-Ruault MC, Boutten A, Dupre T, et al. C-reactive protein and postmenopausal breast cancer risk: results from the E3N cohort study. Cancer Causes Control. 2014;25:533-9.

7. Hong T, Liu A, Cai D, Zhang Y, Hua D, Hang X, et al. Preoperative serum C-reactive protein levels and early breast cancer by BMI and menopausal status. Cancer Invest. 2013;31:279-85.

18

8.      Pooja S, Chaudhary P, Nayak LV, Rajender S, Saini KS, Deol D, et al. Polymorphic

variations in IL-1beta, IL-6 and IL-10 genes, their circulating serum levels and breast cancer risk

in Indian women. Cytokine. 2012;60:122-8.

9.      Alokail MS, Al-Daghri N, Abdulkareem A, Draz HM, Yakout SM, Alnaami AM, et al.

Metabolic syndrome biomarkers and early breast cancer in Saudi women: evidence for the

presence of a systemic stress response and/or a pre-existing metabolic syndrome-related

neoplasia risk? BMC Cancer. 2013;13:54.

10.     Wang J, Lee IM, Tworoger SS, Buring JE, Ridker PM, Rosner B, et al. Plasma C -

reactive Protein and Risk of Breast Cancer in two Prospective Studies and a Meta-analysis.

Cancer Epidemiol Biomarkers Prev. 2015.

11.     Heikkila K, Harris R, Lowe G, Rumley A, Yarnell J, Gallacher J, et al. Associations of

circulating C-reactive protein and interleukin-6 with cancer risk: findings from two prospective

cohorts and a meta-analysis. Cancer Causes Control. 2009;20:15-26.

12.     Gleeson M, Bishop NC, Stensel DJ, Lindley MR, Mastana SS, Nimmo MA. The anti-

inflammatory effects of exercise: mechanisms and implications for the prevention and treatment

of disease. Nat Rev Immunol. 2011;11:607-15.

13.     Ouchi N, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic

disease. Nat Rev Immunol. 2011;11:85-97.

14.     Mathur N, Pedersen BK. Exercise as a Mean to Control Low-Grade Systemic

Inflammation. Mediators of Inflammation. 2008;2008:109502.

15.     Petersen AM, Pedersen BK. The anti-inflammatory effect of exercise. J Appl Physiol.

2005;98:1154-62.

19

16.     Foster-Schubert KE, Alfano CM, Duggan CR, Xiao L, Campbell KL, Kong A, et al. Effect of diet and exercise, alone or combined, on weight and body composition in overweight-to-obese postmenopausal women. Obesity (Silver Spring). 2012;20:1628-38.

17.     Friedenreich CM, Woolcott CG, McTiernan A, Ballard-Barbash R, Brant RF, Stanczyk FZ, et al. Alberta Physical Activity and Breast Cancer Prevention Trial: Sex Hormone Changes in a Year-Long Exercise Intervention Among Postmenopausal Women. J Clin Oncol. 2010;28:1458-66.

18.     McTiernan A, Tworoger SS, Ulrich CM, Yasui Y, Irwin ML, Rajan KB, et al. Effect of exercise on serum estrogens in postmenopausal women: a 12-month randomized clinical trial. Cancer Res. 2004;64:2923-8.

19.     Monninkhof EM, Velthuis MJ, Peeters PH, Twisk JW, Schuit AJ. Effect of exercise on postmenopausal sex hormone levels and role of body fat: a randomized controlled trial. J Clin Oncol. 2009;27:4492-9.

20.     Imayama I, Ulrich CM, Alfano CM, Wang C, Xiao L, Wener MH, et al. Effects of a caloric restriction weight loss diet and exercise on inflammatory biomarkers in overweight/obese postmenopausal women: a randomized controlled trial. Cancer Res. 2012;72:2314-26.

21.     Campbell PT, Campbell KL, Wener MH, Wood BL, Potter JD, McTiernan A, et al. A yearlong exercise intervention decreases CRP among obese postmenopausal women. Med Sci Sports Exerc. 2009;41:1533-9.

