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Changes in C-reactive protein from low-fat diet and/or physical activity in men and women with and without metabolic syndrome

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Abstract

Change in high-sensitivity C-reactive protein (CRP) from low-fat diet (diet) and physical activity (PA) interventions is relatively unknown for adults with metabolic syndrome. The objective of the study was to assess CRP change (ΔCRP) with diet and/or PA in men and women with and without metabolic syndrome. Men (n = 149) and postmenopausal women (n = 125) with elevated low-density lipoprotein cholesterol and low high-density lipoprotein cholesterol were recruited into a 1-year randomized controlled trial. Treatment groups were as follows: control, diet (reduced total fat, saturated fat, and cholesterol intake), PA (45-60 minutes at 60%-85% maximum heart rate), or diet + PA. Weight loss was not an intervention focus. *Metabolic syndrome* was defined using the American Heart Association/National Heart, Lung, and Blood Institute criteria. Stored plasma samples were analyzed for CRP. Change in CRP was compared between treatments, within sex and metabolic syndrome status, using analysis of covariance, including covariates for baseline CRP and body fat change. For women with metabolic syndrome (n = 39), ΔCRP was greater in diet vs control (−1.2 ± 0.4, $P = .009$), diet + PA vs control (−1.3 ± 0.4, $P = .006$), and diet + PA vs PA (−1.1 ± 0.4, $P = .02$). Women with metabolic syndrome receiving the diet component (diet or diet + PA) had greater ΔCRP compared with those who did not (control or PA) ($P = .001$). Change in CRP was not significantly different between intervention groups in men overall, women overall, men with (n = 47) or without metabolic syndrome (n = 102), or women without metabolic syndrome (n = 86). Low-fat diet may be the most effective treatment for reducing CRP in women with metabolic syndrome.

1. Introduction

The process of atherosclerosis leading to cardiovascular disease is hypothesized to be controlled through inflammation [1]. Chronic inflammation is characterized by elevated levels of C-reactive protein (CRP), an acute-phase reactant released from the liver in response to various cytokines, such as interleukin-6 and tumor necrosis factor–α. It is also hypothesized that CRP is a feature of metabolic syndrome, a constellation of metabolic and/or lipid abnormalities that predispose one to cardiovascular disease [2].

Approximately 36% of Americans have metabolic syndrome [3], and most individuals with metabolic syndrome also have elevated CRP [4]. Whereas CRP and metabolic syndrome are each independent predictors of cardiovascular events [5,6], the combination adds predictive and prognostic value to the estimation of cardiovascular disease events [6,7].

Positive lifestyle habits such as incorporation of a low-fat diet and increasing physical activity improve cardiovascular risk and mortality [8,9]. Diet- or physical activity–induced weight loss is associated with improvements of the individual components of metabolic syndrome (waist circumference, high-density lipoprotein cholesterol [HDL-C], triglycerides, blood pressure, fasting glucose) [9] and CRP levels [10]. The release of CRP is controlled, in part, by cytokines that can be stored and released from adipose tissue [11]. Therefore, reduction in body fat [10] is associated with reduction in the level of circulating CRP. Studies that

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combined dietary change and physical activity show reductions in CRP for individuals with metabolic syndrome [12-14], even when weight loss was not an intervention goal [12]. However, few studies have compared the independent and combined effects of low-fat diet and physical activity, without the influence of intentional weight loss, on CRP levels in individuals with metabolic syndrome.

Although inconclusive, some research suggests that women have higher CRP levels than their age-matched male counterparts [15]. Some diet and/or physical activity studies that examine CRP as an outcome either are in a single sex [16,17] or combine sexes in the analysis [12,13,18] without statistical adjustment [12,13]. Higher CRP values at baseline can result in larger decreases in CRP with both low-fat diet [19,20] and exercise [21-23]. Thus, analyses of CRP from lifestyle treatment should test for possible differing sex responses. Sex-stratified analyses in insulin-resistant individuals revealed similar magnitudes of CRP change from diet plus physical activity [24]; however, these results may not be generalizable to individuals who have multiple lipid and metabolic disorders.

Thus, the purpose of this study was to assess CRP change from a low-fat diet and/or physical activity treatment, relative to controls, in men and women with and without metabolic syndrome.

