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Effects of a Caloric Restriction Weight Loss Diet and Exercise on Inflammatory Biomarkers in Overweight/Obese Postmenopausal Women: A Randomized Controlled Trial

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Abstract

Obese and sedentary persons have increased risk for cancer; inflammation is a hypothesized mechanism. We examined the effects of a caloric restriction weight loss diet and exercise on inflammatory biomarkers in 439 women. Overweight and obese postmenopausal women were randomized to 1-year: caloric restriction diet (goal of 10% weight loss, N = 118), aerobic exercise (225 min/wk of moderate-to-vigorous activity, N = 117), combined diet + exercise (N = 117), or control (N = 87). Baseline and 1-year high-sensitivity C-reactive protein (hs-CRP), serum amyloid A (SAA), interleukin-6 (IL-6), leukocyte, and neutrophil levels were measured by investigators blind to group. Inflammatory biomarker changes were compared using generalized estimating equations. Models were adjusted for baseline body mass index (BMI), race/ethnicity, and age. Four hundred and thirty-eight (N = 1 in diet + exercise group was excluded) were analyzed. Relative to controls, hs-CRP decreased by geometric mean (95% confidence interval, *P* value): 0.92 mg/L (0.53–1.31, $P < 0.001$) in the diet and 0.87 mg/L (0.51–1.23, $P < 0.0001$) in the diet + exercise groups. IL-6 decreased by 0.34 pg/mL (0.13–0.55, $P = 0.001$) in the diet and 0.32 pg/mL (0.15–0.49, $P < 0.001$) in the diet + exercise groups. Neutrophil counts decreased by 0.31×10^9/L (0.09–0.54, $P = 0.006$) in the diet and 0.30×10^9/L (0.09–0.50, $P = 0.005$) in the diet + exercise groups. Diet and diet + exercise participants with 5% or more weight loss reduced inflammatory biomarkers (hs-CRP, SAA, and IL-6) compared with controls. The diet and diet + exercise groups reduced hs-CRP in all subgroups of baseline BMI, waist circumference, CRP level, and fasting glucose. Our findings indicate that a caloric restriction weight loss diet with or without exercise reduces biomarkers of inflammation in postmenopausal women, with potential clinical significance for cancer risk reduction. *Cancer Res; 72(9); 2314–26. ©2012 AACR.*

Introduction

Approximately 25% of cancers are due to overweight or obesity and a sedentary lifestyle (1), risk factors that are particularly common in older women (2, 3). A meta-analysis of 31 studies estimated that each 5 kg/m^2 increase in body mass index (BMI) was associated with a 12% increased risk of postmenopausal breast cancer [relative risk, 1.12; 95% confidence interval (CI), 1.08–1.16; ref. 4]. Obesity is an established risk factor for endometrial cancer; three quarters of these cases occur in postmenopausal women (5). Increased age and obesity are risk factors for several additional cancers that affect women, including colon, pancreas, kidney, and lower esophageal (4, 6). Thus, weight loss interventions may be important for reducing risk for several cancers in postmenopausal women.

Obesity and a sedentary lifestyle may affect cancer risk through several mechanisms including effects on inflammatory pathways (1). Individuals with chronic infectious disease and inflammatory conditions are at increased risk for several cancers (7). Repeated tissue damage by reactive nitrogen and oxygen species produced from leukocytes and other inflammatory cells induces DNA damage and gene mutations that initiate carcinogenesis (7). DNA damage resulting from chronic inflammation was shown to affect several critical pathways regulating cellular homeostasis (e.g., cell-cycle

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regulation, apoptosis, DNA repair systems; ref. 8). Elevated inflammatory biomarkers such as C-reactive protein (CRP) and interleukin-6 (IL-6) are associated with increased risk for several cancers including breast (9), colon (10), lung (11), and endometrium (12, 13), although not all studies have shown an association (10, 11).

Further support for a role of inflammation in cancer is the observed association between use of nonsteroidal anti-inflammatory drugs (NSAID) and reduced risk for breast, colon, stomach, esophagus, and other cancers (14). NSAID including aspirin have been investigated as risk reduction strategies against several cancers but have risk of adverse effects (14). Statins also reduce CRP (15), but have some side effects (16) and were not protective against cancer in a meta-analysis of clinical trials (16). Because blood levels of inflammatory biomarkers increase with age (17), obesity (18), and menopause (19), investigating lower risk, nonpharmacologic methods for reducing inflammatory biomarkers may identify feasible methods for reducing cancer risk among overweight and obese postmenopausal women.

Obesity and low cardiopulmonary fitness are associated with increased blood levels of CRP (18). A systematic review concluded that weight loss through various mechanisms reduces CRP (20). Most of the reviewed studies were short-term, however, and few of the cited studies looked at other cancer-related inflammatory biomarkers. Previous long-term (12 or more months) weight loss trials have been conducted in individuals with chronic diseases (21, 22), elevated cardiovascular disease risk (23), and impaired glucose tolerance (24) or in premenopausal women (25) and have not focused on overweight or obese postmenopausal women, a group at increased risk for several types of cancer including breast, colon, endometrium, and other obesity-related cancers (4, 5). Therefore, weight loss effects with and without exercise on inflammatory biomarkers over 12 months or more require further investigation in this population.

Experimental models suggest that exercise could independently affect blood levels of inflammatory biomarkers through increased IL-6 release from skeletal muscle (26). Most studies have not shown an effect of exercise without weight loss on inflammatory biomarkers, however (27–30).

Leukocyte and neutrophil counts are clinical indicators of inflammation, and leukocyte counts are positively associated with cancer incidence and mortality in postmenopausal women (31). However, little is known about the effects of dietary weight loss and exercise on leukocyte and neutrophil counts in postmenopausal women.

Statin and anti-inflammatory medications could reduce inflammatory biomarkers (32). However, few studies have examined whether the use of these medications modifies effects of dietary weight loss and exercise on inflammatory biomarkers (22).

This study examined the independent and combined effects of caloric restriction weight loss diet and exercise interventions on inflammatory biomarkers [high-sensitivity CRP (hs-CRP), serum amyloid A (SAA), IL-6, and leukocyte and neutrophil counts] in overweight and obese, postmenopausal women. We also examined mediators (weight loss, exercise, and diet adherence) and potential moderators [baseline characteristics and use of medications that may affect inflammation (statins and NSAIDs); ref. 32] of intervention effects on inflammatory biomarkers.

Materials and Methods

Study design and participants

The Nutrition and Exercise for Women (NEW) study was a 12-month, randomized controlled trial conducted from 2005 to 2009, which was initially funded to examine the effects of a caloric restriction weight loss diet, aerobic exercise, and combined caloric restriction diet + exercise interventions on cancer biomarkers. The primary outcome was serum estrone. Secondary outcomes were additional sex hormones, glucose metabolism, mammogram density, body composition, quality of life, and complete blood count including leukocyte and neutrophil counts. An ancillary study was conducted to assess the interventions' effects on inflammatory biomarkers (hs-CRP, SAA, IL-6).