22.     Friedenreich CM, Neilson HK, Woolcott CG, Wang Q, Stanczyk FZ, McTiernan A, et al. Inflammatory marker changes in a yearlong randomized exercise intervention trial among postmenopausal women. Cancer Prev Res. 2012;5:98-108.

23.     Trussardi Fayh AP, Lopes AL, Fernandes PR, Reischak-Oliveira A, Friedman R. Impact of weight loss with or without exercise on abdominal fat and insulin resistance in obese individuals: a randomised clinical trial. Br J Nutr. 2013;110:486-92.

24.     Ho SS, Dhaliwal SS, Hills AP, Pal S. Effects of chronic exercise training on inflammatory markers in Australian overweight and obese individuals in a randomized controlled trial. Inflammation. 2013;36:625-32.

25.     Reed JL, De Souza MJ, Williams NI. Effects of exercise combined with caloric restriction on inflammatory cytokines. Appl Physiol Nutr Metab. 2010;35:573-82.

26.     Marques EA, Mota J, Viana JL, Tuna D, Figueiredo P, Guimaraes JT, et al. Response of bone mineral density, inflammatory cytokines, and biochemical bone markers to a 32-week combined loading exercise programme in older men and women. Arch Gerontol Geriatr. 2013;57:226-33.

27.     Ryan AS, Ge S, Blumenthal JB, Serra MC, Prior SJ, Goldberg AP. Aerobic exercise and weight loss reduce vascular markers of inflammation and improve insulin sensitivity in obese women. J Am Geriatr Soc. 2014;62:607-14.

28.     So WY, Song M, Park YH, Cho BL, Lim JY, Kim SH, et al. Body composition, fitness level, anabolic hormones, and inflammatory cytokines in the elderly: a randomized controlled trial. Aging Clin Exp Res. 2013;25:167-74.

29.     Beavers KM, Hsu FC, Isom S, Kritchevsky SB, Church T, Goodpaster B, et al. Long-term physical activity and inflammatory biomarkers in older adults. Med Sci Sports Exerc. 2010;42:2189-96.

21

30.    Friedenreich CM, Neilson HK, O'Reilly R, Duha A, Yasui Y, Morielli AR, et al. Effects

of a High vs Moderate Volume of Aerobic Exercise on Adiposity Outcomes in Postmenopausal

Women: A Randomized Clinical Trial. JAMA Oncol. 2015;1:766-76.

31.    Friedenreich CM, MacLaughlin S, Neilson HK, Stanczyk FZ, Yutaka Y, Duha A, et al.

Study design and methods for the Breast Cancer and Exercise Trial in Alberta (BETA). BMC

Cancer. 2014;14:1-28.

32.    Public Health Agency of Canada. Canada's Physical Activity Guide to Healthy Active

Living. 2011  [cited 2015 9 Mar]; Available from: http://www.phac-aspc.gc.ca/pau-

uap/paguide/index.html

33.    Canadian Society for Exercise Physiology. Canadian Physical Activity Guidelines for

Adults, 18-64 Years. 2011  [cited 2015 9 Mar]; Available from: http://www.csep.ca/guidelines

34.    Kushi LH, Byers T, Doyle C, Bandera EV, McCullough M, Gansler T, et al. American

Cancer Society Guidelines on Nutrition and Physical Activity for Cancer Prevention: Reducing

the Risk of Cancer With Healthy Food Choices and Physical Activity. CA: Cancer J Clin.

2006;56:254-81.

35.    Kushi LH, Doyle C, McCullough M, Rock CL, Demark-Wahnefried W, Bandera EV, et

al. American Cancer Society guidelines on nutrition and physical activity for cancer prevention.

CA: Cancer J Clin. 2012;62:30-67.

36.    Friedenreich CM, Neilson HK, Woolcott CG, Wang Q, Yasui Y, Brant RF, et al.

Mediators and moderators of the effects of a year-long exercise intervention on endogenous sex

hormones in postmenopausal women. Cancer Causes Control. 2011;22:1365-73.

37.    Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO, 3rd, Criqui M, et al.

Markers of inflammation and cardiovascular disease: application to clinical and public health

22

practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation. 2003;107:499-511.