2. Methods

The Diet and Exercise for Elevated Risk Trial (DEER) was a 1-year–long, single-center randomized controlled clinical trial initiated in 1992 at Stanford Medical School's Prevention Research Center [25]. The primary and secondary outcomes were the effects on HDL-C and low-density lipoprotein cholesterol (LDL-C), respectively, of a low-fat diet and/or increased physical activity intervention in individuals with *elevated cardiovascular disease risk* (defined as having low HDL-C and elevated LDL-C). Results of the original study have been published [25]. This project uses the existing data set and stored baseline and 1-year plasma blood samples to examine, retrospectively, the effect of the diet and physical activity interventions on high-sensitivity CRP (hs-CRP).

Specific eligibility criteria were as follows: for men, age 30 to 64 years and HDL-C less than 45 mg/dL combined with LDL-C from 126 to 189 mg/dL; for women, age 45 to 64 years, postmenopausal, and HDL-C less than 60 mg/dL combined with LDL-C from 126 to 209 mg/dL. Exclusion criteria included body mass index (BMI) of at least 34 kg/m^2 for men and at least 32 kg/m^2 for woman, and the following for both sexes: blood pressure of at least 160/85 mm Hg; fasting triglycerides of at least 500 mg/dL; fasting glucose of at least 140 mg/dL; abnormal baseline maximal exercise treadmill test result; history of heart disease, stroke, insulin-dependent diabetes mellitus, recent cancer, or diagnosis of a life-threatening disease; neuromuscular or orthopedic disability that would preclude brisk walking; use of lipid-lowering medication or antihypertensive medications; noneuthyroid; low hematocrit; smoking more than 9 cigarettes per day; more than 4 alcoholic drinks per day; inability to attend sessions; by judgment of a physician; or unwillingness to accept random assignment to a diet or exercise intervention.

Participant eligibility and baseline information were assessed by telephone and clinic screening before randomization. All clinic staff members performing measurement were blinded to the participants' group assignment.

Venous blood was collected in the morning at 2 separate visits at baseline and at 1 year, after participants had fasted, that is, no food or drink (except water) for 12 hours; had no alcohol consumption or vigorous physical activity for 24 hours, and had abstained from smoking for 1 hour. Blood collected for plasma was mixed with 1.5 mg/mL of EDTA and placed on ice before and after refrigerated centrifugation, and aliquoted samples were stored and kept frozen at −80°C.

Plasma hs-CRP concentrations were determined on stored plasma samples randomly chosen from 2 available samples at each time point. Immunoturbidimetric assay was performed on a Hitachi 917 analyzer (Roche Diagnostics, Indianapolis, IN) using reagents and calibrators from DiaSorin (Stillwater, MN). This assay has a sensitivity of 0.03 mg/L. The day-to-day variability of the assay at concentrations of 0.91, 3.07, and 13.38 mg/L are 2.81%, 1.61%, and 1.1%, respectively.

Total cholesterol and triglycerides were measured using enzymatic procedures [26,27]. High-density lipoprotein cholesterol was measured using dextran sulfate–magnesium precipitation [28] as well as enzymatic measurement of nonprecipitated cholesterol [26]. Very low-density lipoprotein was calculated as triglycerides divided by 5 [29], unless triglyceride levels exceeded 400 mg/dL, in which case enzymatic methods were used [26] after ultracentrifugation for 18 hours [30]. Low-density lipoprotein cholesterol was calculated as total cholesterol minus the sum of HDL-C + very low-density lipoprotein [29]. Lipoprotein values were averaged between the 2 baseline fasting values.

Blood pressure was measured from the brachial artery using a mercury sphygmomanometer and stethoscope. Averages for 2 readings of the first and fifth Korotkoff phase were recorded as systolic and diastolic blood pressure [31].

Body weight was measured with a standard medical beam balance scale. Height was measured using a Harpenden stadiometer. Body mass index was calculated as body weight, in kilograms, divided by height, in meters squared. The BMI categories were determined using National Institutes of Health guidelines: (1) normal weight (18.5-24.9 kg/m^2), (2) overweight (25.0-29.9 kg/m^2), and (3) obese ($\geq$30 kg/m^2) [32]. Waist circumference was taken at the narrowest circumference of the torso when viewed from the front. Skinfold measures were made in triplicate on the right side of the body and averaged. For men, the locations of the skinfolds were chest, abdomen, and thigh. For women,

the locations were triceps, suprailiac, and thigh. Body density was estimated using generalized equations [33,34], and percentage of body fat was calculated using the Siri equation [35].

