

# Metabolic Syndrome and Changes in Body Fat From a Low-fat Diet and/or Exercise Randomized Controlled Trial

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It is difficult to identify the successful component(s) related to changes in metabolic syndrome (MetS) from lifestyle interventions: the weight loss, the behavior change, or the combination. The purpose of this study is to determine the effects of a weight-stable randomized controlled trial of low-fat diet and exercise, alone and in combination, on MetS. Men ( $n = 179$ ) and postmenopausal women ( $n = 149$ ) with elevated low-density lipoprotein cholesterol (LDL-C) and low high-density lipoprotein cholesterol (HDL-C) were randomized into a 1-year, weight-stable trial with four treatment groups: control (C), diet (D), exercise (E), or diet plus exercise (D+E). MetS was defined using a continuous score. Changes in MetS score ( $\Delta$ MetS) were compared between groups using analysis of covariance, stratified by gender and using two models, with and without baseline and change in percent body fat ( $\Delta$ BF) as a covariate. In men,  $\Delta$ MetS was higher for D vs. C ( $P = 0.04$ ), D+E vs. C ( $P = 0.0002$ ), and D+E vs. E ( $P = 0.02$ ). For women,  $\Delta$ MetS was greater for D vs. C ( $P = 0.045$ ), E vs. C ( $P = 0.02$ ), and D+E vs. C ( $P = 0.004$ ). After adjusting for  $\Delta$ BF, all differences between groups were attenuated and no longer significant.  $\Delta$ MetS were associated with  $\Delta$ BF for both men ( $P < 0.0001$ ) and women ( $P = 0.004$ ). After adjustment for  $\Delta$ BF, low-fat diet alone and in combination with exercise had no effect on MetS. The key component for MetS from low-fat diet and/or increased physical activity appears to be body fat loss.

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## INTRODUCTION

Metabolic syndrome (MetS) is a clustering of abnormal metabolic, lipid, and nonlipid variables that may predict cardiovascular disease mortality and morbidity better than any of its individual components (1). Individuals with MetS are more likely to die from cardiovascular disease than individuals without MetS (2). The prevalence of MetS has increased over the past 10 years; estimates from the 2002 National Health and Nutrition Examination Survey suggest that 35% of the US population has MetS (3). Therefore, finding effective treatments to reverse MetS is paramount for curbing the progression of cardiovascular disease.

Treatment recommendations for reversing MetS emphasize altering lifestyle behaviors such as reducing intake of saturated fat and cholesterol, increasing physical activity, and achieving weight loss (4). These lifestyle modifications are beneficial for individual risk factors (5); however, evidence for improving MetS has not been convincing. Reductions in MetS are found with low-fat dietary patterns (6), exercise alone (7), and diet plus exercise (8). Though studies may lack a control group for comparison (7), include multiple dietary alterations beyond

reducing fat intake (6) and/or purposeful weight loss (6,8). Weight loss can improve many of the individual metabolic and lipid components of MetS (9). Thus, analyses that do not control for weight loss (change in body composition) make it difficult to identify the successful component(s) of the intervention: the weight loss, the behavior change, or the combination. Thus, the purpose of this study was to systematically examine the effects of low-fat diet and exercise, both individually and in combination, on MetS, using a randomized controlled study design and adjusting for change in body composition.

## METHODS AND PROCEDURES

The Diet and Exercise for Elevated Risk (DEER) trial began in 1992 as a yearlong, single-center randomized controlled clinical trial. The primary objective was to examine the effects of low-fat diet and exercise, alone and together, in men and postmenopausal women identified with low levels of high-density lipoprotein cholesterol (HDL-C) and high levels of low-density lipoprotein cholesterol (LDL-C) (10). The present secondary data analysis determined the effects of the DEER intervention on MetS status.

Specific eligibility criteria for men were: age 30–64 years, HDL-C  $< 1.17$  mmol/l, LDL-C 3.26–4.90 mmol/l, and BMI  $\leq 34$  kg/m<sup>2</sup>. Eligibility criteria for women were: postmenopausal, age 45–64 years,

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HDL-C <1.55 mmol/l, LDL-C 3.26–5.41 mmol/l, and BMI  $\leq$ 32 kg/m<sup>2</sup>. In addition, men and women had blood pressure below 160/95 mm Hg, triglycerides under 5.65 mmol/l, fasting glucose under 7.77 mmol/l, and a normal maximal exercise treadmill test. Exclusion criteria included history of heart disease, abnormal response to symptom-limited treadmill exercise test, insulin-dependent diabetes mellitus, neuromuscular/orthopedic disability, use of lipid, blood pressure or insulin medication, non-euthyroid, low hematocrit, excessive smoking or alcohol consumption, inability to attend sessions, or by judgment of a physician.