38.      Eklund CM. Proinflammatory cytokines in CRP baseline regulation. Adv Clin Chem. 2009;48:111-36.

39.      Kushner I, Rzewnicki D, Samols D. What does minor elevation of C-reactive protein signify? Am J Med. 2006;119:166.e17-28.

40.      Stewart LK, Earnest CP, Blair SN, Church TS. Effects of different doses of physical activity on C-reactive protein among women. Med Sci Sports Exerc. 2010;42:701-7.

41.      Johannsen NM, Swift DL, Johnson WD, Dixit VD, Earnest CP, Blair SN, et al. Effect of different doses of aerobic exercise on total white blood cell (WBC) and WBC subfraction number in postmenopausal women: results from DREW. PLoS One. 2012;7:e31319.

42.      Arsenault BJ, Cote M, Cartier A, Lemieux I, Despres JP, Ross R, et al. Effect of exercise training on cardiometabolic risk markers among sedentary, but metabolically healthy overweight or obese post-menopausal women with elevated blood pressure. Atherosclerosis. 2009;207:530-3.

43.      Greenberg AS, Obin MS. Obesity and the role of adipose tissue in inflammation and metabolism. Am J Clin Nutr. 2006;83:461s-5s.

44.      Galic S, Oakhill JS, Steinberg GR. Adipose tissue as an endocrine organ. Mol Cell Endocrinol. 2010;316:129-39.

45.      Elosua R, Bartali B, Ordovas JM, Corsi AM, Lauretani F, Ferrucci L. Association between physical activity, physical performance, and inflammatory biomarkers in an elderly population: the InCHIANTI study. J Gerontol A Biol Sci Med Sci. 2005;60:760-7.

46.     Pitsavos C, Chrysohoou C, Panagiotakos DB, Skoumas J, Zeimbekis A, Kokkinos P, et al. Association of leisure-time physical activity on inflammation markers (C-reactive protein, white cell blood count, serum amyloid A, and fibrinogen) in healthy subjects (from the ATTICA study). Am J Cardiol. 2003;91:368-70.

47.     Hawkins M, Belalcazar LM, Schelbert KB, Richardson C, Ballantyne CM, Kriska A. The effect of various intensities of physical activity and chronic inflammation in men and women by diabetes status in a national sample. Diabetes Res Clin Pract. 2012;97:e6-8.

48.     Bergstrom G, Behre CJ, Schmidt C. Moderate intensities of leisure-time physical activity are associated with lower levels of high-sensitivity C-reactive protein in healthy middle-aged men. Angiology. 2012;63:412-5.

49.     Sloan RP, Shapiro PA, Demeersman RE, McKinley PS, Tracey KJ, Slavov I, et al. Aerobic exercise attenuates inducible TNF production in humans. J Appl Physiol. 2007;103:1007-11.

50.     Lee MG, Park KS, Kim DU, Choi SM, Kim HJ. Effects of high-intensity exercise training on body composition, abdominal fat loss, and cardiorespiratory fitness in middle-aged Korean females. Appl Physiol Nutr Metab. 2012;37:1019-27.

51.     Krause M, Rodrigues-Krause J, O'Hagan C, Medlow P, Davison G, Susta D, et al. The effects of aerobic exercise training at two different intensities in obesity and type 2 diabetes: implications for oxidative stress, low-grade inflammation and nitric oxide production. Eur J Appl Physiol. 2014;114:251-60.

52.     Pepys MB, Hirschfield GM. C-reactive protein: a critical update. J Clin Invest. 2003;111:1805-12.

53.     Ridker PM, Hennekens CH, Buring JE, Rifai N. C-Reactive Protein and Other Markers

of Inflammation in the Prediction of Cardiovascular Disease in Women. N Engl J Med.

2000;342:836-43.

54.     Deodhar SD. C-reactive protein: the best laboratory indicator available for monitoring

disease activity. Cleve Clin J Med. 1989;56:126-30.

55.     Silva D, Pais de Lacerda A. [High-sensitivity C-reactive protein as a biomarker of risk in

coronary artery disease]. Rev Port Cardiol. 2012;31:733-45.