The presence of metabolic syndrome was determined using the joint American Heart Association/National Heart, Lung, and Blood Institute guidelines [36]. Clinical identification of the metabolic syndrome includes at least 3 of the following: (1) waist circumference greater than 102 cm in men or greater than 88 cm in women, (2) triglycerides of at least 150 mg/dL or on drug treatment, (3) HDL-C less than 40 mg/dL for men or less than 50 mg/dL for women or on drug treatment, (4) blood pressure of at least 130/85 mm Hg or on drug treatment, and (5) fasting glucose of at least 100 mg/dL or on drug treatment [36].

Eligible participants were recruited and then computer randomized within cohort into treatment groups, using a modified Efron [37] procedure that weighted the probability of assignment to balance groups for sample size, HDL-C, and LDL-C measures. The 4 treatment groups were (1) control, (2) diet, (3) physical activity (PA), and (4) diet + PA.

The participants in the control group were instructed to maintain their usual lifestyle habits for the duration of the trial.

The dietary goals for the diet group were based on the National Cholesterol Education Program Step II Guidelines [38]: (1) reduce total fat to less than 30% of total calories, (2) reduce saturated fat to less 7% of total calories, and (3) reduce dietary cholesterol to less than 200 mg per day. Each participant met with a dietician to individualize dietary recommendations and attended 8 group sessions about the National Cholesterol Education Program Step II Guidelines.

Participants in the PA group had an individualized physical activity prescription based on the results of a breath-by-breath maximal treadmill exercise test. All PA participants began with 6 weeks of aerobics sessions 3 days a week for 1 hour. After the adaption phase, PA participants were instructed to perform 20 minutes 3 times a week at 60% to 85% maximum heart rate, increasing duration over the course of the year to 45 to 60 total minutes. Progression of the PA program was negotiated between the exercise leader and the participant. Physical activity individuals who were already active before randomization were asked to add at least 20 minutes 3 times a week to their existing programs to elicit physiologic changes from an increase in PA. Participants opted to either continue supervised training or adopt a home program for the remaining 8 months. The typical PA program involved a minimum of 10 miles per week of brisk walking, jogging, or running.

Participants in the diet + PA group received both the diet and PA treatments as individual treatments. To prevent contamination, diet + PA had separate diet and PA sessions from the other groups; and project staff leading the individual sessions made no reference to the other treatment groups.

The diet, PA, and diet + PA groups did not emphasize weight loss as an intervention goal.

All intervention methods and laboratory analyses were approved by the Institutional Review Board of Stanford University. The CRP secondary data analyses were approved by the Institutional Review Board of the University of Maryland.

2.1. Statistical analysis

All statistical analyses were performed by using SAS software version 9.1 (SAS Institute, Cary, NC). Participants with hs-CRP levels at baseline or follow-up greater than 10 mg/L were excluded from the analysis to eliminate the acute effects of infection (n = 9) [39]. Because the original trial was designed with sex-specific eligibility criteria to identify high-risk individuals, it was powered for sex-stratified analyses [25]. Because of this and our a priori hypotheses, all analyses were stratified by sex.

Wilcoxon rank sum tests were used to compare hs-CRP baseline level between metabolic syndrome status groups. Analysis of covariance (ANCOVA) was used to test the effects of diet and PA on hs-CRP change (ΔCRP) between treatment groups for men overall, women overall, men with metabolic syndrome, women with metabolic syndrome, men without metabolic syndrome, and women without metabolic syndrome. Older age is a known influence for both metabolic syndrome [3] and hs-CRP [15]. Furthermore, hs-CRP also increases with metabolic syndrome status [4]; thus, it was necessary to account for these differences in the analysis. The analyses in men and women with metabolic syndrome are exploratory because of the limited sample size in each intervention group.

The ΔCRP was calculated as the difference between the follow-up and baseline value and was a normally distributed variable; thus, a transformation was not necessary. Differences between treatment groups for ΔCRP were compared for (1) control vs diet, (2) control vs PA, (3) control vs diet + PA, (4) diet vs diet + PA, and (5) PA vs diet + PA. An α level of .01 was adopted to control for type I error and to account for the multiple statistical comparisons. The ANCOVAs controlled for baseline hs-CRP, cohort, baseline body fat (percentage), change in body fat (percentage), cigarettes per day, alcoholic drinks per day, age, and, for women, menopausal hormonal therapy (MHT) status. High-sensitivity CRP was significantly higher at baseline and follow-up for women on MHT; thus, it was included as a covariate. However, change in CRP was not significantly different between women with or without MHT; thus, MHT-stratified analyses were not warranted. Despite weight loss not being a focus of the current intervention, preliminary analysis found significantly greater weight loss, BMI reductions, and percentage body fat loss in the diet and diet + PA groups relative to control in both men and women. To control for group differences and to represent changes in body composition resulting from weight loss, percentage body fat and baseline body fat were chosen as covariates for the models. Analyses were also run without the covariates

for body fat. In case of significant differences in ΔCRP between intervention groups, a 2-way ANCOVA was analyzed in which diet (yes/no), PA (yes/no), and its interaction were used to distinguish the most important lifestyle component(s).

