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# Aerobic Training Does Not Alter CRP Concentrations in Apparently Healthy, Untrained Men

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UNIVERSITY OF MIAMI

AEROBIC TRAINING DOES NOT ALTER CRP CONCENTRATIONS  
IN APPARENTLY HEALTHY, UNTRAINED MEN

By

Mark Stoutenberg

A DISSERTATION

Submitted to the Faculty  
of the University of Miami  
in partial fulfillment of the requirements for  
the degree of Doctor of Philosophy

Coral Gables, Florida

December 2008

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Aerobic Training Does Not Alter CRP  
Concentrations in Apparently Healthy, Untrained Men.

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Regular aerobic exercise may reduce cardiovascular disease (CVD) risk in part by lowering the concentration of inflammatory markers such as C-reactive protein (CRP). While studies in diseased populations have shown significant decreases in CRP concentrations with regular aerobic training, little has been conclusively determined regarding the effects of aerobic training on CRP concentrations in apparently healthy, untrained populations who may not be adequately screened for CVD risk by traditional methods. **PURPOSE:** To examine the effects of a 17-wk half marathon training program (TP) on CRP concentrations, aerobic fitness, and body composition in apparently healthy, untrained men. **METHODS:** Twenty men ( $29.3 \pm 1.0$  yr,  $37.0 \pm 1.6$  mL $\cdot$ kg $^{-1}\cdot$ min $^{-1}$  VO $_{2\max}$ , 29.1  $\pm$  1.8% body fat) registered as training subjects (TRN) in a 17-wk half marathon TP. An additional 22 men ( $27.8 \pm 1.4$  yr,  $38.8 \pm 1.0$  mL $\cdot$ kg $^{-1}\cdot$ min $^{-1}$  VO $_{2\max}$ , 26.8  $\pm$  1.4% BF) served as controls (CON). Fasting blood samples were taken at four time points over the TP and were analyzed for CRP and interleukin-6 (IL-6) concentrations. Aerobic capacity (VO $_{2\max}$ ) and body fat (BF%) were measured before and after the TP. **RESULTS:** No significant changes in CRP ( $P=0.69$ ) or IL-6 concentrations ( $P=0.73$ ) were seen in TRN as a result of the TP despite significant improvements in VO $_{2\max}$  ( $42.2 \pm 1.9$  mL $\cdot$ kg $^{-1}\cdot$ min $^{-1}$ ,  $P<0.0001$ ), resting heart rate ( $P=0.004$ ), BF% ( $P=0.03$ ) and BMI ( $P=0.05$ ). No significant changes in CRP,

aerobic fitness, BMI or BF% were detected in CON over time. **CONCLUSION:** Moderate, long-term aerobic training does not appear to affect CRP concentrations in apparently healthy, untrained men despite significant improvements in BW, BF%, BMI, and  $VO_{2max}$ .

**Key Words:** aerobic fitness, body fat, BMI, cardiovascular disease risk, inflammation

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## Chapter 1 - Introduction

The current cardiovascular disease (CVD) risk assessment model, based on the Framingham scoring system, accounts for approximately 80% of first event myocardial infarctions and many times myocardial infarctions are the first detectable manifestation of CVD (43). More than 50% of those who die from coronary heart disease do not have a documented history of disease, calling attention to the obvious need for the investigation of new markers of CVD that help improve the prediction of future coronary events (49, 59). Recently, it has been discovered that chronic concentrations of several inflammatory blood markers, including C-reactive protein (CRP), are highly associated with the incidence of CVD and other vascular events (50, 51). These inflammatory markers provide promise for increasing the predictive power of the current CVD risk assessment model as well as providing alternative, independent risk factors (3, 44, 53, 59).

The ability to predict CVD from CRP concentrations varies considerably between subgroups with different risk factor profiles. In high and low risk individuals, CRP concentrations do not add a new dimension to CVD risk prediction. However, patients at intermediate risk (i.e. 10-20% risk of coronary heart disease within 10 yrs) may benefit the most from the use of CRP screening as an additional predictor of coronary risk (5, 44). An estimated 35-50% of myocardial infarctions occur in *low-to-moderate* risk individuals (as determined by their TC:HDL ratio) (30, 50) and the relationship between CRP and CVD risk detection may be particularly compelling for individuals in this “grey zone” (43, 53) who “fall through the cracks” of traditional CVD screening (5, 30, 50).

Recent studies have examined the relationship between physical activity and CRP concentrations in middle aged (2, 7, 15, 42, 45, 47), young (46) and elderly populations (1, 17). The majority of these studies have indicated that a strong, inverse relationship exists with higher levels of physical activity being associated with lower concentrations of CRP even after adjustment for age, gender, and other risk factors associated with CVD. The influence of exercise on CRP concentrations may be more accurately and objectively assessed by examining physical fitness rather than physical activity (34). Several studies (25, 27, 60) have demonstrated a similar, inverse relationship between fitness level and CRP concentrations with individuals at higher levels of fitness having the lowest CRP concentrations. The results of these studies emphasize the potential role of aerobic exercise in reducing systemic inflammation and suggest that improving aerobic fitness may be an effective therapeutic alternative for reducing CRP concentrations. While these studies support a relationship between physical fitness and reductions in CRP, their cross-sectional nature prevents the establishment of a causal link.