56.     Steensberg A, Fischer CP, Keller C, Moller K, Pedersen BK. IL-6 enhances plasma IL-

1ra, IL-10, and cortisol in humans. Am J Physiol Endocrinol Metab. 2003;285:E433-7.

**Table 1.** Baseline characteristics of study participants, Breast Cancer and Exercise Trial in Alberta, Canada, 2010-2013, n=400

| Baseline characteristic | Moderate volume exercisers (n=200) Mean±SD | High volume exercisers (n=200) Mean±SD |
|---|---|---|
| Age (y) | 59.5 ± 5.1 | 59.4 ± 4.8 |
| Body composition measurements | | |
| BMI (kg/m$^2$) | 29.4 ± 4.4 | 29.1 ± 4.4 |
| Percent body fat | 40.7 ± 5.9 | 40.5 ± 5.8 |
| | *n* (%) | *n* (%) |
| Regular NSAID user | 18 (9.0) | 14 (7.0) |
| Regular statin user | 25 (12.5) | 21 (10.5) |
| **Biomarkers** | Median (IQR) | Median (IQR) |
| CRP (mg/L) | 1.90 (0.95, 4.27) | 1.56 (0.86, 3.47) |
| IL-6 (pg/mL) | 0.40 (0.25, 0.71) | 0.41 (0.28, 0.69) |
| TNF-α (pg/mL) | 3.02 (2.15, 3.78) | 3.16 (2.12, 3.96) |

Abbreviations: SD, standard deviation; IQR, interquartile range; CRP, C-reactive protein; IL-6, interleukin-6; TNF-α, tumour necrosis factor α; BMI, body mass index; NSAID, nonsteroidal anti-inflammatory drug.

**Table 2.** Intention-to-treat analysis of inflammatory biomarker concentrations for high volume and moderate volume exercisers in the Breast Cancer and Exercise Trial in Alberta at 6 and 12 months from baseline

| | Baseline Geometric mean (95% CI)[a] | 6 Months Geometric mean (95% CI)[a] | 12 Months Geometric mean (95% CI)[a] | n | Percent change from baseline to 12 months | TER of High / Moderate (95% CI)[b] | Between-Group P-value |
|---|---|---|---|---|---|---|---|
| CRP (mg/L) | | | | | | | |
| High | 1.63 (1.41, 1.88) | 1.69 (1.46, 1.95) | 1.46 (1.26, 1.68) | 192 | -10.56 | 1.07 (0.97, 1.19) | 0.15 |
| Moderate | 2.00 (1.73, 2.31) | 1.76 (1.54, 2.02) | 1.66 (1.45, 1.89) | 188 | -17.16 | | |
| IL-6 (pg/mL) | | | | | | | |
| High | 0.43 (0.38, 0.47) | 0.43 (0.39, 0.48) | 0.40 (0.36, 0.45) | 191 | -6.19 | 1.04 (0.96, 1.13) | 0.36 |
| Moderate | 0.43 (0.39, 0.48) | 0.41 (0.37, 0.45) | 0.41 (0.37, 0.45) | 190 | -6.35 | | |
| TNF-α (pg/mL) | | | | | | | |
| High | 2.84 (2.65, 3.04) | 2.80 (2.62, 3.00) | 2.78 (2.60, 2.98) | 193 | -1.91 | 1.00 (0.95, 1.05) | 0.96 |
| Moderate | 2.70 (2.51, 2.90) | 2.69 (2.50, 2.90) | 2.66 (2.47, 2.87) | 191 | -1.46 | | |

[a]Blood samples from n=386 participants were obtained. Participants with extremely high inflammatory biomarker values were excluded from the analysis. The threshold for removal and number of participants removed for each biomarker were: CRP: 30 mg/L, 4 participants; IL-6: 20 pg/mL, 2 participants; TNF-α: no extreme values, 0 participants. Participants missing a blood sample at any time point were also removed.