Participants underwent telephone screening and a number of tests including laboratory blood analysis, dietary screening, current exercise habits, and a physical examination. All measures were taken at baseline before randomization and then repeated at 1-year follow-up. Clinic staff who performed the measures were blinded to the participants' treatment status.

Body weight was measured with a standard medical beam balance scale. Height was measured using a Harpenden stadiometer. BMI was calculated by dividing the participant's body weight in kilograms by height in meters squared (kg/m<sup>2</sup>). BMI categories were determined using the guidelines recommended by the National, Heart, Lung and Blood Institute (NHLBI) (11). Three measures of waist circumference were taken from the narrowest circumference of the torso when viewed from the front, and averaged. Percent body fat was estimated from skinfold measurements. Gender-specific skinfold thickness (men: chest, abdomen, and thigh; women: triceps, suprailiac, and thigh) were taken three times on the right side of the body and averaged. Body density was estimated using generalized equations (12,13). Percent body fat was calculated using the Siri equation (14).

Blood pressure was measured using a mercury sphygmomanometer from the brachial artery. The average of two readings of the first and fifth phase Korotkoff were noted as systolic and diastolic blood pressure readings, respectively.

Before venous blood collection, participants were asked to refrain from smoking for the hour prior, fast with no food or drink (except water) for at least 12 h, and abstain from alcohol consumption and vigorous activity for at least 24 h. Blood samples were taken in the morning on two different visits at baseline and once at follow-up. All collected blood was mixed with 1.5 mg/ml of EDTA. Serum was allowed to clot for 30–60 min, centrifuged, put on ice, and then plasma was transferred to the freezer at –80°C.

Details of the cardiovascular risk factor laboratory procedures can be found published in the original study (10). Both baseline fasting blood samples were analyzed for lipoproteins and averaged. Total cholesterol and triglycerides were measured using standard enzymatic procedures. HDL-C was measured using dextran sulfate–magnesium precipitation as well as enzymatic measurement of nonprecipitated cholesterol. Very low-density lipoprotein cholesterol (VLDL-C) was calculated as triglycerides divided by five, and LDL-C was calculated as total cholesterol minus the sum of HDL-C and VLDL-C.

The MetS was defined as having at least three of the following abnormal cardiovascular risk factors according to the joint statement from the American Heart Association and NHLBI (AHA/NHLBI): (i) waist circumference >102 cm in men, 88 cm in women; (ii) triglycerides  $\geq$ 1.7 mmol/l, or on drug treatment; (iii) HDL-C <1.03 mmol/l for men, 1.3 mmol/l for women, or on drug treatment; (iv) blood pressure  $\geq$ 130/85 mm Hg, or on drug treatment; and (v) fasting glucose  $\geq$ 5.55 mmol/l, or on drug treatment (4).

Individuals were randomized by the Efron procedure into four groups: (i) control, (ii) diet, (iii) exercise, and (iv) diet plus exercise. Participants randomized to the control group was asked to maintain their usual diet and exercise habits until tests were completed 1 year after randomization.

Participants randomized to the low-fat diet group were instructed on methods to achieve the dietary goals set by the National Cholesterol Education Program Step II Guidelines (15): (i) reduce total fat to <30% of total calories, (ii) reduce saturated fat to <7% of total calories, and (iii) reduce dietary cholesterol to <200 mg/day. Each participant met with

a dietitian to establish individualized dietary recommendations. Eight weekly group sessions were conducted to provide information and counseling on how to achieve treatment goals. After completion of group sessions, participants were contacted every other month through individual appointments, group sessions, telephone calls, and/or mailings.

Participants randomized to the exercise group met with a member of the exercise intervention team to develop an individualized exercise prescription. The adoption phase for exercise training consisted of 6 weeks of 1-h supervised aerobics classes conducted 3 days per week. After the adoption period, participants began with 20-min duration, three times a week and incrementally increased the exercise duration over the course of a year to achieve 45–60 min total per session. Intensity recommendations were to achieve 60–85% maximum heart rate previously determined from a baseline maximal graded treadmill test. Individuals who were active at baseline were asked to add 20 min three times a week to their existing physical activity programs. After 3 months, participants continued with supervised activity or were encouraged to adopt a home program for the remaining 7–8 months.