The NEW trial was designed to enroll 503 participants to have at least 80% power for a 0.05/3-level (Bonferroni corrected) test to detect a difference of 10% in estrone changes over a 12-month period making 3 primary pairwise comparisons: diet + exercise versus exercise; diet + exercise versus diet; and diet versus exercise groups. Because of funding limitations and expected adherence and retention, after half of the women completed 12 months, we recalculated power estimates that indicated sufficient power to detect primary and secondary endpoint changes with a sample size of 439. Participants were recruited from the greater Seattle area through targeted mass mailings, media placements, and community outreach (Fig. 1). The study design and recruitment process (33) and intervention effects on weight (33), body composition (33), quality of life (34) and serum insulin (35), glucose (35), and vitamin D (36) have been reported elsewhere. Eligibility criteria included 50–75 years; BMI $\geq$ 25.0 kg/m^2 (if Asian-American, $\geq$23.0 kg/m^2); <100 min/wk of moderate activity; postmenopausal; not taking postmenopausal hormone therapy for the past 3 months; no history of breast cancer, heart disease, diabetes mellitus, or other serious medical conditions; fasting glucose < 126 mg/dL; nonsmoking; alcohol intake of $\leq$2 drinks/d; able to attend intervention sessions at the study facility; and a normal exercise tolerance test. The study procedures were reviewed and approved by the Fred Hutchinson Cancer Research Center (Seattle, WA) Institutional Review Board. All participants provided signed informed consent.

A total of 439 women were randomized to caloric restriction diet with a goal of 10% weight reduction (N = 118), moderate-to-vigorous intensity aerobic exercise for 45 min/d, 5 d/wk (N = 117), combined exercise and diet (N = 117), or control group (N = 87). Random allocation sequences were generated by a computer-based program developed by the study statistician with stratification by BMI (<30.0, $\geq$30.0 kg/m^2) and race/ethnicity (non-Hispanic white, black, other). To allocate a smaller number of women to the control group, we used

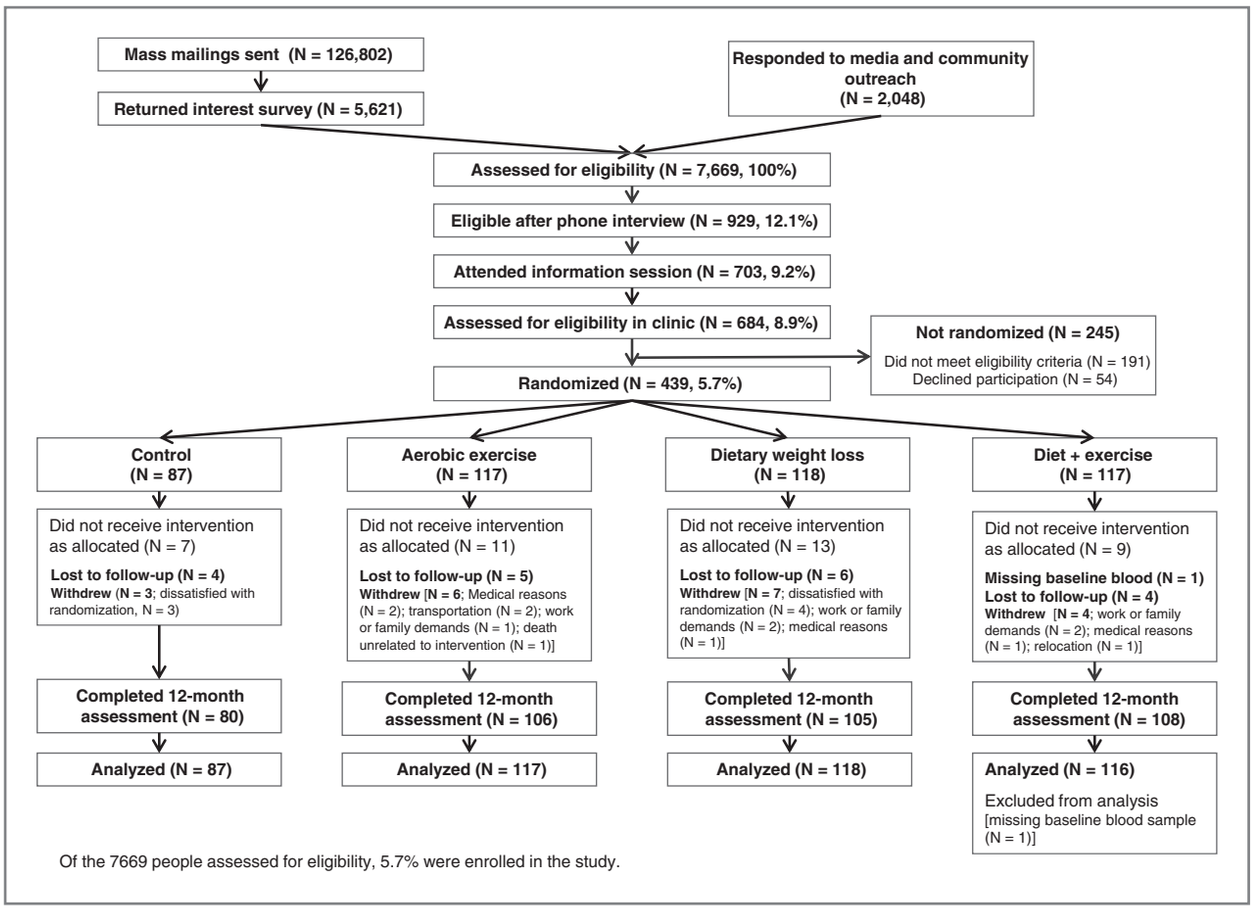


Figure 1. CONSORT diagram of the Nutrition and Exercise for Women (NEW) trial.

permuted blocks randomization with a block size of 4 where control assignment was eliminated with a probability of 1 in 4. The sequence was concealed until the allocation was determined. Study staff enrolled the participants and assigned them to an intervention or the control group. Study staff involved in assessments and investigators other than statisticians were blinded to randomization status.

Interventions

The caloric restriction diet intervention was a modification of the Diabetes Prevention Program (37) and the Look AHEAD trial lifestyle interventions (38) with goals of caloric intake of 1,200 to 2,000 kcal/d based on weight, $\leq$30% calories from fat, 10% weight loss within the first 24 weeks, and maintenance thereafter. The diet intervention was conducted by dietitians with training in behavior modification. Participants had 2 to 4 individual sessions with the dietitians, then met weekly in groups (5–10 women) until week 24, and afterward attended monthly group sessions in addition to e-mail or phone contacts. The diet sessions of diet + exercise group were separate from those of the diet-only group.

The goal of the exercise intervention was 225 min/wk of moderate-to-vigorous intensity exercise for 12 months. Participants attended 3 supervised sessions per week at the facility and 2 per week at home. At both facility and home exercise sessions, participants wore Polar heart rate monitors (Polar Electro). They gradually increased exercise training to 70% to 85% of maximal heart rate (as determined during the baseline Vo_2max treadmill test) for 45 minutes per session by week 7 and maintained thereafter. Exercise mode, duration, peak heart rate, and perceived exertion were recorded at each session in facility and home activity logs for all 12 months. Activities with 4 or more metabolic equivalents were counted toward the prescribed exercise target (33). Participants used treadmills, ellipticals, rowing machines, and stationary bikes during the facility exercise sessions; walking was the most common home exercise. Exercise-only and diet-only participants were asked not to change their diet and exercise habits, respectively.

Controls were asked not to change their diet or exercise habits. After 12 months, controls were offered 4 group diet sessions and 8 weeks of supervised exercise sessions.