[b]The TER was calculated based on a linear mixed model for each biomarker, adjusted for time and baseline value of the biomarker. The TER represents the adjusted ratio of geometric means for the high exercise group over the moderate exercise group. A TER of less than 1.0 indicates lower inflammatory marker levels in the high exercise group relative to the moderate exercise group at 6 and 12 months; a TER greater than 1.0 indicates higher inflammatory marker levels in the high exercise group; and a ratio of 1.0 indicates no difference between exercise groups.

Abbreviations: CI, confidence interval; TER, treatment effect ratio; CRP, C-reactive protein; IL-6, interleukin-6; TNF-α, tumour necrosis factor α.

**Table 3.** Exercise intervention effects on inflammatory biomarkers, stratified by potential moderators in the Breast Cancer and Exercise Trial in Alberta, 2010-2013

| Potential moderator[a] | CRP[b] | | IL-6[b] | | TNF-α[b] | |
|---|---|---|---|---|---|---|
| Baseline level | $n^c$ | TER[d] | $n^c$ | TER[d] | $n^c$ | TER[d] |
| Physical fitness (VO$_2$max) | | | | | | |
| <27.2 mL/kg/min | 92/96 | 1.13 (1.00, 1.28) | 92/96 | 1.11 (0.99, 1.24) | 93/97 | 1.01 (0.94, 1.09) |
| ≥27.2 | 96/96 | 1.03 (0.88, 1.19) | 98/95 | 0.98 (0.86, 1.11) | 98/96 | 0.99 (0.93, 1.05) |
| | | $P^e = 0.41$ | | $P^e = 0.11$ | | $P^e = 0.99$ |
| Age, y | | | | | | |
| ≤60 | 108/120 | 1.04 (0.92, 1.18) | 108/119 | 1.01 (0.91, 1.12) | 108/120 | 0.96 (0.91, 1.01) |
| >60 | 80/72 | 1.11 (0.94, 1.31) | 82/72 | 1.10 (0.96, 1.27) | 83/73 | 1.05 (0.97, 1.15) |
| | | $P^e = 0.23$ | | $P^e = 0.22$ | | $P^e = 0.16$ |
| Past year recreational activity | | | | | | |
| <5.7 MET-h/wk | 97/93 | 1.03 (0.90, 1.18) | 99/92 | 0.98 (0.88, 1.11) | 99/93 | 0.98 (0.91, 1.06) |
| ≥5.7 | 91/99 | 1.12 (0.97, 1.29) | 91/99 | 1.11 (0.98, 1.25) | 92/100 | 1.02 (0.96, 1.08) |
| | | $P^e = 0.40$ | | $P^e = 0.84$ | | $P^e = 0.77$ |
| BMI | | | | | | |
| ≤25 kg/m$^2$ | 38/41 | 1.00 (0.81, 1.23) | 38/40 | 0.97 (0.78, 1.21) | 38/41 | 0.98 (0.89, 1.08) |
| >25-≤30 | 76/77 | 1.00 (0.85, 1.18) | 77/78 | 1.03 (0.90, 1.18) | 78/78 | 0.98 (0.92, 1.05) |
| >30 | 102/94 | 1.17 (1.00, 1.36) | 92/93 | 1.09 (0.97, 1.22) | 89/102 | 1.03 (0.94, 1.13) |
| | | $P^e = 0.19$ | | $P^e = 0.43$ | | $P^e = 0.28$ |
| Body fat percentage | | | | | | |
| <40.3% | 93/96 | 1.01 (0.88, 1.17) | 94/95 | 1.01 (0.88, 1.16) | 95/96 | 0.99 (0.94, 1.05) |
| ≥40.3 | 95/96 | 1.13 (1.00, 1.29) | 96/96 | 1.07 (0.96, 1.19) | 96/97 | 1.01 (0.94, 1.09) |
| | | $P^e = 0.60$ | | $P^e = 0.97$ | | $P^e = 0.38$ |
| CRP | | | | | | |
| <3.0 mg/L | 86/98 | 1.03 (0.90, 1.18) | | | | |
| ≥3.0 | 102/94 | 1.11 (0.96, 1.29) | | | | |
| | | $P^e = 0.36$ | | | | |
| IL-6 | | | | | | |
| <0.4 pg/mL | | | 98/98 | 1.03 (0.93, 1.14) | | |
| ≥0.4 | | | 92/93 | 1.06 (0.93, 1.21) | | |

$P^e = 0.34$

| | | |
|---|---|---|
| TNF-α | | |
| <1.4 pg/mL | 102/91 | 1.01 (0.93, 1.10) |
| ≥1.4 | 89/102 | 0.99 (0.94, 1.04) |
| | | $P^e = 0.08$ |

[a]Level of potential moderator at baseline.