While associations between CRP concentrations and physical activity and fitness levels have been extensively explored in cross-sectional studies, fewer longitudinal studies have been completed. Studies in populations with CVD have shown decreases (17-48%) in CRP concentrations with regular aerobic training (18, 35, 55, 57). Longitudinal studies in children (52) and the elderly (24) have also shown significant reductions in interleukin-6 (IL-6) and CRP concentrations after participation in a 2-wk and 10-mo aerobic training program (TP), respectively. However, the effect of aerobic TPs on CRP concentrations in apparently healthy, adult populations remains unclear.

While some studies have shown reductions in CRP concentrations ranging from 31-58% as a result of exercise TPs (21, 33, 56), others have found little or no change in CRP concentrations with aerobic training (9, 31, 39). Differences in subject populations and TPs in these previous studies calls attention to the need for more well-controlled studies regarding the effect of aerobic training on CRP concentrations in apparently healthy individuals.

The purpose of this study was to determine the effects of a 17-wk half marathon TP on CRP concentrations and to examine the potential association between changes in cardiovascular fitness and CRP concentrations in a population of apparently healthy, untrained men. It was hypothesized that the half marathon TP would result in significant reductions in CRP that would be highly associated with improvements in cardiovascular fitness.

## Chapter 2 - Methods

### Subjects

Twenty-four untrained, apparently healthy men (TRN) were recruited from a local half marathon TP. An additional 23 untrained, apparently healthy men, who chose not to participate in the half marathon TP or undergo any other lifestyle modification program over the duration of the study, were enrolled as control subjects (CON). Subjects were considered untrained if they performed less than 2 h•wk<sup>-1</sup> of aerobic activity and had an aerobic capacity (VO<sub>2max</sub>) less than 50 mL•kg<sup>-1</sup>•min<sup>-1</sup>. Subjects were included in the study if they had a low to moderate risk of cardiovascular disease (according to American College of Sports Medicine guidelines (58)), were non-smokers, had no history of metabolic or chronic inflammatory diseases, were not injured, and did not use medications known to reduce CRP concentrations (NSAID, statins, or ACE inhibitors). The procedures and risks were explained to the subjects, and their written, informed, voluntary consent was obtained. The study was approved by the Medical Science Subcommittee for the Protection of Human Subjects at the University of Miami.

### Experimental Design

After baseline screening and fitness assessment, fasting blood samples were collected from subjects before, at two points during, and at the conclusion of the 17-wk half marathon TP. Blood samples were analyzed for CRP and IL-6. Fitness was assessed again at the completion of the TP (see Figure 2.1).

### Screening and Fitness Assessment

The cardiovascular disease risk of all subjects was assessed with PAR-Q and health history questionnaires. The baseline fitness assessment of both TRN and CON

took place during the 2 wks before the start of the half marathon TP. This assessment consisted of measurements of height, body weight (BW), blood pressure (BP) and resting heart rate (RHR), body fat percentage (BF%) by dual x-ray absorptiometry, and pulmonary screening (forced vital capacity and FEV<sub>1</sub> tests). To assess changes throughout the course of the TP, all measurements were taken at weeks 6, 11, and 16 of training, except for BF% and the graded exercise test, which were measured only at weeks 0 and 16.

A modified Bruce protocol, in which the speed and grade of the treadmill were increased every 3 min until subjects reached volitional exhaustion or presented an absolute or relative indication for the termination of exercise testing as outlined by ACSM (58), was used to assess VO<sub>2max</sub>. Expired gases were continually analyzed during the graded exercise test using an open circuit, indirect calorimetry system (Sensormedics Vmax 229, Conshohocken, PA). Heart rate was measured by telemetry (Polar, Kempele, Finland) and recorded every min while RPE was recorded at the end of every 3-min stage using the Borg scale (6-20). Subjects were asked to continue walking on the treadmill following the VO<sub>2max</sub> test as part of the cool down protocol and remained in the laboratory until their HR and BP returned to within 15% of baseline levels. Aerobic capacity was assessed after training using a similar testing procedure except that the first stage of the protocol was eliminated for TRN because of anticipated improvements in VO<sub>2max</sub>.