Measures

Demographics, medication use, lifestyle behaviors, anthropometrics, and cardiopulmonary fitness were assessed at

baseline and 12 months. Demographic information was assessed using standard questionnaires. Participants brought current prescription and over-the-counter medication bottles to clinic visits. Participants taking statin or NSAID (including over-the-counter) medications at baseline were classified as users. Type, intensity, and duration of physical activity for the past 3 months were assessed (33). All participants wore pedometers (Accusplit) and recorded steps for 7 consecutive days at baseline, 6, and 12 months. A food frequency questionnaire assessed usual dietary intake (33). Intervention women completed daily diet logs (for the first 6 months) and/or facility and home activity logs (for all 12 months), depending on assigned group.

Height and weight were measured with a stadiometer and standard scale, and BMI was calculated as kg/m^2. Waist circumference was measured to the nearest 0.5 cm at the end of normal expiration at the minimal waist. Body fat was measured by a dual-energy X-ray absorptiometry whole-body scanner (GE Lunar). Cardiopulmonary fitness was assessed using a modified branching treadmill protocol monitored by a MedGraphics automated cart (MedGraphics; ref. 33).

Blood samples were collected at baseline and 12 months after 12-hour fasting and no exercise for 24 hours. Samples were processed within an hour, and serum was stored at −70°C. Serum hs-CRP and SAA were analyzed at the Department of Laboratory Medicine, University of Washington, Seattle, WA (M.H. Wener). Serum IL-6, insulin, and glucose were analyzed at the Northwest Lipid Research Laboratories at the University of Washington. Hs-CRP and SAA were measured using assay kits from Siemens Healthcare Diagnostics Products GmbH. IL-6 was measured by an ultrasensitive solid-phase sandwich ELISA on a high-sensitivity human IL-6 Immunoassay kit (R&D Systems, Inc.). The lower detection limits were 0.2 mg/L, 0.7 mg/L, and 0.039 pg/mL for hs-CRP, SAA, and IL-6, respectively. Intra- and interbatch coefficients of variation (CV) were as follows: hs-CRP (4.1%, 4.7%), SAA (5.4%, 6.2%), and IL-6 (9.7%, 12.4%). Glucose and insulin were measured using a Clinical Chemistry Autoanalyzer by hexokinase method and a polyethylene glycol-accelerated, double-antibody radioimmunoassay (39), respectively. The intra- and interassay CVs for glucose were 1.1% and 3.5%, respectively. The intra-assay CV was 4.5% for insulin. Homeostasis assessment–insulin resistance [HOMA-IR = fasting insulin (mU/L) × fasting glucose (mmol/L)/22.5] was calculated (35). Serum samples were analyzed in batches and each participant's samples were assayed in the same batch. The number of samples from each study arm was approximately equal and participant randomization dates were similar within each batch. Whole blood for complete blood counts was collected and stored at room temperature. Leukocyte and neutrophil counts were analyzed at Quest Diagnostics Inc. on the same day.

Statistical analysis

Baseline characteristics between women who completed 12-month assessments (completers) and those who did not (noncompleters) were compared using a χ^2 test and t tests. All randomized participants were included in the analysis (intention-to-treat). We conducted additional analyses eliminating individuals with extremely high hs-CRP values (≥20.0 mg/L, above 99 percentile) at baseline or 12 months. There were no differences between completers and noncompleters by group assignments, most baseline characteristics or inflammatory biomarkers (Supplementary Table S1). On the basis of our understanding of the drop-out reasons (Fig. 1), the follow-up outcomes did not appear to have a nonignorable missing data mechanism (informative missingness). Thus, missing data were imputed by multiple imputation using PROC MI (SAS Institute). Inflammatory biomarkers were imputed on the basis of age, race/ethnicity, BMI, and baseline values of each inflammatory biomarker. Five imputed data sets were created (40), and results were combined by PROC MIANALYZE. We also conducted the analyses using available data and last observation carried forward. No substantive differences were observed among these methods, and therefore we present only the results from the multiple imputation method. Results of the main analyses using available data are presented in Supplementary Table S6.

The primary analysis compared 12-month changes using a generalized estimating equation approach to account for repeated assessments on the same subjects: $E(Y) = \alpha + \beta1 \times \text{group} + \beta2 \times \text{time} + \beta3 \times \text{group} \times \text{time} + \beta4 \times Z + \beta5 \times Z \times \text{time}$, where $E(Y)$ = expected value of an inflammatory outcome variable Y, Z = covariates (41). All models were adjusted for randomization strata [i.e., baseline BMI (<30, ≥30 kg/m^2) and race/ethnicity (white, black, and others)] and age, except for the subgroup analyses stratified by baseline age (≤60, >60 years old) and BMI (<30, ≥30 kg/m^2). Age was included as a covariate because of its associations with CRP (17). Adjusted and unadjusted results were very similar and therefore we present only the adjusted model. We used the Bonferroni correction to adjust for multiple comparisons (e.g., 2-sided $\alpha = 0.05/6 = 0.008$ for 6 comparisons) for the primary analysis. Treatment effects were calculated as relative differences to the control group in absolute and percentage changes in inflammatory biomarkers from baseline to 12 months, with 95% CIs.

The secondary analyses examined the intervention effects stratified by 4 adherence measures [weight loss, exercise adherence (min/wk), diet session attendance, and changes in percentage calorie intake from fat] and by baseline characteristics and medication use. We created subgroups on the basis of weight loss during the trial (lost <5%, ≥5% of baseline body weight) within each intervention arm and compared 12-month changes in inflammation in these subgroups with the control group. Participants with missing 12-month weight were classified as "lost <5%." Five percent was used as a cutoff point, because few participants in the exercise group lost 5% or more of body weight and 5% weight loss is a common clinical endpoint (42). Tertiles were used as cutoff points for other adherence variables. We also stratified by baseline age (≤60, >60 years old), BMI (<30, ≥30 kg/m^2; ref. 43), waist circumference (<88, ≥88 cm; ref. 44), CRP risk category (≤3, >3 mg/L; ref. 45), insulin resistance defined by a median HOMA-IR (<2.7, ≥2.7), fasting glucose (<100, ≥100 mg/dL; ref. 44), and use of medications with anti-inflammatory properties (statins and

NSAIDs; ref. 32), because of their clinical importance. Interactions between stratification (baseline characteristics) × intervention effects were tested in the models to assess effect modification. In addition, we compared the changes in inflammatory biomarkers between caloric restriction diet (diet and diet + exercise groups) versus no caloric restriction diet (exercise and control groups); and exercise (exercise and diet + exercise groups) versus no exercise (diet and control groups).

All outcome variables were log-transformed, due to skewed distributions of the original variables. Geometric means of outcome variables were reported unless otherwise described. All analyses were conducted with SAS software version 9.2.

Results

Of 439 women randomized, baseline serum samples were available from 438 participants. One participant did not have data for baseline neutrophil counts. A total of 399 (90.9%) of randomized participants returned for a 12-month blood draw. Twenty women dropped the intervention during weeks 0 to 24, 6 during weeks 25 to 48, and 13 did not return for the 12-month assessment. The numbers of noncompleters in each group did not differ across the groups ($P = 0.72$). Likelihood of bias from missing data was considered minimal because of the low dropout rate (N = 39, 9%) and because there were no statistically significant differences by group assignments, baseline characteristics, or inflammatory biomarkers between completers and noncompleters of 12-month assessments except for waist circumference (Supplementary Table S1).