[b]Blood samples from n=386 participants were obtained. Participants with extremely high inflammatory biomarker values were excluded from the analysis. The threshold for removal and number of participants removed for each biomarker were: CRP: 30 mg/L, 4 participants, IL-6: 20 pg/mL, 2 participants, TNF-α: no extreme values, 0 participants. Participants missing a blood sample at any time point were also removed.

[c]Number of high volume exercisers/number of moderate volume exercisers.

[d]The TER represents the adjusted ratio of geometric means for the high exercise group over the moderate exercise group. A TER of less than 1.0 indicates lower inflammatory marker levels in the high exercise group relative to the moderate exercise group at 6 and 12 months; a TER greater than 1.0 indicates higher inflammatory marker levels in the high exercise group; and a ratio of 1.0 indicates no difference between exercise groups.

[e]P-value refers to the statistical significance of the interaction term between the high volume exercise group and the potential moderator. All moderators were treated as continuous variables for this calculation.

Abbreviations: CI, confidence interval; CRP, C-reactive protein; IL-6, interleukin-6; TNF-α, tumour necrosis factor α; BMI, body mass index.

**Table 4.** Inflammatory biomarker concentrations at baseline and 12 months in controls and exercisers stratified by adherence level in the Breast Cancer and Exercise Trial in Alberta[a]

| | Baseline Geometric Mean (95% CI)[b] | 12 Months Geometric Mean (95% CI)[b] | n | Ratio 12 Months / Baseline (95% CI)[c] | Percent Change[d] | P[e] | P$_{trend}$[f] |
|---|---|---|---|---|---|---|---|
| CRP (mg/L) | | | | | | | |
| <110 min/wk | 2.14 (1.68, 2.73) | 2.06 (1.63, 2.61) | 76 | 1.00 (0.87, 1.15) | 0.07 | Ref | 0.04 |
| 110-135 min/wk | 1.71 (1.38, 2.13) | 1.55 (1.26, 1.92) | 76 | 0.90 (0.78, 1.03) | -10.37 | 0.26 | |
| 135-152 min/wk | 2.12 (1.70, 2.65) | 1.53 (1.25, 1.89) | 77 | 0.76 (0.66, 0.87) | -24.29 | <0.01 | |
| 152-246 min/wk | 1.60 (1.27, 2.02) | 1.55 (1.23, 1.95) | 77 | 0.93 (0.81, 1.06) | -7.19 | 0.44 | |
| >246 min/wk | 1.50 (1.19, 1.89) | 1.22 (0.99, 1.49) | 77 | 0.79 (0.69, 0.90) | -21.45 | 0.01 | |
| IL-6 (pg/mL) | | | | | | | |
| <110 min/wk | 0.46 (0.39, 0.54) | 0.44 (0.38, 0.51) | 77 | 0.98 (0.87, 1.10) | -2.42 | Ref | 0.24 |
| 110-135 min/wk | 0.40 (0.34, 0.48) | 0.39 (0.32, 0.48) | 76 | 0.96 (0.86, 1.08) | -3.71 | 0.87 | |
| 135-152 min/wk | 0.45 (0.38, 0.52) | 0.41 (0.35, 0.48) | 77 | 0.91 (0.81, 1.03) | -8.71 | 0.43 | |
| 152-246 min/wk | 0.41 (0.35, 0.48) | 0.39 (0.33, 0.47) | 76 | 0.94 (0.84, 1.06) | -5.52 | 0.70 | |
| >246 min/wk | 0.44 (0.37, 0.53) | 0.39 (0.32, 0.47) | 77 | 0.88 (0.78, 0.99) | -11.80 | 0.23 | |
| TNF-α (pg/mL) | | | | | | | |
| <110 min/wk | 2.68 (2.36, 3.06) | 2.58 (2.26, 2.95) | 77 | 0.96 (0.89, 1.02) | -4.40 | Ref | 0.44 |
| 110-135 min/wk | 2.94 (2.66, 3.25) | 2.89 (2.60, 3.21) | 77 | 0.99 (0.93, 1.06) | -0.75 | 0.43 | |
| 135-152 min/wk | 2.75 (2.47, 3.07) | 2.68 (2.40, 2.98) | 77 | 0.97 (0.91, 1.04) | -2.90 | 0.74 | |
| 152-246 min/wk | 2.67 (2.37, 3.02) | 2.70 (2.43, 3.00) | 77 | 1.01 (0.94, 1.07) | 0.54 | 0.29 | |
| >246 min/wk | 2.82 (2.54, 3.13) | 2.78 (2.48, 3.12) | 78 | 0.99 (0.93, 1.06) | -1.06 | 0.47 | |