#### Exercise Training Program

All TRN enrolled in a local 17-wk half marathon TP that included more than 300 male and female participants registered in the 2007 ING Miami Half Marathon. The TP



consisted of running  $3 \text{ d}\cdot\text{wk}^{-1}$  (two 30-45 min weekday runs and a progressively longer run each weekend) and  $2 \text{ d}\cdot\text{wk}^{-1}$  of light-to-moderate cross-training (cycling, swimming, resistance training). Details of the TP are included in Table 2.1. TRN also received information on stretching, basic nutrition, strength training, and cross-training as part of their participation in the TP. CON agreed to continue their inactive lifestyle and not to participate in exercise or weight loss programs during the course of the study. All subjects were asked to maintain a training log detailing all daily training activities and their weekly running mileage. Subjects submitted their completed training logs at each blood draw in exchange for new logs for the next segment of the TP.

#### Dietary Assessment

Dietary logs were used to detail any changes to the diet across the duration of the TP. Subjects were asked to complete 3-d dietary logs on the Sunday, Monday, and Tuesday at baseline and weeks 6, 11, 16 of training. Dietary logs were analyzed using Food Processor SQL version 10.0 software (Salem, OR).

#### Blood Sampling

A total of four blood samples were taken during the course of the 17-wk TP (baseline, weeks 6, 11, 16) with the final blood sample being taken 1 wk prior to the 2007 ING Miami Half Marathon (Figure 2.1).

Immediately prior to all blood draws, subjects had their BW, RHR and BP measured. Subjects were asked a set of questions designed to monitor their current health status and describe any recent injuries or illnesses that may have influenced their CRP concentration. Subjects exposed to minor illnesses (i.e. common cold or flu) or injury (i.e.

ankle sprain) had their blood draw delayed to a morning no more than 1 wk from the original blood draw date to allow recovery from acute phase inflammatory responses.

Blood samples from TRN were taken on Saturday mornings (between the hours of 4:30-6:00 AM) after an overnight fast and before that week's long run to standardize the day and time of collection. Subjects were asked to refrain from exercise for 30-36 h prior to blood draws to reduce the effects of an acute bout of exercise on CRP concentrations. Following the blood draw, TRN were provided with a morning snack bag to provide energy for that morning's run. Blood samples from CON were drawn later the same Saturday morning (8:00-10:00 AM). CON were asked to follow similar dietary and exercise guidelines as the TRN in the 24 h prior to the blood draw.

A 15-mL venous blood sample was obtained by a licensed phlebotomist through venipuncture of the antecubital vein using a Vacutainer system. Blood samples from TRN were collected at a field location and transported to the Biochemistry Laboratory at the Laboratory of Clinical and Applied Physiology on ice. Once at the laboratory, 3 mL of whole blood was aliquoted for a complete blood cell count that was performed within 48 h. Two plain 10-mL vacutainer tubes were each filled with 6 mL of whole blood and allowed to clot at room temperature for 45 min and then centrifuged at 4°C for 15 min at 3000 rpm. Serum from these samples was divided into multiple aliquots designated for a Basic Metabolic Profile, CRP, and cytokine panel analyses. The results of the CBC and BMP analyses are not presented in this paper. All prepared samples, except the blood designated for CBC analysis, were stored at -80 °C until analysis at the conclusion of the study.

### Analysis of Blood Samples

CRP analyses were performed in duplicate at the Diabetes Research Institute at the University of Miami Leonard M. Miller School of Medicine. C-reactive protein analyses were performed using a Dade-Behring BN-100 nephelometer (Dade-Behring Diagnostic, Westwood, Massachusetts) using the manufacturer's reagents. This method had a detection limit of  $0.16 \text{ mg}\cdot\text{L}^{-1}$  and subjects with values below this lower limit were assigned a CRP concentration of  $0.10 \text{ mg}\cdot\text{L}^{-1}$ . The intra-assay and interassay CVs were  $< 4.4\%$  and  $< 5.7\%$ , respectively.

### Statistical Analyses

Statistical analyses were completed using SAS<sup>®</sup> version 9.1 (SAS Institute, Inc., Cary, NC). Prior to the analyses, preliminary data were screened to detect outliers and provide an assessment of the distribution of all variables to ensure that the appropriate statistical models were used. All data points greater than three standard deviations from the group mean at a single time point were eliminated from all analyses. As CRP values were not normally distributed, logarithmic transformations were performed prior to analyses. The geometric means of the CRP values are presented in the results. A linear mixed model ANOVA was used to examine changes in CRP concentrations, BMI, RHR, systolic (SBP) and diastolic (DBP) blood pressure over the time course of the TP. Least Significance Difference (LSD) comparisons were performed when significant main or interaction effects were found. A Spearman Rank correlation coefficient analysis was used to determine the significance of relationships between variables at baseline and to assess the strength of the association of changes between CRP concentrations and BW,

BF%, BMI,  $VO_{2\text{ max}}$ , RHR, SBP and DBP blood pressure over the course of the TP. The significance level was set *a priori* at  $P < 0.05$ . All data are reported as mean  $\pm$  SE.