3. Results

Of the total 377 DEER participants who were randomized for the study, 278 participants (73%, 149 men and 125 women) were analyzed for ΔCRP. Participants were not included in the analysis because of incomplete data, which were assumed to be missing completely at random. hs-CRP baseline levels were not significantly different between participants included in this analysis and participants with incomplete data (data not shown).

Men and women had an average age of 49.0 ± 8.8 and 57.6 ± 5.0 years, respectively. Participants mostly were white (~85%), were nonsmokers (~98%), and consumed less than 1 alcoholic drink per day (~95%). Men and women were highly educated: 61% of men and 43% of women had a college degree or greater. The mean BMI for men was approximately 26 kg/m^2, with 26% normal weight, 58% overweight, and 16% obese. For women, mean BMI was approximately 26 kg/m^2, with 38% normal weight, 48% overweight, and 14% obese. Approximately 43% of women were on MHT. Mean ± SD baseline values for hs-CRP were 1.3 ± 1.3 mg/L (median, 0.9; interquartile range, 0.5-1.4) for men and 2.0 ± 1.8 mg/L (median, 1.5; interquartile range, 0.6-2.6) for women. There were no between-intervention group differences at baseline for hs-CRP in either men or women. Table 1 shows the baseline study variables by treatment groups for men and women.

Metabolic syndrome was present in 30% of men and 32% of women at baseline. In men with metabolic syndrome, baseline hs-CRP (mean ± SD) was 1.5 ± 1.4 mg/L (median, 0.9; interquartile range, 0.3-1.5), compared with 1.2 ± 1.2 mg/L (median, 0.9; interquartile range, 0.4-1.4) in men without metabolic syndrome ($P = .24$). Baseline hs-CRP was 2.4 ± 1.7 mg/L (median, 1.9; interquartile range, 0.4-3.4) in women with metabolic syndrome and 1.8 ± 1.9 mg/L (median, 1.3; interquartile range, 0.6-2.1) in women without metabolic syndrome ($P = .008$).

Table 1
Baseline characteristics for men and women according to intervention group

	Control	Diet	PA	Diet + PA
Men (n = 149)				
n	33	39	35	42
Age	48.8 ± 9.8	49.3 ± 9.2	49.5 ± 8.7	48.5 ± 8.1
White (%)	91	80	91	81
Nonsmokers (%)	97	100	100	100
≤1 Alcoholic drink per day (%)	88	92	91	95
HDL-C (mg/dL)	33.6 ± 5.7	35.1 ± 5.3	34.7 ± 4.2	34.5 ± 4.8
LDL-C (mg/dL)	158.6 ± 16.8	156.2 ± 17.9	156.1 ± 16.2	156.5 ± 16.4
Waist circumference (cm)	95.3 ± 9.4	95.9 ± 10.2	95.4 ± 7.9	94.8 ± 8.5
Body fat (%)	21.1 ± 3.6	21.3 ± 4.5	22.3 ± 5.0	21.6 ± 4.1
BMI (kg/m^2)	26.7 ± 3.2	26.9 ± 3.1	26.9 ± 2.6	26.6 ± 2.6
Metabolic syndrome, n (%)	9 (28)	13 (33)	11 (31)	14 (33)
hs-CRP (mg/L)				
Mean ± SD	1.4 ± 1.5	1.0 ± 1.2	1.3 ± 1.3	1.4 ± 1.3
Median[a] (interquartile range)	0.9 (0.3-1.4)	0.7 (0.4-1.0)	0.8 (0.4-1.3)	1.0 (0.4-1.7)
High-risk CRP (>3 mg/L), n (%)	3 (9)	2 (5)	5 (14)	5 (12)
Women (n = 125)				
n	34	32	28	31
Age	58.4 ± 4.8	57.9 ± 5.4	57.5 ± 5.4	56.6 ± 4.7
White (%)	85	91	89	90
Nonsmokers (%)	100	100	100	90
≤1 Alcoholic drink per day (%)	94	97	93	100
HDL-C (mg/dL)	45.1 ± 7.3	44.7 ± 7.3	44.3 ± 7.8	45.0 ± 7.2
LDL-C (mg/dL)	166.1 ± 19.1	163.1 ± 24.3	166.1 ± 23.3	165.7 ± 20.6
Waist circumference (cm)	85.4 ± 11.6	85.3 ± 7.8	83.7 ± 7.0	83.8 ± 9.8
Body fat (%)	31.7 ± 5.7	31.8 ± 4.8	31.9 ± 4.8	32.7 ± 5.3
BMI (kg/m^2)	26.0 ± 3.9	26.6 ± 2.8	25.9 ± 2.4	26.4 ± 3.5
Metabolic syndrome, n (%)	9 (26)	9 (28)	9 (32)	12 (39)
hs-CRP (mg/L)				
Mean ± SD	2.2 ± 2.2	1.9 ± 1.6	1.8 ± 1.6	2.0 ± 1.9
Median[a] (interquartile range)	1.4 (0.3-2.6)	1.3 (0.4-2.2)	1.5(0.6-2.2)	1.5 (0.6-2.5)
High risk CRP (>3 mg/L), n (%)	9 (25)	6 (21)	4 (14)	5 (19)