[a]Adherence was calculated as the mean minutes of exercise per week over the 52 weeks of the study.

[b]Blood samples from n=386 participants were obtained. Participants with extremely high inflammatory biomarker values were excluded from the analysis. The threshold for removal and number of participants removed for each biomarker were: CRP: 30 mg/L, 4 participants, IL-6: 20 pg/mL, 2 participants, TNF-α: no extreme values, 0 participants. Participants missing a blood sample at any time point were also removed.

[c]Ratio of geometric means at 12 months to geometric means at baseline, adjusted for the baseline inflammatory marker level, age, $VO_2$ max and body mass index.

[d]Percentage change in adherence group mean of each inflammatory biomarker at 12 months from baseline, adjusted for the baseline inflammatory marker level, age, $VO_2$ max and body mass index.

[e]P-value tests difference in changes in inflammatory biomarker levels between the lowest quintile adherence group and the specified adherence group, adjusted for the baseline value of the inflammatory biomarker, age, $VO_2$ max and body mass index. A unified model, where the adherence group was treated as a categorical variable was used to calculate the p-values, which correspond to beta-coefficients for the other quintile groups, using the lowest quintile group as the referent group.

[f]P-value for trend represents a test of linear association between adherence quintile and change in inflammatory marker from baseline to 12 months. This test is based on a linear model predicting change at 12 months from baseline, with predictors: baseline inflammatory marker, age, VO2 max, BMI, and adherence quintile, where quintiles are numbered 1-5 and these values are treated as a continuous variable.

Abbreviations: CI, confidence interval; CRP, C-reactive protein; IL-6, interleukin-6; TNF-$\alpha$, tumour necrosis factor $\alpha$.

**Table 5.** Inflammatory biomarker concentrations at baseline and 12 months in controls and exercisers stratified by adherence level based on time in heart rate zone in the Breast Cancer and Exercise Trial in Alberta[a]