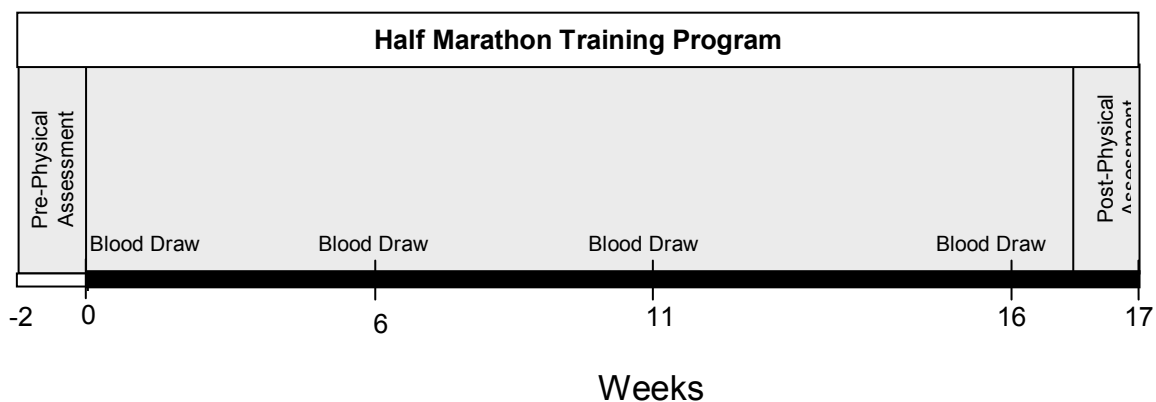


Fig 2.1. Overall research study design. Thick black line indicates the half marathon training program. Physical assessment consisted of measurements of height, body weight (BW), blood pressure (BP) and resting heart rate (RHR), body fat percentage (BF%), and pulmonary screening (forced vital capacity and FEV<sub>1</sub> tests). All measurements (except for BF% and the graded exercise test which were measured only at weeks 0 and 16) were taken again at weeks 6, 11, and 16 of training.

*Table 2.1 - Sample training week for the half marathon program.*

<b>Monday</b>	<b>Tuesday</b>	<b>Wednesday</b>	<b>Thursday</b>	<b>Friday</b>	<b>Saturday</b>	<b>Sunday</b>
30-45 min. run	45-60 min. of x-training	OFF (rest day)	45 min. run	OFF (rest day)	Long Weekend Run (10 miles)	45 min. of non-weight bearing x-training

## Chapter 3 - Results

### Subject Characteristics.

Twenty two of the 23 CON and 20 of 24 TRN completed all blood draws and physical assessments. One CON was unable to continue as a result of difficulty scheduling testing. Three TRN were unable to continue due to injury obtained during training and one withdrew due to time restraints. The physical characteristics of the subjects who completed the study are presented in Table 3.1.

### Adherence to the Training Program and Habitual Diet.

Twenty-one of 22 CON submitted complete training logs at each of the four time points throughout the TP. CON averaged  $1.8 \pm 0.2 \text{ km}\cdot\text{wk}^{-1}$  of running and a total of  $17.4 \pm 1.4 \text{ min}\cdot\text{wk}^{-1}$  of aerobic training. Fifteen of the 20 TRN submitted complete training logs at each of the four time points throughout the TP. TRN averaged  $17.2 \pm 1.2 \text{ km}\cdot\text{wk}^{-1}$  of running and a total of  $117 \pm 7.3 \text{ min}\cdot\text{wk}^{-1}$  of aerobic training (91% of which was running). Overall, TRN completed an average of 30 of the 48 scheduled training runs (62.6%). There were no significant changes in total energy intake ( $2412 \pm 66 \text{ kcal}\cdot\text{d}^{-1}$ ) over the course of the study and all values were averaged. The proportion of total energy intake from fat (28.6%), carbohydrate (54.1%), or protein (17.4%) during the TP did not differ for either the TRN or CON groups.

### CRP Concentrations.

There was no significant difference in CRP concentrations between the CON and TRN prior to the TP ( $0.61 \pm 1.20 \text{ mg}\cdot\text{L}^{-1}$  vs.  $0.96 \pm 1.28 \text{ mg}\cdot\text{L}^{-1}$ ). No significant time, treatment or interaction effects were observed in CRP concentrations over the TP (Figure 3.1).

### Aerobic Fitness and Hemodynamics.

There were no significant differences between groups at baseline in RHR or  $VO_{2max}$  (Tables 3.1 and 3.2). Systolic blood pressure ( $P=0.025$ ) and DBP ( $P=0.042$ ) were significantly higher in the TRN prior to the TP. At the conclusion of the TP, separate mixed model ANOVA's revealed significant treatment x time interactions for  $VO_{2max}$  ( $P=0.0003$ ), RHR ( $P=0.018$ ), SBP ( $P=0.0081$ ), and DBP ( $P=0.0031$ ). TRN showed a significant 13.6% increase in  $VO_{2max}$  ( $P<0.0001$ ) as well as significant decreases in RHR ( $P=0.0004$ ), SBP ( $P<0.0001$ ), and DBP ( $P=0.0024$ ). No significant changes were seen in any aerobic or hemodynamic variables in the CON.