Mean ± SD is presented. No significant differences in any variable presented between groups in either men or women at baseline.

[a] High-sensitivity CRP is a skewed variable; thus, both mean and median values are provided.

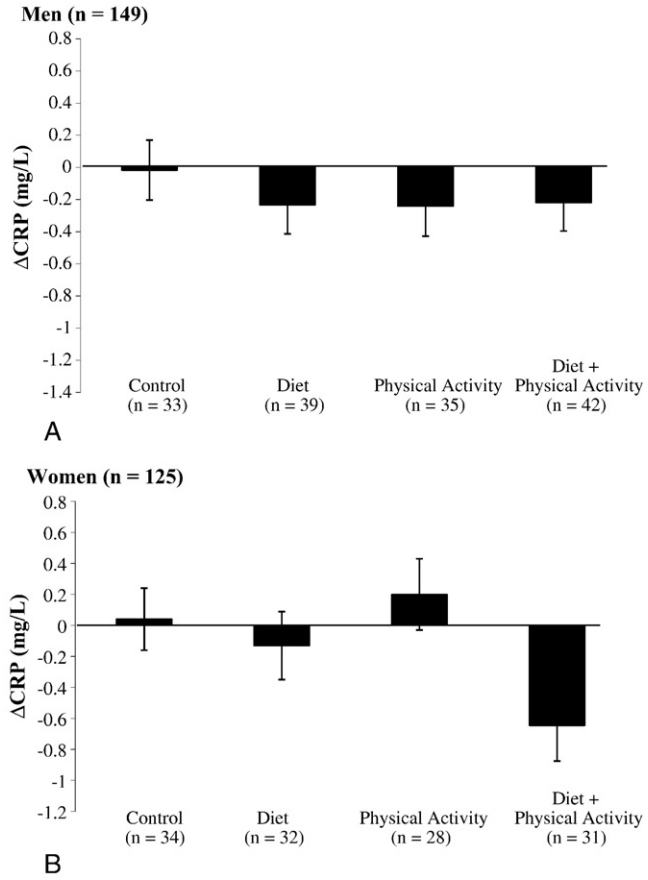

Fig. 1. Adjusted ΔCRP (in milligrams per liter) is presented (mean ± SE) for men and woman overall. Analysis of covariance statistical comparisons between treatment groups adjusted for the following: baseline hs-CRP, baseline body fat percentage, change in body fat, cohort, cigarettes per day, alcoholic drinks per day, age, and MHT (as appropriate). A, No differences for ΔCRP were found in men (n = 149) between control, diet, PA, or diet + PA groups. B, No differences for ΔCRP were found in women (n = 125) between control, diet, PA, or diet + PA groups.