Although the content that was delivered was the same, participants randomized into the diet plus exercise group received both interventions in sessions separate from the diet-only and exercise-only groups. Dietitians made no reference to physical activity and the exercise interventionists made no references to dietary changes.

None of the treatment groups emphasized weight loss as an intervention goal.

### Statistical analysis

All statistical analyses were performed using SAS software version 9.1 (SAS Institute, Cary, NC). As enrollment criteria for cardiovascular risk factors were different for men and women, all analyses were done separately by gender. General linear models were used to explore potential between-group differences in demographic, physiological, and behavioral variables at baseline.  $\chi^2$  was used to examine treatment group differences for baseline prevalence of MetS.

Continuous MetS scores have been recently introduced to assess MetS status, though several statistical methodologies are utilized (16–18). We used a continuous MetS score, previously used in the Johnson *et al.* study, which standardizes the individual risk factor values and creates a summed score (17). Specifically, the individual cardiovascular risk factors were standardized for mean arterial pressure (MAP = 1/3 (SBP – DBP) + DBP), waist circumference, glucose, triglycerides, and HDL-C by subtracting a participant's individual value for each variable from the AHA/NHLBI MetS criteria, and then dividing by the sample's standard deviation. Individual standardized cardiovascular risk factor scores were summed together to create a continuous standardized MetS score at baseline and follow-up. Change in MetS score ( $\Delta$ MetS) was calculated by subtracting the follow-up score from the baseline score. Thus, a greater absolute  $\Delta$ MetS (decrease) denotes a favorable outcome.

Differences in the  $\Delta$ MetS between control, diet, exercise, and diet plus exercise groups were assessed using general linear modeling with two separate models. Model 1 controlled for baseline MetS score, cohort, age, and menopausal hormonal therapy (MHT). Model 2 included covariates for baseline body fat and the change in body fat (%).

Change in percent body fat ( $\Delta$ BF) was calculated as the difference between follow-up and baseline. Between-group  $\Delta$ BF was analyzed within gender using general linear modeling adjusting for baseline percent body fat, age, cohort, and MHT (as appropriate).  $\Delta$ BF was also divided into tertiles and its association with  $\Delta$ MetS was assessed with correlations and general linear models adjusted for age, cohort, baseline MetS score, and MHT.

### RESULTS

Of the total 377 DEER participants who were randomized into the trial, 328 (87%, 179 men and 149 women) had sufficient data for modeling  $\Delta$ MetS. The smaller sample size is the result of missing values for predictors and covariates. The average

age in years for men and women was  $48.6 \pm 8.7$  and  $57.6 \pm 5.1$ , respectively. Participants were mostly white (~86%) and 57% of men and 40% of women had completed a college degree. Men and women had elevated LDL-C, low HDL-C, normal blood pressure and normal fasting glucose levels, with no differences between groups at baseline (Table 1). Approximately 47% of women were on MHT. The mean BMI was  $26.7 \pm 2.8 \text{ kg/m}^2$  for men and  $26.3 \pm 3.2 \text{ kg/m}^2$  for women. Baseline characteristics and demographics for men and women are presented in Table 1.

The previously published main results indicated adherence to the assigned treatment groups for men and women: change in fitness ( $\text{VO}_{2\text{max}}$ ) was greater in the exercise and diet plus exercise groups relative to controls and changes in dietary total fat, saturated fat, and cholesterol were greater in the diet group and diet plus exercise groups relative to the

controls (10). There was little loss to follow-up, with 98 and 96% of men and women, respectively, completed follow-up data collection (10).

No baseline differences in MetS prevalence or MetS score were found between treatment groups (Table 1). For men, mean  $\Delta\text{MetS}$  from baseline to follow-up was different between treatment groups in model 1 (covariates: baseline MetS score, cohort, age, and MHT) ( $P = 0.003$ ). The absolute  $\Delta\text{MetS}$  was greater in the low-fat diet group relative to the control group ( $0.9 \pm 0.4$ ,  $P = 0.04$ ), greater in diet plus exercise group compared with the controls ( $1.6 \pm 0.4$ ,  $P = 0.0002$ ), and greater for the diet plus exercise group compared with the exercise group ( $1.0 \pm 0.4$ ,  $P = 0.02$ ). When adding baseline percent body fat and percent body fat change as covariates (model 2), differences between treatment groups for the  $\Delta\text{MetS}$  were attenuated and no longer significant ( $P = 0.11$ ) (Figure 1a).