| | Baseline Geometric Mean (95% CI)[b] | 12 Months Geometric Mean (95% CI)[b] | n | Ratio 12 Months / Baseline (95% CI)[c] | Percent Change[d] | P[e] | P_trend[f] |
|---|---|---|---|---|---|---|---|
| CRP (mg/L) | | | | | | | |
| <57 min/wk | 2.29 (1.79, 2.92) | 2.30 (1.83, 2.89) | 76 | 1.07 (0.93, 1.22) | 6.60 | Ref | 0.01 |
| 57-86 min/wk | 1.78 (1.46, 2.18) | 1.42 (1.15, 1.75) | 77 | 0.79 (0.69, 0.90) | -21.03 | <0.01 | |
| 86-111 min/wk | 1.75 (1.41, 2.17) | 1.61 (1.33, 1.96) | 76 | 0.92 (0.80, 1.05) | -8.46 | 0.12 | |
| 111-143 min/wk | 1.78 (1.40, 2.27) | 1.51 (1.20, 1.88) | 76 | 0.84 (0.73, 0.96) | -16.09 | 0.01 | |
| >143 min/wk | 1.48 (1.16, 1.88) | 1.18 (0.95, 1.46) | 78 | 0.77 (0.67, 0.88) | -23.27 | <0.01 | |
| IL-6 (pg/mL) | | | | | | | |
| <57 min/wk | 0.47 (0.39, 0.56) | 0.46 (0.40, 0.53) | 77 | 1.00 (0.89, 1.12) | -0.17 | Ref | 0.04 |
| 57-86 min/wk | 0.42 (0.36, 0.49) | 0.40 (0.33, 0.49) | 78 | 0.96 (0.85, 1.07) | -4.17 | 0.62 | |
| 86-111 min/wk | 0.41 (0.34, 0.49) | 0.42 (0.35, 0.51) | 75 | 1.00 (0.89, 1.13) | 0.46 | 0.94 | |
| 111-143 min/wk | 0.46 (0.40, 0.54) | 0.39 (0.33, 0.45) | 76 | 0.85 (0.76, 0.96) | -14.76 | 0.06 | |
| >143 min/wk | 0.40 (0.34, 0.48) | 0.36 (0.29, 0.43) | 77 | 0.87 (0.78, 0.98) | -12.77 | 0.11 | |
| TNF-α (pg/mL) | | | | | | | |
| <57 min/wk | 2.81 (2.46, 3.21) | 2.76 (2.43, 3.14) | 77 | 0.98 (0.92, 1.05) | -1.60 | Ref | 0.93 |
| 57-86 min/wk | 2.66 (2.39, 2.96) | 2.60 (2.32, 2.91) | 78 | 0.97 (0.91, 1.04) | -2.85 | 0.79 | |
| 86-111 min/wk | 2.62 (2.34, 2.95) | 2.63 (2.36, 2.93) | 76 | 0.99 (0.93, 1.06) | -0.85 | 0.88 | |
| 111-143 min/wk | 3.00 (2.71, 3.33) | 2.92 (2.61, 3.26) | 77 | 0.99 (0.92, 1.05) | -1.41 | 0.97 | |
| >143 min/wk | 2.78 (2.50, 3.08) | 2.73 (2.45, 3.04) | 78 | 0.98 (0.92, 1.05) | -1.88 | 0.95 | |

[a]Mean time in zone was calculated as the mean minutes of exercise time in the target heart rate zone over weeks 1-52 of the study.

[b]Blood samples from n=386 participants were obtained. Participants with extremely high inflammatory biomarker values were excluded from the analysis. The threshold for removal and number of participants removed for each biomarker were: CRP: 30 mg/L, 4 participants, IL-6: 20 pg/mL, 2 participants, TNF-α: no extreme values, 0 participants. Participants missing a blood sample at any time point were also removed.

[c]Ratio of geometric means at 12 months to geometric means at baseline, adjusted for the baseline inflammatory marker level, age, VO$_2$ max and body mass index.

[d]Percentage change in adherence group mean of each inflammatory biomarker at 12 months from baseline, adjusted for the baseline inflammatory marker level, age, $VO_2$ max and body mass index.

[e]P-value tests difference in changes in inflammatory biomarker levels between the lowest quintile adherence group and the specified adherence group, adjusted for the baseline value of the inflammatory biomarker, age, $VO_2$ max and body mass index. A unified model, where the adherence group was treated as a categorical variable was used to calculate the p-values, which correspond to beta-coefficients for the other quintile groups, using the lowest quintile group as the referent group.

[f]P-value for trend represents a test of linear association between adherence quintile and change in inflammatory marker from baseline to 12 months. This test is based on a linear model predicting change at 12 months from baseline, with predictors: baseline inflammatory marker, age, VO2 max, BMI, and adherence quintile, where quintiles are numbered 1-5 and these values are treated as a continuous variable.

Abbreviations: CI, confidence interval; CRP, C-reactive protein; IL-6, interleukin-6; TNF-α, tumour necrosis factor α.

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# Cancer Prevention Research

## Inflammatory marker changes in postmenopausal women after a year-long exercise intervention comparing high versus moderate volumes

Christine M. Friedenreich, Rachel O'Reilly, Eileen Shaw, et al.

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