Baseline characteristics are displayed in Table 1. The arithmetic mean of baseline hs-CRP was 3.57 mg/L. Data on weight at 6 months were available for 387 women (74 in control, 107 in diet, 94 in exercise, 112 in diet + exercise). Weight losses at 6 months were 0.1 (3.6) kg in the control, 6.6 (5.0) kg in the diet, 1.0 (5.6) kg in the exercise, and 7.5 (3.8) kg in the diet + exercise group. At 6 months, 41.5% (N = 49) in the diet, 21.4% (N = 25) in the exercise, and 46.2% (N = 54) in the diet + exercise groups lost 10% or more of baseline weight. Inflammatory biomarkers were not measured at 6 months.

Results of the intervention effects on body composition at 12 months have been published elsewhere (33). Briefly, the diet, exercise, and diet + exercise groups decreased weight by 8.5% ($P < 0.01$), 2.4% ($P = 0.03$), and 10.8% ($P < 0.01$), respectively, compared with controls. Waist circumference decreased in diet (−4.4 cm, $P < 0.01$), exercise (−2.0 cm, $P = 0.02$), and diet + exercise (−7.0 cm, $P < 0.01$) groups compared with controls (+1.1 cm). All intervention groups had decreased percentage of body fat (Δdiet = −4.2%, $P < 0.01$; Δexercise = −1.6%, $P < 0.01$; Δdiet + exercise = −5.9%, $P < 0.01$) compared with controls. At 12 months, 41.5% (N = 49) in the diet, 3.8% (N = 4) in the exercise, and 59.5% (N = 69) in the diet + exercise groups lost 10% or more of baseline weight. The exercise and diet + exercise groups completed a mean 80.2% and 84.7% of the exercise goal (225 min/wk). The exercise and diet + exercise groups increased pedometer counts by 2,415 steps/d ($P < 0.01$, vs. controls) and 3,468 steps/d ($P < 0.01$, vs. controls), respectively. Aerobic fitness increased by 0.17 L/min ($P < 0.01$) and 0.12 L/min ($P < 0.01$), respectively, in the exercise and diet + exercise groups (vs. control).

Main intervention effects on inflammatory biomarkers

The diet and diet + exercise groups experienced marked and significant decreases in most inflammatory biomarkers compared with controls (Table 2). Compared with controls, hs-CRP decreased by 0.92 mg/L (36.1%, $P < 0.001$) in the diet group and by 0.87mg/L (41.7%, $P < 0.001$) in the diet + exercise group. IL-6 decreased by 0.34 pg/mL (23.1%, $P = 0.001$ vs. control) in the diet group and by 0.32 pg/mL (24.3%, $P < 0.001$ vs. control) in the diet + exercise group. Neutrophil counts reduced by 0.31×10^9/L (9.6%, $P = 0.006$) in the diet group and by 0.30×10^9/L (9.0%, $P = 0.005$) in the diet + exercise group (vs. control). SAA decreased, by 0.82 mg/L (17.5%), in the diet group ($P = 0.005$ vs. control). Leukocyte counts reduced, by 0.41×10^9/L (7.2%), in the diet + exercise group ($P = 0.001$ vs. control). There were no significant differences between the diet and diet + exercise groups or between the exercise and control groups, in any inflammatory biomarker. The results were similar when women with hs-CRP ≥20.0 mg/L (N = 5 in exercise, N = 1 in diet, N = 2 in diet + exercise groups) were excluded (Supplementary Table S2).

Intervention effects stratified by intervention adherence

Compared with controls, participants who lost 5% or more of baseline weight reduced hs-CRP by 49.5% in the diet ($P < 0.001$) and by 49.2% in the diet + exercise groups ($P < 0.001$; Table 3). No differences were observed among those who lost less than 5% of baseline weight. In the diet and diet + exercise groups, women who lost 5% or more of baseline weight reduced SAA ($P < 0.001$ for diet, $P = 0.016$ for diet + exercise) and IL-6 ($P < 0.001$ for diet, $P < 0.001$ for diet + exercise) compared with controls. In the diet + exercise group, leukocyte and neutrophil counts significantly reduced among women who lost 5% or more of weight. Although exercisers who lost 5% or more of baseline weight reduced hs-CRP by 19.1%, the effect did not reach statistical significance ($P = 0.088$ vs. control). When we eliminated data from women with hs-CRP ≥20.0 mg/L, we observed a decrease in hs-CRP among exercisers who lost 5% or more of baseline weight ($\Delta = -25.1\%$, $P = 0.005$ vs. controls; Supplementary Table S3).

In the exercise group, there were no associations between exercise adherence (weekly minutes of exercise) and inflammatory biomarkers (Table 4). In the diet + exercise group, women significantly reduced hs-CRP in all tertile groups of exercise adherence compared with controls. The middle and highest tertile groups significantly reduced IL-6 and leukocyte and neutrophil counts compared with controls in the diet + exercise group.

Twelve-month changes in inflammatory biomarkers stratified by diet adherence (session attendance and 12-month changes in percentage calorie intake from fat) are presented in Table 5. In the diet group, both the middle and highest tertile

Table 1. Baseline characteristics of study participants

	Control (N = 87)	Exercise (N = 117)	Diet (N = 118)	Diet + exercise (N = 116)
Age, mean (SD), y	57.4 (4.4)	58.1 (5.0)	58.1 (5.9)	58.0 (4.4)
Ethnicity, *n* (%)				
Non-Hispanic white	74 (85.1)	98 (83.8)	101 (85.6)	99 (85.3)
Non-Hispanic black	6 (6.9)	15 (12.8)	9 (7.6)	5 (4.3)
Hispanic	3 (3.5)	2 (1.7)	2 (1.7)	5 (4.3)
Other (American Indian, Asian, or unknown)	4 (4.6)	2 (1.7)	6 (5.1)	7 (6.0)
College degree, *n* (%)	59 (67.8)	70 (59.8)	76 (64.4)	81 (69.8)
Married or have partner, *n* (%)	59 (67.8)	71 (60.7)	79 (67.0)	69 (60.0)
Ever smoked,[a] *n* (%)	32 (36.8)	47 (40.2)	55 (46.6)	47 (40.5)
Statin users, *n* (%)	19 (21.8)	19 (16.2)	10 (8.5)	25 (21.6)
NSAID users, *n* (%)	26 (29.9)	36 (30.8)	51 (43.2)	44 (37.9)
BMI, mean (SD), kg/m^2	30.7 (3.9)	30.7 (3.7)	31.1 (3.9)	31.0 (4.3)
Waist circumference, mean (SD), cm	94.8 (10.2)	95.1 (10.1)	94.6 (10.2)	93.7 (9.9)
Aerobic fitness, mean (SD), mL/kg/min	23.1 (4.1)	22.5 (4.1)	22.7 (3.8)	23.6 (4.1)
Physical activity, mean (SD), min/wk	23.8 (41.2)	37.7 (43.7)	33.6 (45.5)	33.6 (44.7)
Calorie intake, mean (SD), kcal/d	1,988 (669)	1,986 (589)	1,884 (661)	1,890 (638)
Percent calorie intake from fat (%), mean (SD)	35.6 (6.9)	33.6 (6.9)	33.1 (6.3)	35.3 (7.3)
Insulin, mean (SD), pmol/L	93.20 (44.80)	86.95 (55.84)	91.26 (60.56)	87.23 (59.80)
Fasting glucose, mean (SD), mmol/L	5.38 (0.46)	5.32 (0.45)	5.37 (0.48)	5.33 (0.43)
HOMA-IR, mean (SD)	3.22 (1.65)	2.99 (2.19)	3.17 (2.25)	3.01 (2.22)
Inflammatory biomarkers				
Hs-CRP, mg/L				
Mean (SD)	3.22 (3.53)	3.84 (3.90)	4.01 (4.05)	3.10 (2.65)
Median	2.20	2.40	2.80	2.40
Interquartile range (Q1–Q3)	0.90–3.60	1.40–4.60	1.50–4.9	1.15–4.40
Serum amyloid A, mg/L				
Mean (SD)	6.73 (5.81)	6.75 (5.47)	6.70 (5.36)	5.93 (4.02)
Median	4.80	4.70	4.80	4.90
Interquartile range (Q1–Q3)	3.40–8.40	3.40–8.40	3.20–9.10	3.05–7.15
IL-6, pg/L				
Mean (SD)	1.69 (1.22)	1.93 (2.06)	1.87 (1.77)	1.53 (0.82)
Median	1.43	1.38	1.44	1.39
Interquartile range (Q1–Q3)	0.98–1.99	1.00–2.00	0.96–2.26	0.94–1.81
Leukocytes ($\times 10^9$/L)				
Mean (SD)	5.70 (1.31)	5.84 (1.33)	6.02 (1.47)	5.84 (1.22)
Median	5.70	5.80	5.85	5.75
Interquartile range (Q1–Q3)	4.70–6.30	4.90–6.70	5.00–6.80	4.95–6.50
Neutrophils ($\times 10^9$/L)				
Mean (SD)	3.26 (0.95)	3.40 (1.08)	3.54 (1.13)	3.41 (0.91)
Median	3.20	3.25	3.37	3.33
Inter-quartile range (Q1–Q3)	2.56–3.82	2.65–4.01	2.80–3.89	2.73–3.84