**Table 1** Baseline characteristics in men and women by treatment groups

	Control	Diet	Exercise	Diet plus exercise
Men ( $n = 179$ )				
<i>N</i> (%)	44 (25)	47 (26)	42 (23)	46 (26)
LDL-C (mmol/l)	$4.1 \pm 0.5$	$4.1 \pm 0.5$	$4.0 \pm 0.4$	$4.1 \pm 0.4$
HDL-C (mmol/l)	$0.9 \pm 0.1$	$0.9 \pm 0.1$	$0.9 \pm 0.1$	$0.9 \pm 0.1$
Systolic blood pressure (mm Hg)	$112.5 \pm 10.4$	$113.2 \pm 11.7$	$113.1 \pm 12.6$	$113.2 \pm 11.3$
Diastolic blood pressure (mm Hg)	$76.0 \pm 7.6$	$75.4 \pm 8.4$	$75.7 \pm 6.3$	$75.4 \pm 8.3$
Triglycerides (mmol/l)	$2.0 \pm 1.0$	$2.1 \pm 1.1$	$2.0 \pm 0.7$	$1.8 \pm 0.7$
Fasting glucose (mmol/l)	$5.2 \pm 4.8$	$5.4 \pm 0.4$	$5.4 \pm 3.5$	$5.3 \pm 0.4$
Waist circumference (cm)	$94.9 \pm 8.7$	$95.3 \pm 10.0$	$94.9 \pm 7.8$	$95.4 \pm 8.5$
Percent body fat (%)	$21.0 \pm 3.8$	$21.4 \pm 4.5$	$22.0 \pm 4.9$	$22.0 \pm 4.1$
BMI ( $\text{kg/m}^2$ )	$26.7 \pm 2.9$	$26.8 \pm 3.1$	$26.7 \pm 2.7$	$26.8 \pm 2.6$
Metabolic syndrome <sup>a</sup> <i>n</i> (%)	9 (20)	15 (32)	13 (31)	16 (35)
Metabolic syndrome score <sup>b</sup>	$-1.5 \pm 3.1$	$-1.2 \pm 2.8$	$-1.1 \pm 2.6$	$-1.5 \pm 2.6$
Women ( $n = 149$ )				
<i>N</i> (%)	37 (25)	40 (27)	35 (23)	37 (25)
LDL-C (mmol/l)	$4.2 \pm 0.5$	$4.2 \pm 0.6$	$4.4 \pm 0.6$	$4.3 \pm 0.5$
HDL-C (mmol/l)	$1.2 \pm 0.2$	$1.2 \pm 0.2$	$1.2 \pm 0.2$	$1.2 \pm 0.2$
Systolic blood pressure (mm Hg)	$113.3 \pm 12.6$	$116.1 \pm 15.7$	$115.2 \pm 13.2$	$114.0 \pm 13.3$
Diastolic blood pressure (mm Hg)	$72.2 \pm 7.7$	$73.7 \pm 8.8$	$73.4 \pm 7.8$	$71.7 \pm 7.9$
Triglycerides (mmol/l)	$1.8 \pm 0.8$	$1.8 \pm 0.9$	$1.9 \pm 1.0$	$1.8 \pm 0.9$
Fasting glucose (mmol/l)	$5.2 \pm 0.5$	$5.2 \pm 0.4$	$5.3 \pm 0.5$	$5.2 \pm 0.6$
Waist circumference (cm)	$85.1 \pm 11.7$	$84.9 \pm 7.7$	$84.0 \pm 7.1$	$83.6 \pm 9.2$
Percent body fat (%)	$31.6 \pm 5.7$	$31.9 \pm 4.7$	$32.2 \pm 4.9$	$33.3 \pm 5.2$
BMI ( $\text{kg/m}^2$ )	$25.9 \pm 3.9$	$26.5 \pm 2.9$	$26.1 \pm 2.4$	$26.5 \pm 3.4$
Metabolic syndrome <sup>a</sup> <i>n</i> (%)	10 (27)	12 (30)	11 (31)	14 (38)
Metabolic syndrome score <sup>b</sup>	$-1.7 \pm 3.3$	$-1.6 \pm 2.6$	$-1.3 \pm 2.7$	$-1.8 \pm 3.3$

Data are presented as mean  $\pm$  s.d. There were no significant differences between treatment groups for any of the lipid, metabolic, or anthropometric variables in either men or women at baseline.