### Anthropometry.

There were no significant differences between groups at baseline in BW, BMI, or BF% (Table 3.1). There were significant treatment x time interactions for BMI ( $P=0.01$ ), BW ( $P=0.011$ ), and BF ( $P=0.0084$ ) between TRN and CON. TRN exhibited significant 1.5% ( $P=0.05$ ) and 3.2% ( $P=0.03$ ) reductions in BMI and BF%, respectively while CON showed a trend towards increasing BMI and BF% of 1.0% ( $P=0.06$ ) and 2.3% ( $P=0.10$ ), respectively, over the same time period. CON also experienced a significant 1.0% increase in BW ( $P=0.047$ ).

### Correlations.

Baseline correlations of the cohort of subjects are shown in Table 3.3. Significant correlations at baseline existed between baseline CRP concentrations and BMI, BF%, and  $VO_{2max}$  values. At the conclusion of the TP, significant training-related changes were only seen between CRP concentrations and BMI ( $r= -0.456$ ,  $P=0.05$ ) and BW ( $r= -0.464$ ,  $P=0.046$ ) in TRN (Table 3.4).



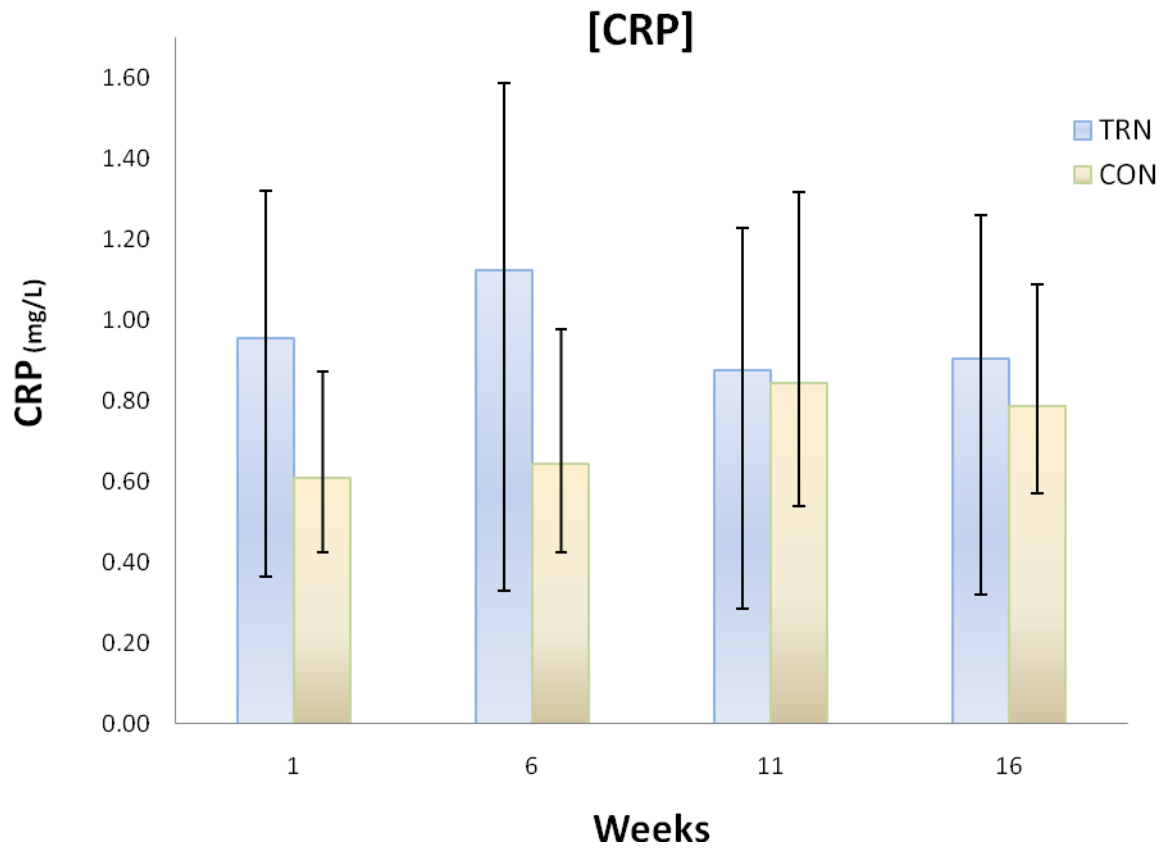


Fig 3.1. Change in CRP concentrations in training (TRN) and control (CON) subjects over the course of a half marathon training program. Values are mean  $\pm$  95% CI.