There was little loss to follow-up. Retention was 98% and 96% in men and women, respectively [25]. Data from the original DEER study indicate adherence to the assigned treatment groups: the change in fitness (in milliliters per kilogram per minute from Vo_2max) from baseline was significantly greater in the PA group (men, +1.9 ± 4.3 mL/kg/min women, +2.4 ± 3.3 mL/kg/min and diet + PA groups (men, 4.7 ± 4.8 mL/kg/min women, 3.7 ± 3.8 mL/kg/min) relative to controls [25]. Changes in total fat, saturated fat, and cholesterol were significantly greater within the diet group and diet + PA group relative to the control group for both men and women. For example, for women, reductions in total fat intake (percentage) were greater in the diet (−5.7% ± 7.4%) and diet + PA (−8.0% ± 5.8%) groups relative to controls [25]. The main findings from DEER with respect to the lipid parameters showed similar changes in men and women: no change in HDL-C for any group and a significant decrease in LDL-C in the diet + PA vs control [25].

3.1. ΔCRP for men and women overall

For men, 15 (10%) were classified as high CRP risk (>3 mg/L) [39] at baseline; and at follow-up, 9 (6%) remained in the high-risk category. For women, 24 (19%) were identified as high-risk CRP at baseline; and 21 (17%) women remained in the high-risk category at follow-up. There were no differences for ΔCRP between control, diet, PA, and diet + PA for men overall (P = .99) and women overall (P = .06) (Fig. 1).

3.2. ΔCRP for men and women with metabolic syndrome

For men with metabolic syndrome, no differences were found for ΔCRP between treatments (P = .77) (Fig. 2). For

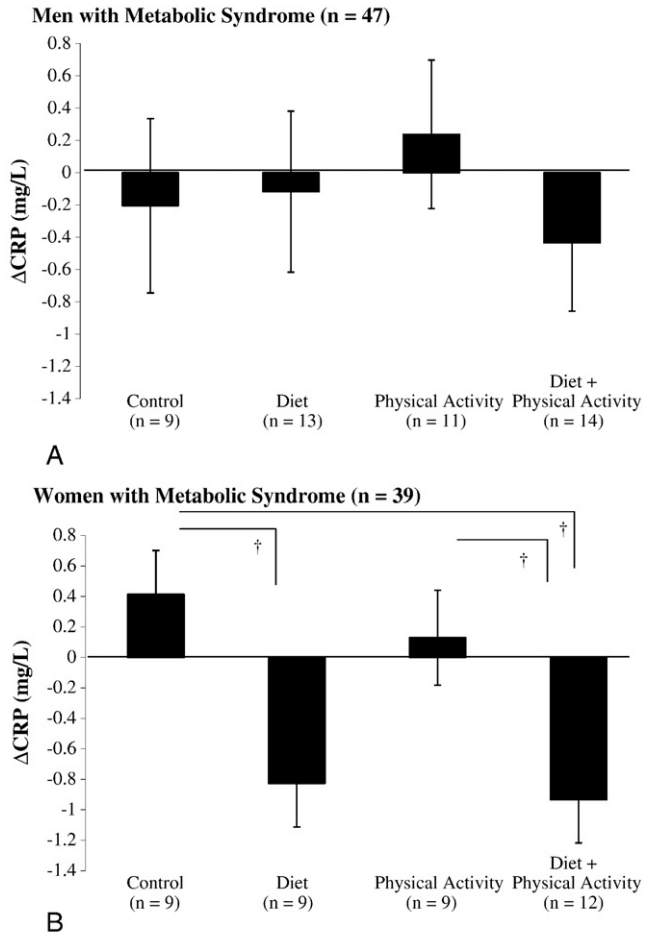

Fig. 2. Adjusted ΔCRP (in milligrams per liter) is shown (mean ± SE) for men and woman with metabolic syndrome. Analysis of covariance comparisons between treatment groups adjusted for the following: baseline hs-CRP, baseline body fat percentage, cohort, change in body fat, cigarettes per day, alcoholic drinks per day, age, and MHT (as appropriate). A, Change in CRP for men with metabolic syndrome (n = 47) was not different between control, low-fat diet, PA, or diet + PA in men with metabolic syndrome. B, Change in CRP for women with metabolic syndrome (n = 39) was different between the control and diet groups (P = .009), control and diet + PA groups (P = .006), and PA and diet + PA groups (P = .02).

women with metabolic syndrome, ΔCRP differed between treatment groups ($P < .01$): Women with metabolic syndrome had greater ΔCRP when comparing the diet vs control (−1.2 ± 0.4 mg/L, $P = .009$), diet + PA vs control (−1.3 ± 0.4 mg/L, $P = .006$), and diet + PA vs PA (−1.1 ± 0.4 mg/L, $P = .02$) groups (Fig. 2). The 2-way ANCOVA analysis found that woman with metabolic syndrome who received the diet component (diet and diet + PA) had greater ΔCRP than those who did not receive the diet (control and PA) (1.2 ± 0.3 mg/L, $P = .001$).