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

<sup>a</sup>Metabolic syndrome prevalence as defined by the American Heart Association/National Heart, Lung and Blood Institute (AHA/NHLBI) (4). No significant differences between groups in men or women. <sup>b</sup>Metabolic syndrome score: sum of standardized scores of systolic mean arterial pressure, HDL-C, triglycerides, waist circumference, and fasting glucose created from subtracting the individual cardiovascular risk factor from the NHLBI/AHA criteria and dividing by the sample standard deviation. No significant differences between groups in men or women at baseline.

**Table 2** Changes in standardized scores for individual metabolic syndrome components by treatment group in men and women

	Control	Diet	Exercise	Diet plus exercise	P value
Men					
Waist circumference					
Model 1	-0.21 ± 0.06	-0.49 ± 0.06 <sup>*,***</sup>	0.20 ± 0.06	-0.69 ± 0.06 <sup>**,†,††</sup>	<b>&lt;0.0001</b>
Model 2	-0.31 ± 0.05	-0.44 ± 0.05 <sup>***</sup>	0.25 ± 0.05	-0.63 ± 0.05 <sup>**,†,††</sup>	<b>&lt;0.0001</b>
Triglycerides					
Model 1	0.21 ± 0.16	-0.03 ± 0.15	-0.05 ± 0.15	-0.11 ± 0.15	0.48
Model 2	0.12 ± 0.16	-0.005 ± 0.15	-0.08 ± 0.16	-0.03 ± 0.15	0.81
HDL-C					
Model 1	0.42 ± 0.10	0.34 ± 0.09	0.57 ± 0.10	0.43 ± 0.09	0.29
Model 2	0.52 ± 0.10	0.27 ± 0.09	0.62 ± 0.09 <sup>***,††</sup>	0.36 ± 0.09	<b>0.04</b>
MAP					
Model 1	0.27 ± 0.10	-0.05 ± 0.10 <sup>*</sup>	0.04 ± 0.10	-0.17 ± 0.10 <sup>**</sup>	<b>0.02</b>
Model 2	0.19 ± 0.10	-0.01 ± 0.10	0.001 ± 0.10	-0.12 ± 0.09	0.17
Fasting glucose					
Model 1	-0.65 ± 0.16	-0.86 ± 0.15	-0.67 ± 0.16	-0.99 ± 0.15	0.31
Model 2	-0.70 ± 0.16	-0.84 ± 0.15	-0.70 ± 0.16	-0.97 ± 0.15	0.54
Women					
Waist circumference					
Model 1	-0.10 ± 0.08	-0.24 ± 0.08 <sup>*</sup>	-0.10 ± 0.08	-0.40 ± 0.08 <sup>***,††</sup>	<b>0.004</b>
Model 2	-0.07 ± 0.08	-0.18 ± 0.07	-0.12 ± 0.08	-0.32 ± 0.08	0.14
Triglycerides					
Model 1	0.23 ± 0.14	-0.04 ± 0.14	-0.14 ± 0.15	-0.10 ± 0.15	0.25
Model 2	0.17 ± 0.14	0.005 ± 0.14	-0.16 ± 0.14	-0.01 ± 0.15	0.42
HDL-C					
Model 1	0.37 ± 0.14	0.33 ± 0.14	0.75 ± 0.15	0.26 ± 0.15	0.07
Model 2	0.39 ± 0.14	0.31 ± 0.14	0.75 ± 0.15	0.25 ± 0.15	0.06
MAP					
Model 1	0.05 ± 0.13	0.03 ± 0.15	0.06 ± 0.13	-0.22 ± 0.13	0.35
Model 2	0.06 ± 0.12	0.04 ± 0.13	0.07 ± 0.13	-0.26 ± 0.13	0.21
Fasting glucose					
Model 1	-0.03 ± 0.15	-0.46 ± 0.14	-0.31 ± 0.15	-0.49 ± 0.15	0.09
Model 2	-0.08 ± 0.15	-0.41 ± 0.15	-0.43 ± 0.15	-0.43 ± 0.15	0.31