Table 3.1 - Physical characteristics at baseline and week 16

Variable	Control (n=22)		Treatment (n=20)	
	Week 0	Week 16	Week 0	Week 16
Age (yr)	27.8 ± 1.4	-	29.3 ± 1.0	-
Height (cm)	178.9 ± 1.2	-	177.1 ± 0.9	-
Weight (kg)	85.4 ± 2.5	86.2 ± 2.5	88.8 ± 2.8	87.5 ± 2.7
BMI	26.7 ± 0.7	27.0 ± 0.7	28.3 ± 0.9	27.9 ± 0.8*
BF%	26.8 ± 1.4	27.5 ± 1.4	29.1 ± 1.8	28.2 ± 1.9*
VO <sub>2max</sub> L•min <sup>-1</sup>	3.3 ± 0.1	3.3 ± 0.1	3.3 ± 0.1	3.6 ± 0.2*
mL•kg <sup>-1</sup> •min <sup>-1</sup>	38.8 ± 1.0	39.0 ± 1.4	37.0 ± 1.6	42.2 ± 1.9*

Values are means ± SE. BMI, body mass index; BF%, body fat percentage; VO<sub>2max</sub>, maximal aerobic capacity. \*Significantly different than week 0 ( $P < 0.05$ ).

Table 3.2 - Hemodynamic data at baseline and weeks 6, 11, and 16

Variable	Group	Week			
		0	6	11	16
RHR (beats•min <sup>-1</sup> )	CON	73 ± 3	67 ± 2*	75 ± 3 <sup>^</sup>	76 ± 3 <sup>^</sup>
	TRN	77 ± 3	68 ± 2*	72 ± 2*	68 ± 3 <sup>*#†</sup>
SBP (mm Hg)	CON	117 ± 2	117 ± 2	119 ± 2	113 ± 2 <sup>#</sup>
	TRN	123 ± 2 <sup>†</sup>	126 ± 2 <sup>*†</sup>	118 ± 2 <sup>*^</sup>	114 ± 2 <sup>*^</sup>
DBP (mm Hg)	CON	76 ± 2	76 ± 1	81 ± 1 <sup>*^</sup>	77 ± 1 <sup>#</sup>
	TRN	81 ± 2 <sup>†</sup>	80 ± 2 <sup>†</sup>	78 ± 2	73 ± 2 <sup>*^#</sup>

Values are means ± SE. RHR, heart rate at rest; SBP, systolic blood pressure; DBP, diastolic blood pressure. \*Significantly different than week 0 ( $P < 0.05$ ). <sup>^</sup>Significantly different than week 6 ( $P < 0.01$ ). <sup>#</sup>Significantly different than week 11 ( $P < 0.05$ ). <sup>†</sup>Significantly different than control group ( $P < 0.05$ ).

*Table 3.3 - Spearman Rank Correlation Coefficients between CRP and other variables at baseline for all subjects combined, the training group (TRN), and the control group (CON).*

<b>Variable</b>	<b>CRP</b> (combined, n=42)	<b>P</b>	<b>CRP</b> (TRN, n=20)	<b>P</b>	<b>CRP</b> (CON, n=22)	<b>P</b>
Weight	.324	.039	0.448	0.055	0.156	0.487
BMI	.478	.002	0.493	0.032	0.417	0.054
BF%	.525	.000	0.561	0.013	0.468	0.028
RHR	.141	.379	-0.027	0.912	0.265	0.233
SBP	.192	.236	0.531	0.019	-0.131	0.572
DBP	.271	.091	0.437	0.061	0.020	0.931
VO <sub>2 max</sub>	-.338	.031	-0.428	0.068	-0.195	0.384

CRP, C-reactive protein; BMI, body mass index; BF%, body fat percentage; RHR, heart rate at rest; SBP, systolic blood pressure; DBP, diastolic blood pressure; VO<sub>2max</sub>, maximum volume of oxygen consumption.

*Table 3.4 - Spearman Rank Correlation Coefficients between changes in CRP and changes in other variables in the training (TRN) and control (CON) groups over the course of the training program.*

<b>Variable</b>	<b>CRP</b> (TRN, n=20)	<b>P</b>	<b>CRP</b> (CON, n=22)	<b>P</b>
Weight	<b>-.464*</b>	.046	-0.280	0.207
BMI	<b>-.456*</b>	.050	-0.124	0.579
% BF	-.189	.437	0.219	0.329
RHR	-.231	.341	-0.151	0.502
SBP	-.239	.324	-0.141	0.543
DBP	.142	.561	0.005	0.984
VO <sub>2max</sub>	.011	.964	-0.179	0.424

CRP, C-reactive protein; BMI, body mass index; BF%, body fat percentage; RHR, heart rate at rest; SBP, systolic blood pressure; DBP, diastolic blood pressure; VO<sub>2max</sub>, maximum volume of oxygen consumption.