[a]All study participants were currently nonsmokers.

groups of diet session attendance significantly reduced hs-CRP ($\Delta_{middle} = -43.9\%$, $\Delta_{highest} = -49.4\%$), SAA ($\Delta_{middle} = -17.7\%$, $\Delta_{highest} = -30.8\%$), IL-6 ($\Delta_{middle} = -24.6\%$, $\Delta_{highest} = -33.3\%$), and neutrophil counts ($\Delta_{middle} = -8.9\%$, $\Delta_{highest} = -11.0\%$) compared with controls, with greater reductions in the highest tertile group. In the diet + exercise group, the middle and highest tertile groups of diet session attendance significantly reduced hs-CRP ($\Delta_{middle} = -44.9\%$, $\Delta_{highest} = -47.3\%$), IL-6 ($\Delta_{middle} = -25.7\%$, $\Delta_{highest} = -28.9\%$), and leukocyte ($\Delta_{middle} = -8.2\%$, $\Delta_{highest} = -7.2\%$) and neutrophil ($\Delta_{middle} = -10.0\%$, $\Delta_{highest} = -8.2\%$) counts compared with controls.

In the diet and diet + exercise groups, hs-CRP and IL-6 significantly reduced in all tertile groups of changes in percentage of calorie intake from fat. Reductions in hs-CRP tended to be greater in higher tertile groups in both diet ($\Delta_{lowest} = -27.1\%$, $\Delta_{middle} = -35.9\%$, $\Delta_{highest} = -51.9\%$) and diet + exercise ($\Delta_{lowest} = -26.8\%$, $\Delta_{middle} = -38.5\%$, $\Delta_{highest} = -51.6\%$) groups.

Table 2. Intervention effects on inflammatory biomarkers

	Control (N = 87)	Exercise (N = 117)		Diet (N = 118)		Diet + exercise (N = 116)	
	Geometric means (95% CI)	Geometric means (95% CI)	*P*	Geometric means (95% CI)	*P*	Geometric means (95% CI)	*P*
Hs-CRP, mg/L							
Baseline	1.90 (1.50–2.40)	2.48 (2.00–3.06)		2.57 (2.08–3.18)		2.15 (1.74–2.66)	
12 mo	2.06 (1.84–2.30)	2.46 (2.23–2.72)		1.78 (1.61–1.97)		1.36 (1.23–1.50)	
Δ12 mo vs. control			$P_c = 0.367$		$P_c \leq 0.001$		$Pc \leq 0.001$
Absolute change	—	−0.19 (−0.60 to 0.22)	$P_D \leq 0.001$	−0.92 (−1.31 to −0.53)	$P_E \leq 0.001$	−0.87 (−1.23 to −0.51)	$P_D = 0.353$
Percent change, %	—	−8.5 (−24.7 to 11.1)	$P_{D+E} \leq 0.001$	−36.1 (−46.7 to −23.4)	$P_{D+E} = 0.353$	−41.7 (−52.3 to −28.8)	$P_E \leq 0.001$
SAA, mg/L							
Baseline	5.20 (4.42–6.11)	5.17 (4.47–5.99)		5.17 (4.46–5.99)		4.77 (4.11–5.53)	
12 mo	5.21 (4.79–5.66)	5.86 (5.43–6.31)		4.27 (3.96–4.61)		4.20 (3.89–4.53)	
Δ12 mo vs. control			$Pc = 0.149$		$P_c = 0.005$		$Pc = 0.075$
Absolute change	—	0.64 (−0.23 to 1.52)	$P_D \leq 0.001$	−0.82 (−1.47 to −0.17)	$P_E \leq 0.001$	−0.48 (−1.16 to 0.20)	$P_D = 0.384$
Percent change, %	—	12.9 (−4.3 to 33.2)	$P_{D+E} = 0.006$	−17.5 (−27.9 to −5.6)	$P_{D+E} = 0.384$	−12.2 (−23.8 to 1.3)	$P_E = 0.006$
IL-6, pg/mL							
Baseline	1.43 (1.25–1.64)	1.47 (1.30–1.66)		1.50 (1.33–1.70)		1.38 (1.22–1.56)	
12 mo	1.60 (1.50–1.69)	1.57 (1.48–1.65)		1.29 (1.22–1.36)		1.16 (1.10–1.23)	
Δ12 mo vs. control			$P_c = 0.485$		$P_c = 0.001$		$Pc \leq 0.001$
Absolute change	—	−0.04 (−0.23 to 0.14)	$P_D = 0.002$	−0.34 (−0.55 to −0.13)	$P_E = 0.002$	−0.32 (−0.49 to −0.15)	$P_D = 0.824$
Percent change, %	—	−4.5 (−16.1 to 8.7)	$P_{D+E} \leq 0.001$	−23.1 (−33.9 to −10.5)	$P_{D+E} = 0.824$	−24.3 (−33.2 to −14.1)	$P_E \leq 0.001$
Leukocytes, $\times 10^9$/L							
Baseline	5.39 (5.10–5.71)	5.54 (5.26–5.83)		5.67 (5.39–5.97)		5.54 (5.27–5.84)	
12 mo	5.36 (5.12–5.50)	5.47 (5.34–5.60)		5.34 (5.22–5.47)		5.12 (5.00–5.24)	
Δ12 mo vs. control			$P_c = 0.740$		$P_c = 0.019$		$Pc = 0.001$
Absolute change	—	−0.02 (−0.27 to 0.24)	$P_D = 0.023$	−0.30 (−0.55 to −0.04)	$P_E = 0.023$	−0.41 (−0.65 to −0.16)	$P_D = 0.369$
Percent change, %	—	−0.8 (−5.1 to 3.8)	$P_{D+E} = 0.003$	−5.3 (−9.5 to −0.9)	$P_{D+E} = 0.369$	−7.2 (−11.2 to −3.0)	$P_E = 0.003$
Neutrophils, $\times 10^9$/L							
Baseline	2.97 (2.76–3.20)	3.10 (2.90–3.31)		3.20 (3.00–3.42)		3.11 (2.91–3.33)	
12 mo	3.02 (2.92–3.13)	3.13 (3.03–3.23)		2.94 (2.85–3.04)		2.88 (2.80–2.97)	
Δ12 mo vs. control			$P_c = 0.796$		$P_c = 0.006$		$Pc = 0.005$
Absolute change	—	0.00 (−0.21 to 0.20)	$P_D = 0.002$	−0.31 (−0.54 to −0.09)	$P_E = 0.002$	−0.30 (−0.50 to −0.09)	$P_D = 0.821$
Percent change, %	—	−0.9 (−7.1 to 5.8)	$P_{D+E} = 0.003$	−9.6 (−15.9 to −2.9)	$P_{D+E} = 0.821$	−9.0 (−14.8 to −2.8)	$P_E = 0.003$