3.3. ΔCRP for men and women without metabolic syndrome

No differences were found for ΔCRP between treatments for men without metabolic syndrome ($P = .79$) or for women without metabolic syndrome ($P = .31$) (Fig. 3).

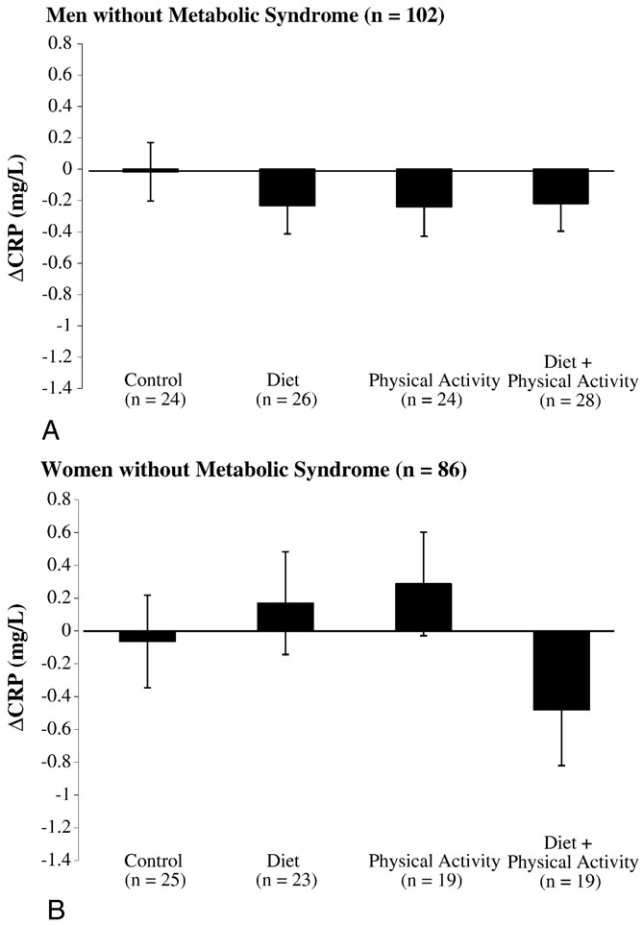

Fig. 3. Adjusted ΔCRP (in milligrams per liter) is shown for men and woman without metabolic syndrome (means ± SE). Analysis of covariance statistical comparisons between treatment groups adjusted for the following: baseline hs-CRP, baseline body fat percentage, cohort, change in body fat, cigarettes per day, alcoholic drinks per day, age, and MHT (as appropriate). A, Change in CRP for men without metabolic syndrome (n = 102) did not show significant differences between treatment groups. B, Change in CRP in women without metabolic syndrome (n = 86) did not show differences between treatment groups.

No change in results were noted when ΔCRP was analyzed as a percentage of change or when removing the covariates for baseline and changes in percentage body fat for men and women overall, and with or without the metabolic syndrome. Change in percentage body fat was not a significant covariate for hs-CRP change for men or women overall, or men or women with or without metabolic syndrome.

4. Discussion

To our knowledge, this is the first article to explore lifestyle changes on hs-CRP stratified by metabolic syndrome separately in men and women. Women with metabolic syndrome randomized to diet or diet plus physical activity had greater reductions in hs-CRP compared with both the control group and physical activity group. These results suggest that the diet component was an effective treatment for women with metabolic syndrome, although it is difficult to know whether the reduction was due to a decrease in total fat, saturated fat, or cholesterol intake; change in macronutrient content; or a combination of these factors. Results were not observed for men.

In the present study, women with metabolic syndrome had significantly higher hs-CRP levels than women without metabolic syndrome at baseline. Some low-fat diet and physical activity interventions found decreased hs-CRP levels only in individuals who initially had elevated levels of hs-CRP [19,21,22]. As expected, we found baseline hs-CRP to be a significant predictor of change in CRP (men, $r^2 = 0.19$; women, $r^2 = 0.16$), such that the higher the baseline hs-CRP, the greater the magnitude of change in CRP. The hs-CRP levels for men with metabolic syndrome were not significantly elevated above those of their healthy counterparts, which may have weakened the hs-CRP response to diet and/or physical activity. Future studies are needed to clarify whether the significant hs-CRP reductions were an influence of sex or a result of higher baseline values. Our results found that women with metabolic syndrome reduced their hs-CRP levels with diet and diet plus physical activity; however, no differences were found between these 2 groups. Further analysis revealed that the subjects who received the diet component resulted in a significantly different hs-CRP than those who did not. Taken together, these results suggest that low-fat diet may be the most important component for reducing hs-CRP levels for women with metabolic syndrome. Other comparisons between low-fat diet and diet plus exercise have shown that the combination results in larger changes in CRP than diet alone, although none of these studies included a control condition [13,17,18].