## Chapter 4 - Discussion

The purpose of this study was to determine the effects of a 17-wk half marathon TP on CRP concentrations and to examine the potential association between changes in cardiovascular fitness and CRP concentrations in a population of apparently healthy, untrained men. Despite training-induced improvements in several cardiovascular ( $VO_{2max}$ , RHR, SBP, and DBP) and anthropometric (BW, BF%, BMI) variables, mean CRP concentrations remained unchanged. The apparent disconnect between improvements in cardiovascular fitness and CRP concentrations may be due to subject population, baseline CRP values, or training methods as discussed below.

Cross-sectional evidence of the relationship between physical activity/cardiovascular fitness and CRP concentrations has been consistently established (1, 2, 4, 8, 10, 25, 45). High levels of physical activity and cardiovascular fitness have been shown to correlate with lower CRP concentrations independent of other variables including body composition (1, 2). A cross-sectional examination of the subjects in the current study at baseline demonstrates significant correlations (a positive linear relationship between CRP and BMI and BF% and an inverse correlation between CRP and fitness level) similar to those published in previous cross-sectional studies. However, the cross-sectional nature of these results precludes establishment of a causal link between physical activity/cardiovascular fitness and CRP concentrations.

Despite the abundance of cross-sectional evidence that supports a relationship between physical activity/cardiovascular fitness and CRP concentrations, only a limited number of longitudinal studies have shown significant decreases in CRP concentrations with exercise training (19, 33). Hewitt et al. (19) found significant improvements in CRP

concentrations over the first 8 wks of a progressive aerobic exercise-training program in healthy but sedentary civil servants. However, several other longitudinal training studies have found little or no effect of aerobic exercise training on CRP concentrations in relatively healthy individuals (9, 14, 31, 39). The subjects in the current study exhibited improvements in  $VO_{2max}$  (15%) that are comparable (9-33%) to training studies of similar durations (8 wks to 9 mos) (16, 20, 31, 36, 51). Similarly, the TP was associated with a 3.2% decrease in BF%, which is consistent with other studies that also found decreases of 1.7-11.3% after training programs of 6-40 wks in length (20, 22, 37, 48). The current study agrees with the results of Marcell et al. (31) who reported that despite an 18.1% increase in aerobic capacity, neither moderate (30 min of exercise, 5 d•wk<sup>-1</sup>) nor intense (30 min of exercise, 5 d•wk<sup>-1</sup> at 80-90% of  $HR_{max}$ ) aerobic training over 16-wks resulted in significant changes in CRP concentrations. The results of Marcell et al. (31) are especially convincing given that even a subset of subjects with the greatest improvement in estimated  $VO_{2max}$  ( $\approx 18\%$ ) exhibited no change in CRP concentrations.

One possible explanation for the lack of change in CRP concentrations across the 17-wk TP in this study may involve the relatively low baseline values of the subjects. Current American Heart Association guidelines suggest that CRP concentrations less than 1.0 mg•L<sup>-1</sup>, between 1.0-3.0 mg•L<sup>-1</sup>, and greater than 3.0 mg•L<sup>-1</sup> correspond to low, average, and high risks for a future cardiovascular event, respectively (44). The training group had a geometric mean baseline CRP concentration of 0.96 mg•L<sup>-1</sup> (1.47 mg•L<sup>-1</sup> prior to log transformation) that would qualify them as low risk and possibly leave them with little room for improvement due to aerobic training. Marcell et al. (31), Murphy et al. (39) and Campbell et al. (9) found no aerobic-training-induced improvements in CRP

concentrations in subjects having average baseline CRP concentrations of 3.4, 1.9, and 1.16 mg•L<sup>-1</sup>, respectively. Longitudinal training studies that have reported significant reductions in CRP concentrations with aerobic training have examined elderly (24) and diseased populations (18, 35, 57) with baseline CRP concentrations ranging from 4.8–7.5 mg•L<sup>-1</sup>. Only one study has shown a decrease in CRP concentrations in healthy subjects with low baseline values undergoing a 9-month marathon training program (33). However, the findings in this study may be due largely to the contributions of two subjects (n=12) with relatively high baseline values of 5.44 and 4.04 mg/L who demonstrated reductions of 4.48 (82%) and 3.07 (76%) mg/L, respectively. Therefore, as reported by Lakka et al. (26), it is likely that exercise-induced changes in CRP concentrations, much like changes in blood lipids (29), are strongly influenced by the baseline concentrations prior to starting the TP.