NOTE: $P < 0.008$ is considered significant due to multiple comparisons (Bonferroni correction): (i) exercise versus control, (ii) diet versus control, (iii) diet + exercise versus control, (iv) exercise versus diet, (v) exercise versus diet + exercise, and (vi) diet versus diet + exercise. All models were adjusted for randomization strata [i.e., baseline BMI (<30, ≥30 kg/m^2) and race/ethnicity (white, black, and others)] and age.

Abbreviations: P_C, *P* values for comparing the 12-month changes versus control group; P_D, *P* values for comparing the 12-month changes versus diet group; P_{D+E}, *P* values for comparing the 12-month changes versus diet + exercise group; P_E, *P* values for comparing the 12-month changes versus exercise group.

Table 3. Twelve-month changes in inflammatory biomarkers stratified by weight loss

	Exercise				Diet				Diet + exercise			
		Δ12 mo vs. control				Δ12 mo vs. control				Δ12 mo vs. control		
	N	Absolute	Percent	*P*	N	Absolute	Percent	*P*	N	Absolute	Percent	*P*
Hs-CRP, mg/L												
Weight loss < 5%	87	−0.08	−2.6	0.739	42	−0.04	−0.7	0.805	27	−0.19	−10.6	0.434
Weight loss ≥ 5%	30	−0.49	−19.1	0.088	76	−1.26	−49.5	<0.001	89	−1.05	−49.2	<0.001
SAA, mg/L												
Weight loss < 5%	87	0.69	14.4	0.181	42	0.36	7.5	0.656	27	0.45	8.8	0.626
Weight loss ≥ 5%	30	0.49	10.2	0.567	76	−1.26	−28.3	<0.001	89	−0.76	−17.4	0.016
IL-6, pg/mL												
Weight loss < 5%	87	0.00	0.4	0.814	42	−0.11	−7.7	0.429	27	−0.20	−14.1	0.114
Weight loss ≥ 5%	30	−0.17	−11.4	0.077	76	−0.45	−29.9	<0.001	89	−0.36	−27.0	<0.001
Leukocytes, $\times 10^9$/L												
Weight loss < 5%	87	0.01	−0.1	0.769	42	−0.31	−5.0	0.034	27	−0.27	−4.5	0.284
Weight loss ≥ 5%	30	−0.05	−0.7	0.670	76	−0.29	−5.1	0.063	89	−0.45	−8.1	<0.001
Neutrophils, $\times 10^9$/L												
Weight loss < 5%	87	0.01	0.4	0.895	42	−0.29	−8.5	0.022	27	−0.24	−6.8	0.128
Weight loss ≥ 5%	30	−0.04	−1.2	0.644	76	−0.32	−9.8	0.019	89	−0.31	−9.8	0.008

NOTE: *P* values testing differences in changes from baseline to 12 months in inflammatory biomarkers compared with controls. All models were adjusted for randomization strata [i.e., baseline BMI (<30, ≥30 kg/m^2) and race/ethnicity (white, black, and others)] and age.

Intervention effects on hs-CRP stratified by baseline characteristics and medication use

Intervention effects on hs-CRP were independent of baseline age, BMI, hs-CRP level, HOMA-IR, fasting glucose, and statin use ($P_{interaction} > 0.05$; Table 6). The reduction in hs-CRP among women with baseline waist circumference (≥88 cm) was greater than those with baseline waist circumference (<88 cm; $P_{interaction} = 0.012$). The diet and diet + exercise groups reduced mean hs-CRP only among individuals not taking NSAIDs at baseline (vs. controls).

Comparison of intervention effects between caloric restriction diet versus no caloric restriction diet and exercise versus no-exercise groups

Women in the caloric restriction weight loss diet intervention groups (diet and diet + exercise groups) significantly reduced all inflammatory biomarkers compared with those not in a diet intervention (exercise and control groups; Supplementary Table S4). Those in the exercise intervention groups (exercise and diet + exercise groups) did not reduce any inflammatory biomarkers compared with those not in an exercise intervention (diet and control groups; Supplementary Table S5).

Discussion

This study found that a 12-month caloric restriction weight loss diet intervention, with or without exercise, produced large, significant reductions in several biomarkers of inflammation. This trial tested a caloric restriction diet intervention consistent with the recommendations of the NIH Obesity Education Initiative Expert Panel (calorie reduction of 500–1,000 kcal/d), and an exercise intervention consistent with federal guidelines for physical activity (30–45 min/d of moderate or greater intensity activity, ≥5 d/wk; refs. 43, 46). Our caloric restriction diet intervention groups experienced mean weight losses of 9% to 11% (33). The exercise and diet + exercise groups, respectively, completed mean (SD) of 163.3 (70.6) and 171.7 (62.7) min/wk of moderate-to-vigorous intensity activity (target 225 min/wk). These results suggest that modest amounts of weight loss can have large beneficial effects on clinically relevant inflammatory biomarkers, which could impact risk reduction of several cancers in overweight or obese, postmenopausal women.

A systematic review of 33 intervention studies has shown that each 1 kg of weight loss corresponds to 0.13 mg/L reduction in CRP (20). The mean weight loss in our diet + exercise group was 8.9 kg. The expected mean reduction of 1.157 mg/L in CRP is consistent with our observed mean reduction of 1.05 mg/L [hs-CRP outliers ≥ 20 mg/L (N = 2) were removed from this estimate].