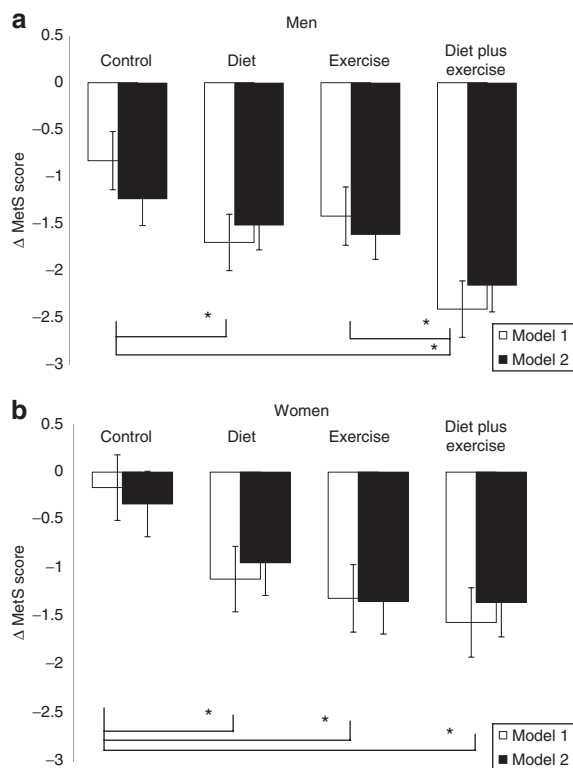
Mean ± s.e. are presented as standardized scores calculated from individual risk factors subtracted from the American Heart Association/National Heart, Lung and Blood Institute (AHA/NHLBI) criteria, then divided by standard deviation. Model 1: adjusts for baseline individual risk factor standardized score, cohort, age, and menopausal hormonal therapy (as appropriate). Model 2: adjusts for the previous covariates as well as baseline body fat (%) and the change in body fat (%). Bold face values indicate statistical significance.

HDL-C, high-density lipoprotein cholesterol; MAP, mean arterial pressure; WC, waist circumference.

\*Control different from diet ( $P < 0.05$ ). \*\*Control different from diet plus exercise ( $P < 0.05$ ). \*\*\*Diet different from exercise ( $P < 0.05$ ). †Diet different from diet plus exercise ( $P < 0.05$ ). ††Exercise different from diet plus exercise ( $P < 0.05$ ).

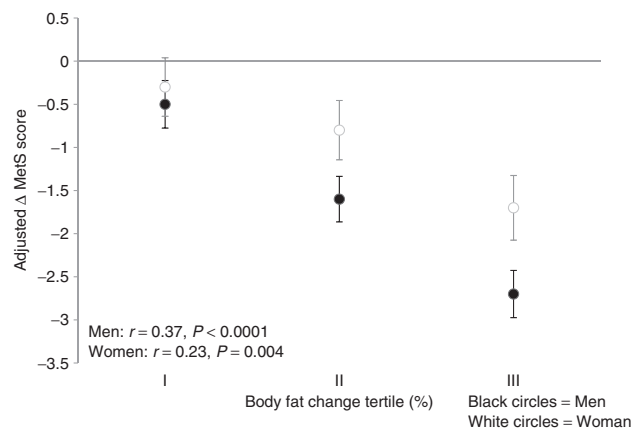
For women, mean  $\Delta$ MetS from baseline to follow-up were different between treatment groups for model 1 ( $P = 0.03$ ). The absolute  $\Delta$ MetS was greater in the exercise group compared with the control group ( $1.1 \pm 0.5$ ,  $P = 0.02$ ), greater in the low-fat group relative to the controls ( $0.9 \pm 0.5$ ,  $P = 0.045$ ), and greater in the diet plus exercise group vs. the control group ( $1.4 \pm 0.5$ ,  $P = 0.004$ ). In model 2, mean differences between treatment groups for  $\Delta$ MetS were attenuated and no longer significant in women ( $P = 0.12$ ) (Figure 1b).

Changes in the individual components of MetS are presented in Table 2. When using model 1 to examine changes for the individual standardized cardiovascular risk factors, waist circumference and MAP were significantly different between treatment groups for men, and waist circumference was significantly different between groups for women. However, once adjusting for the baseline body fat (%) and change in body fat (%), MAP was no longer significant in men, and waist circumference was no longer significant in women (Table 2).