Another possible explanation for the lack of change in CRP concentrations in the current study may arise from the intensity and volume of training. A recent meta-analysis of studies on high density lipoprotein cholesterol (HDL-C) and triglycerides (TG) suggests that a threshold volume of exercise is needed to produce positive improvements in HDL-C and TG (12, 13). Durstine et al. (13) suggest that a minimum running volume of 11-23 km may be required to favorably alter blood lipid concentrations when training is performed at a low intensity. Another recent study suggests that changes in coronary heart risk factors are influenced by training intensity (40). It is therefore likely that a similar threshold of training may be required to affect CRP concentrations. On the low end of the training volume spectrum, a worksite walking program, consisting of 45 min of walking 2 d•wk<sup>-1</sup> for 8 wks, revealed no significant changes in CRP concentrations



despite significant improvements in BF% and SBP in a healthy, middle-aged population (39). Conversely, Mattusch et al. (33) found a significant decrease in CRP concentrations in moderately trained marathon runners over the course of a 36-wk training program. The training volume used (mean of 53 km•wk<sup>-1</sup>) far exceeded the level of training performed by the subjects in the current study (17.2 ± 1.2 km•wk<sup>-1</sup>). When considered together, these studies suggest that a higher threshold of training volume and/or intensity may be needed to induce simultaneous cardiovascular and CRP improvements in apparently healthy individuals. The training volume and intensity of the current study is between those of Murphy et al. (39) and Mattusch et al. (33) and failed to reduce CRP concentrations. It is possible that either higher volumes of training or a greater training intensity may be necessary as a training stimulus. However, this has not been systematically studied and future research is needed to elucidate the potential influence of exercise volume and intensity on CRP concentrations. With varying levels of training volume and intensity, consideration should be given to potential changes in the duration of the acute phase response that may mask the effect of the TP.

The baseline BMI of 28.3 ± 0.9 of the subjects in this study classified them as overweight and borderline obese. Cross-sectional studies have suggested a strong, positive relationship between BMI and CRP concentrations (10, 45-47) that may be more profound than the association between fitness level and CRP concentrations (38). Similar cross-sectional results have linked measurements of BF% to CRP concentrations (6, 15, 28, 54). However, as evidenced in the current study, and in other recent longitudinal studies (14, 31, 41, 56), there has been a failure to conclusively demonstrate a relationship between changes in body composition and changes in CRP concentrations. In

a study that focused primarily on weight loss and dietary changes, Okita et al. (41) evaluated Japanese women before and after a 2-mo weight reduction program. Despite significant reductions in both CRP concentrations (-35%) and BW (-4.6%), the decrease in CRP concentrations was not significantly correlated with the rate of weight reduction ( $r=0.03$ ). In the current study, TRN actually demonstrated a minor inverse association between changes in body weight and BMI and changes in CRP concentrations (Table 5). However, this inverse relationship was influenced by two subjects with very large increases in CRP concentrations (132%) and modest reductions in BMI (-4.7%) in comparison to the remaining subjects who had an average  $1.2 \pm 0.01\%$  reduction in BMI and a  $4.7 \pm 16.9\%$  increase in CRP concentration. Exclusion of these two subjects renders the correlation of change between CRP and BMI insignificant ( $r=-0.34$ ,  $P=0.18$ ). Regardless, this data fails to demonstrate a positive relationship between changes in BMI and CRP concentrations in apparently healthy, untrained men.

This study had a number of limitations that should be discussed. The field-based nature of this study did not allow for an accurate assessment of exercise intensity and compliance to the training protocol was not assured by daily supervision. Overall, TRN completed an average of 30 of the 48 scheduled training runs ( $62.6 \pm 6.0\%$ ) with some subjects completing extra runs while others struggled to make the weekly minimum volumes. This level of adherence agrees well with the exercise adherence range of 63-88% reported in a meta-analysis of intention to treat models by Martin et al. (32) and exceeds the 50% adherence level suggested by Dishman et al. (11). The limitations in experimental control of this field-based study are balanced by a greater translation to the general public. The TRN subjects received a realistic level of instruction and supervision

that was identical to the other TP participants not in the study. This is far different from the highly supervised, exercise training programs of other studies (19, 23, 56) that required extensive manpower not readily available to the general exercising public. These studies, therefore, may not represent a viable method of reducing the concentration of inflammatory markers in the general population.

The current guidelines for the analysis of CRP concentrations recommend using independent sampling performed 2 wks apart to account for possible acute fluctuations (44). The longitudinal study design limited our ability to perform repeated sampling of our subjects at a given time point without disrupting their TP. Furthermore, serum samples were frozen and analyzed together at the conclusion of the study to reduce intra- and inter-subject assay variability. Therefore, it was not possible to identify acute CRP fluctuations immediately after a blood draw. Instead, subjects were asked to fill out a questionnaire regarding their recent health and injury status before each blood draw. In extreme cases, blood draws were delayed for individuals who were at risk for acute CRP responses. However, there were few reported injuries or illnesses that corresponded with elevated or abnormal CRP concentrations.

In conclusion, our study showed that training-related increases in cardiovascular fitness and its beneficial impact on bodyweight and body composition does not appear to affect CRP concentration in apparently healthy, untrained men. Although assessing CRP concentrations in addition to traditional risk factors may improve CVD prediction in individuals considered to be at intermediate risk, there appears to be little utility in monitoring exercise training-induced changes in CRP concentrations in apparently healthy, untrained men with low baseline concentrations.

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