A small number of studies have investigated the long-term (≥12 months) combined and independent effects of dietary weight loss and exercise on inflammatory biomarkers. In an 18-month randomized controlled trial among 316 older (≥60 years old), overweight, or obese adults with knee osteoarthritis, dietary weight loss with or without exercise, but not exercise-alone, reduced CRP and IL-6 particularly in men (21), similar to the findings in our study. Another 12-month randomized controlled trial comparing individual and combined effects of

Table 4. Twelve-month changes in inflammatory biomarkers stratified by exercise intervention adherence

	Exercise				Diet + exercise			
		12-mo changes vs. control				12-mo changes vs. control		
Weekly minutes of exercise	N	Absolute	Percent	*P*	N	Absolute	Percent	*P*
Hs-CRP, mg/L								
<154 min/wk	41	−0.40	−12.7	0.316	39	−0.60	−28.2	0.043
157–196 min/wk	41	−0.17	−6.1	0.652	36	−1.30	−56.0	<0.001
≥196 min/wk	35	−0.05	−4.5	0.781	41	−0.72	−37.2	0.002
SAA, mg/L								
<154 min/wk	41	0.29	5.5	0.608	39	0.04	−2.5	0.831
157–196 min/wk	41	0.43	9.0	0.528	36	−0.95	−22.0	0.003
≥196 min/wk	35	1.11	28.3	0.106	41	−0.51	−10.6	0.302
IL-6, pg/mL								
<154 min/wk	41	−0.10	−6.7	0.431	39	−0.13	−10.6	0.179
157–196 min/wk	41	0.12	7.0	0.445	36	−0.57	−37.0	<0.001
≥196 min/wk	35	−0.2	−14.1	0.051	41	−0.29	−23.3	0.007
Leukocytes, $\times 10^9$/L								
<154 min/wk	41	0.00	−0.9	0.777	39	−0.38	−7.1	0.077
157–196 min/wk	41	−0.02	−0.6	0.842	36	−0.43	−7.3	0.005
≥196 min/wk	35	−0.04	−0.6	0.848	41	−0.41	−6.7	0.010
Neutrophils, $\times 10^9$/L								
<154 min/wk	41	0.01	−1.3	0.769	39	−0.27	−8.9	0.072
157–196 min/wk	41	0.07	2.0	0.614	36	−0.32	−8.7	0.024
≥196 min/wk	35	−0.10	−3.0	0.506	41	−0.30	−8.3	0.036

NOTE: *P* values testing differences in changes from baseline to 12 months in inflammatory biomarkers compared with controls. All models were adjusted for randomization strata [i.e., baseline BMI (<30, ≥30 kg/m^2) and race/ethnicity (white, black, and others)] and age.

low-fat diet and/or exercise programs among 274 adults found that diet with or without exercise significantly reduced CRP only among postmenopausal women with metabolic syndrome (23).

In our study, higher adherence to the caloric restriction diet intervention, whether measured by weight loss, session attendance, or reduction in percentage of calories from fat, was associated with greater reductions in hs-CRP. Conversely, no associations were observed between exercise adherence and inflammatory biomarkers. Direct comparisons of diet versus no diet groups showed significant reduction in all inflammatory biomarkers in the diet groups.

We found that hs-CRP decreased to the greatest degree in women who lost 5% or more of baseline weight regardless of intervention group. Trials testing lifestyle interventions to produce weight loss in other populations, including persons with impaired glucose tolerance, type II diabetes, and premenopausal women, have found significant correlations between changes in BMI and inflammatory biomarkers (e.g., CRP, IL-6) over 1 to 2 years (22, 24, 25).

Previous meta-analyses and reviews support a lack of effect of either short- or long-term aerobic exercise on inflammatory biomarkers in the absence of weight loss (28, 47). Among 115 overweight or obese postmenopausal women, we found significant linear trends of greater weight loss associated with a larger decrease in CRP during a 12-month exercise trial in which exercisers attained a mean 171 min/wk (30). Similarly, a 6-month trial designed to test exercise dose (70–120 min/wk) on CRP in 464 overweight and obese postmenopausal women found that exercise decreased mean CRP only in women with 2.6 kg or higher weight loss (28).

There is little information on long-term effects of other types of exercise on inflammatory biomarkers. Two randomized clinical trials showed measurable declines in CRP over 4 to 12 months with resistance exercise compared with controls in diabetic men (48) or in premenopausal women (49). Therefore, the effects on inflammatory biomarkers of resistance training alone or combined with aerobic exercise in postmenopausal women are unknown.

Representative population data show positive associations between adiposity and leukocyte counts (50). To our knowledge, our study is the first investigation reporting long-term (12 months) effects of a caloric restriction weight loss diet with and without exercise on leukocyte and neutrophil counts. Leukocyte and neutrophil counts decreased in the diet and diet + exercise, but not exercise, groups. We also found reduced leukocyte and neutrophil counts among individuals who lost 5% or more of initial weight in the diet + exercise groups.

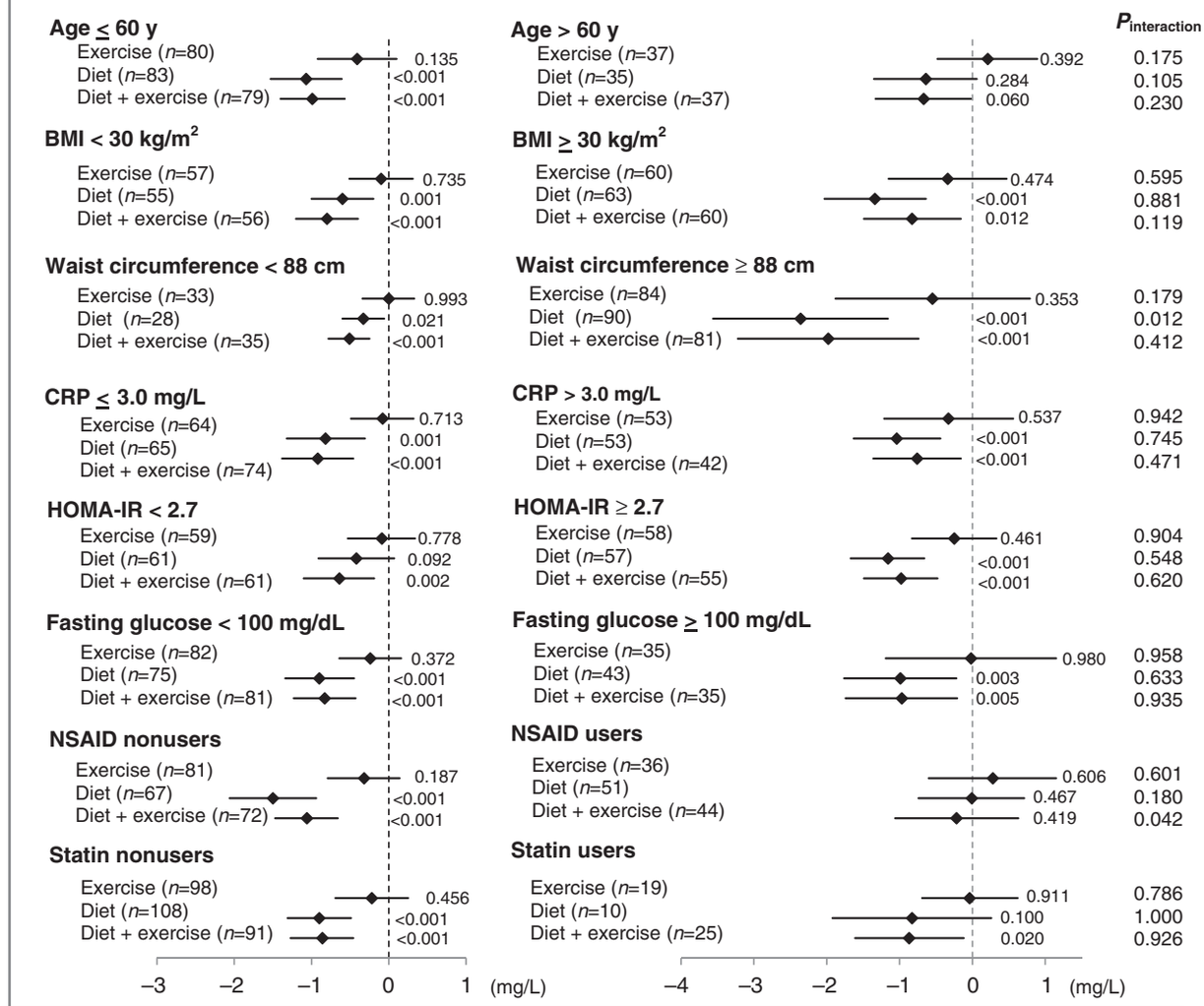
Table 5. Twelve-month changes in inflammatory biomarkers stratified by diet intervention adherence