Several diet plus physical activity interventions incorporated purposeful weight loss [13,17,18,24], which may be related to the change in CRP [24]. Thus, comparisons between the independent and combined effects of diet and exercise on CRP are difficult to distinguish from the

influence of weight loss or, more likely, fat loss. Our study specifically did not promote weight loss and adjusted for changes in body composition using baseline body fat percentage and change in body fat. Only a few studies also accounted for the change in body fat in their analysis [13] or allowed ad libitum dietary consumption [16]. All of these studies found CRP reductions to be significant within the diet plus physical activity group, which is consistent with our work.

Several lifestyle interventions explored the effects of low-fat diet and/or physical activity treatments in other high–cardiovascular risk adults. Jenkins et al [20] also found that a low-fat diet lowered CRP in dyslipidemic women, but not men, compared with a control group. Exercise training has shown equivocal results for the changes in CRP in dyslipidemic adults [22,23]. The combination of diet and physical activity has shown decreases in CRP for insulin-resistant adults [24] and adults with multiple cardiovascular risk factors [12,16]. Dyslipidemia and hypertension are only part of the metabolic syndrome, and the clustering of multiple risk factors could alter changes in CRP in response to diet or increased physical activity. A few studies have examined changes in CRP in adults with metabolic syndrome [13,14]. However, these study designs cannot account for differences in sex; nor do they include a control group for comparison. Although previous studies in high–cardiovascular risk individuals likely include participants with metabolic syndrome, our study exclusively examined the results based on the metabolic syndrome status of the men and women.

Several physiologic mechanisms exist to explain the changes in CRP from low-fat diet and/or physical activity. Low-fat foods may simultaneously change macronutrient intake and quality [20] that can increase intake of naturally anti-inflammatory foods, such as fruits and vegetables, which may ultimately lower CRP [40]. Another proposed mechanism involves low-fat foods limiting the postprandial glucose response, thereby inhibiting the cytokine release into the bloodstream [41] and subsequent CRP release from the endothelium [42]. Physical activity releases interleukin-6 from muscle tissue, initiating the secretion of anti-inflammatory markers (interleukin-10 and interleukin-1 receptor antagonist) that down-regulate the proinflammatory effects of tumor necrosis factor–α [11]. This negative feedback loop suggests that continuous physical activity decreases CRP levels. Although the mechanisms that describe low-fat diet and physical activity and their relationship to CRP reduction appear to be independent, one could theorize that physiologic effects could be additive. However, the exact physiologic mechanism relating the decrease in CRP from diet plus physical activity is poorly understood.

We did not directly compare men and women for hs-CRP response to lifestyle treatment. Because of eligibility criteria for the enrollment, women were approximately 10 years older than the men. As previously mentioned, hs-CRP levels may be higher in women [15], but also increase with aging [15]. Therefore, we performed sex-stratified analyses. Furthermore, because metabolic syndrome status increases with age [3] and hs-CRP increases with metabolic syndrome status [4], we also stratified the metabolic syndrome status analyses by sex. However, these analyses had a small sample size, which may have reduced power. Although significant findings were found for women, these analyses were exploratory and further study is warranted. Because our participants had elevated cardiovascular disease risk (elevated LDL-C and low HDL-C), women were postmenopausal, and most were white, highly educated, and highly motivated, our results may be limited to persons with similar characteristics. Despite these limitations, our study included a randomized controlled design that examined both the independent and combined effects of diet and physical activity. Our analysis included individuals free of existing disease, excluded those on lipid-lowering medications, and adjusted for baseline body fat and changes in body fat, all of which have known influences on the level of circulating CRP.

In conclusion, women with metabolic syndrome reduced hs-CRP levels with low-fat diet and diet plus physical activity compared with controls, suggesting that lifestyle approaches may have benefit. Furthermore, low-fat diet appears to be the most effective component.

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