**Figure 1** Change in metabolic syndrome (MetS) score between groups in men and women. Model 1 is adjusted for baseline MetS score, cohort, age, and menopausal hormonal therapy (as appropriate). Model 2 adjusts for the previous covariates as well as baseline body fat (%) and the change in body fat (%). **(a)** Change in MetS scores between treatment groups in men ( $n = 179$ ) showed differences between the control group vs. diet ( $P = 0.04$ ), control group vs. diet plus exercise ( $P = 0.0002$ ), and exercise vs. diet plus exercise ( $P = 0.02$ ). Model 2 did not have any differences between groups in men. **(b)** Changes in scores between treatment groups in women ( $n = 149$ ) showed differences in control vs. diet ( $P = 0.045$ ), control vs. exercise ( $P = 0.02$ ), and control vs. diet plus exercise ( $P = 0.004$ ). Model 2 did not have any differences between groups in women. Asterisks denote significant differences for the change in percent body fat between treatment groups from baseline to follow-up.

$\Delta$ BF was different between control vs. diet (men:  $1.9 \pm 0.7$ ,  $P = 0.005$ ; women:  $2.6 \pm 0.9$ ,  $P = 0.004$ ), control vs. diet plus exercise (men:  $2.2 \pm 0.7$ ,  $P = 0.001$ ; women:  $3.1 \pm 0.9$ ,  $P = 0.001$ ), and exercise vs. diet plus exercise (men:  $-1.6 \pm 0.7$ ,  $P = 0.02$ ; women:  $-2.1 \pm 0.9$ ,  $P = 0.02$ ). The correlation between the  $\Delta$ BF and  $\Delta$ MetS was significant in men ( $r = 0.37$ ,  $P < 0.0001$ ) and women ( $r = 0.23$ ,  $P = 0.004$ ), indicating a decrease in percent body fat was associated with an improved MetS score.  $\Delta$ BF tertile (tertile I: men ( $\geq 0.9\%$ ), women ( $\geq 1.2\%$ ); tertile II: men (0.9 to  $-2.3\%$ ), women (1.2 to  $-2.3\%$ ); tertile III: men (less than  $-2.3\%$ ), women (less than  $-2.3\%$ )) was associated with  $\Delta$ MetS. Differences occurred for men between adjusted  $\Delta$ MetS for  $\Delta$ BF tertile I vs. II ( $1.1 \pm 0.4$ ,  $P = 0.003$ ), II vs. III ( $1.2 \pm 0.4$ ,  $P = 0.001$ ), and I vs. III ( $2.2 \pm 0.4$ ,  $P < 0.0001$ ) (Figure 2). In women, differences existed for  $\Delta$ MetS and tertile of  $\Delta$ BF between II and III ( $0.9 \pm 0.4$ ,  $P = 0.02$ ) and between I and III ( $1.4 \pm 0.4$ ,  $P = 0.001$ ) (Figure 2).



**Figure 2** Adjusted change in metabolic syndrome (MetS) scores by tertiles of body fat change (%) (tertile I: men ( $\geq 0.9\%$ ), women ( $\geq 1.2\%$ ); tertile II: men (0.9 to  $-2.3\%$ ), women (1.2 to  $-2.3\%$ ); tertile III: men (less than  $-2.3\%$ ), women (less than  $-2.3\%$ )) in men (filled circles) and women (empty circles). Covariates included in the model were baseline body fat (%), age, cohort, and menopausal hormonal therapy (as appropriate). A decrease in MetS score is desirable. Differences occurred for men between change in MetS scores and tertile of body fat (%) change: tertile I vs. II ( $P = 0.003$ ), II vs. III ( $P = 0.001$ ), and I vs. III ( $P < 0.0001$ ). In women, differences existed for the change in MetS score and tertile of body fat (%) change: II vs. III ( $P = 0.02$ ), as well as I vs. III ( $P = 0.001$ ).

## DISCUSSION

We systematically compared the independent and combined effects of low-fat diet and exercise on change in MetS. In men, the MetS score improved to a greater extent (decreased) in both the low-fat diet and diet plus exercise groups in comparison to the control group. Furthermore, men in the diet plus exercise group had greater improvements in MetS score than those in the exercise-only group. In women, the  $\Delta$ MetS was greater in the low-fat diet and exercise and diet plus exercise groups relative to the control group. However, once baseline and  $\Delta$ BF were included as covariates, the independent and combined effects of low-fat diet and exercise on MetS were no longer significant.

Although the intervention itself did not promote weight loss per se for any treatment group, percent body fat loss was significant for both men and women in the diet and diet plus exercise groups compared to control. Percent body fat loss was associated with the change in MetS, whereby the larger the magnitude of percent body fat loss, the greater the reduction in MetS score. Furthermore, changes in waist circumference were significantly different between intervention groups for men and women, and significance remained for men even after additional statistical adjustments for baseline body fat and change in body fat. These results suggest that for men and women who are normal weight or overweight but with elevated cardiovascular disease risk, change in MetS from low-fat diet or exercise may be largely explained by the  $\Delta$ BF.

Interventions that combine intentional weight loss with low-fat diet and/or exercise are challenging to determine the exact stimulus for change in MetS (19,20). Weight loss can favorably

change the individual components of MetS (9,21), whereby the greater the weight loss, the larger the magnitude of change in cardiovascular risk factors (21). Another diet plus exercise intervention which controlled for weight loss in the analysis still found reductions in MetS status (19), although this study was not a randomized controlled trial. We evaluated  $\Delta$ BF, which is a better estimate of body composition change than overall body weight loss.

The current study did not promote purposeful weight loss in any treatment arm, and we controlled for the modest 1–2%  $\Delta$ BF in order to isolate the independent effect of the low-fat diet or exercise behavior. Our results suggest that the decrease in percent body fat appears to act as a mediator for MetS change regardless of the specific diet and/or exercise behavior. This finding is supported by research from Katzmarzyk *et al.*, who found that the change in body fat was more highly correlated with the change in cardiovascular risk factors (HDL-C, LDL-C, and total cholesterol) than with the change in cardiorespiratory fitness (22) following an exercise training program. Our study extends this previous research by contributing  $\Delta$ BF loss directly to MetS, rather than its individual components.

A post hoc analysis indicated that the sample sizes of the treatment groups in this study were not powered to detect differences using a dichotomous outcome for MetS. However, the use of a continuous score for MetS allowed us to analyze between-group changes. A continuous score for MetS is hypothesized to be more sensitive for evaluating overall change in the cardiovascular risk factors, as opposed to change in MetS from the AHA/NHLBI definition (three or more abnormal risk factors determined from dichotomous definitions for “high” and “low”) (17). For example, a change in fasting glucose from 8.3 to 6.1 mmol/l would not be detectable using the AHA/NHLBI definition, however, would be reflected in the continuous score. Continuous scores for MetS have been utilized in other research to assess changes in MetS (16–18); however, it is important to note that these methodologies are relatively new, and have not yet been validated to predict type 2 diabetes or cardiovascular disease. However, a benefit to utilizing Johnson *et al.*, continuous score (17) allows equal weighting of each risk factor which is in parallel with the AHA/NHLBI definition and statement (4). Although we did not have sufficient power to detect differences in the AHA/NHLBI-defined MetS across groups, the reduction in prevalence was greater in the intervention groups than the control group, and the pattern of results followed the trends observed in the analysis of the continuous MetS score.

Other strengths and limitations for this study warrant further discussion. Our work directly compares the effects of low-fat diet and exercise on MetS by using a randomized controlled design. This study utilized percent body fat change as a measure of body composition change, as opposed to weight loss. Skinfolts were utilized in this study to assess  $\Delta$ BF and all measures were taken by skilled technicians. Previous research has validated their use to examine body fat changes over time (23). Men and women in this study were analyzed separately in order to account for the gender differences in recruitment and eligibility criteria concerning age and cardiovascular risk factors. Because MetS is directly

assessed from these variables, we felt that it was more appropriate to stratify genders for analyses. Men and women in this study were recruited to have elevated LDL-C and low HDL-C, thus caution should be used in generalizing these results to the general population. Women in the current study were all postmenopausal, which reduces the generalizability of results of this study. However, postmenopausal status does increase a woman’s risk for MetS (24) which may be an important target group to study the effects of diet and exercise. Also, the sample was limited to mostly highly educated whites. However, these participants were highly motivated which resulted in high adherence and retention to measurement at follow-up. Finally, none of the participants were on drug treatment for hypertension, dyslipidemia, or diabetes which could interfere with the effects of lifestyle on MetS.

In summary, our results demonstrate no effect of low-fat diet alone or in combination with exercise on MetS after adjusting for percent body fat loss in men and postmenopausal women. This study provides evidence that the key component for change in MetS is reducing percent body fat. These results are especially encouraging, as marginal losses of body fat occurred in our study in both men and women who were mostly normal weight and overweight at baseline. Small changes in body fat can elicit changes in MetS which may ultimately translate into changes in cardiovascular disease risk. Future studies are needed to further elucidate biological mechanisms to explain the relationship between MetS and body fat. Clinical trials are also needed which can identify the specific threshold and location of body fat loss that corresponds to a significant change in MetS.

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#### DISCLOSURE

The authors declared no conflict of interest.

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