	Diet				Diet + exercise			
		12-mo changes vs. control				12-mo changes vs. control		
	N	Absolute	Percent	*P*	N	Absolute	Percent	*P*
Percent session attended								
Hs-CRP, mg/L								
Attended < 84.3%	41	−0.17	−8.8	0.462	33	−0.59	−27.4	0.056
84.3% ≤ attended < 106%	37	−1.30	−43.9	<0.001	43	−0.95	−44.9	<0.001
Attended ≥ 106%	40	−1.22	−49.4	<0.001	41	−0.93	−47.3	<0.001
SAA, mg/L								
Attended < 84.3%	41	0.11	−0.7	0.941	33	−0.07	−6.0	0.592
84.3% ≤ attended < 106%	37	−0.87	−17.7	0.018	43	−0.64	−13.7	0.160
Attended ≥ 106%	40	−1.57	−30.8	<0.001	41	−0.68	−14.4	0.141
IL-6, pg/mL								
Attended < 84.3%	41	−0.12	−8.4	0.414	33	−0.22	−15.5	0.049
84.3% ≤ attended < 106%	37	−0.38	−24.6	0.006	43	−0.36	−25.7	0.003
Attended ≥ 106%	40	−0.48	−33.3	<0.001	41	−0.36	−28.9	<0.001
Leukocytes, $\times 10^9$/L								
Attended < 84.3%	41	−0.20	−4.1	0.165	33	−0.27	−5.2	0.168
84.3% ≤ attended < 106%	37	−0.32	−5.1	0.057	43	−0.50	−8.2	0.004
Attended ≥ 106%	40	−0.37	−6.2	0.063	41	−0.42	−7.2	0.008
Neutrophils, $\times 10^9$/L								
Attended < 84.3%	41	−0.23	−8.3	0.073	33	−0.22	−7.3	0.132
84.3% ≤ attended < 106%	37	−0.32	−8.9	0.045	43	−0.37	−10.0	0.019
Attended ≥ 106%	40	−0.39	−11.0	0.029	41	−0.28	−8.2	0.043
Change in percent calorie intake from fat[a]								
Hs-CRP, mg/L								
Reduced ≤ 4.32%	35	−0.70	−27.1	0.010	31	−0.67	−26.8	0.017
4.32% < reduced ≤ 10.08%	33	−0.91	−35.9	<0.001	32	−0.74	−38.5	<0.001
Reduced > 10.08%	33	−1.48	−51.9	<0.001	35	−1.36	−51.6	<0.001
SAA, mg/L								
Reduced ≤ 4.32%	35	−0.92	−20.0	0.036	31	−0.21	−6.6	0.431
4.32% < reduced ≤ 10.08%	33	−0.68	−12.1	0.145	32	−0.92	−16.1	0.062
Reduced > 10.08%	33	−1.18	−27.6	<0.001	35	−0.58	−13.5	0.303
IL-6, pg/mL								
Reduced ≤ 4.32%	35	−0.45	−25.5	0.009	31	−0.30	−19.9	0.006
4.32% < reduced ≤ 10.08%	33	−0.30	−20.7	0.012	32	−0.25	−18.7	0.020
Reduced > 10.08%	33	−0.40	−26.0	<0.001	35	−0.42	−26.0	0.005
Leukocytes, $\times 10^9$/L								
Reduced ≤ 4.32%	35	−0.26	−4.7	0.134	31	−0.38	−5.7	0.078
4.32% < reduced ≤ 10.08%	33	−0.50	−7.5	0.011	32	−0.30	−3.5	0.269
Reduced > 10.08%	33	−0.30	−4.8	0.095	35	−0.57	−8.3	0.010
Neutrophils, $\times 10^9$/L								
Reduced ≤ 4.32%	35	−0.30	−8.7	0.055	31	−0.31	−8.8	0.055
4.32% < reduced ≤ 10.08%	33	−0.46	−11.3	0.014	32	−0.27	−5.7	0.204
Reduced > 10.08%	33	−0.30	−7.8	0.077	35	−0.38	−9.3	0.043

NOTE: *P* values testing differences in changes from baseline to 12 months in inflammatory biomarkers compared with controls. All models were adjusted for randomization strata [i.e., baseline BMI (<30, ≥30 kg/m^2) and race/ethnicity (white, black, and others)] and age.

[a]Participants with data on percentage of calorie intake from fat at both baseline and 12 months were included in the analysis. (N = 101 for diet group, N = 98 for diet + exercise group).

Table 6. Intervention effects on hs-CRP stratified by baseline characteristics



NOTE: Relative differences to the control group in hs-CRP within intervention groups. Diamonds indicate relative differences in 12-month changes in hs-CRP versus controls. Lines indicate 95% CIs. The numbers next to the line indicate *P* values testing the differences between intervention arm versus controls within each stratum. *P*interaction tested the interactions between baseline characteristics × intervention effects. All models were adjusted for randomization strata [i.e., baseline BMI (<30, ≥30 kg/m^2) and race/ethnicity (white, black, and others)] and age, except that age and baseline BMI were not included in the models stratified by age (≤60, >60 years old) and baseline BMI.

However, leukocytes and neutrophil counts reduced in women with less than 5% weight loss in the diet group. Future studies are required to understand effects and underlying mechanisms of caloric restriction weight loss diet and exercise interventions on leukocyte and neutrophil counts.

We found no difference in intervention effects on inflammatory biomarkers in statin users and nonusers. A meta-analysis of 65 statin intervention studies concluded that statin reduced CRP by 30.8% (95% CI, 22.3%–39.4%; ref. 15). In our study, women in the diet and diet + exercise groups decreased hs-CRP by 36% to 42%, similar to the highest impact of statins. In addition, these women significantly reduced hs-CRP independent of statin use at baseline, consistent with results from the Look AHEAD trial in patients with type II diabetes (22). Our results suggest that weight loss through a caloric restriction diet with or without exercise could have additive effects on pharmacologic treatments for reducing inflammation.

Our observed 40% reductions in hs-CRP in the diet and diet + exercise groups could be expected to reduce breast, endometrial, and other cancer risks in postmenopausal women. A meta-analysis of 8 case–control and 6 cohort studies concluded that each log unit increase in CRP was associated with

increase in overall cancer risk (random-effects risk estimate, 1.10; 95% CI, 1.02–1.18) and lung cancer risk (random-effects risk estimate, 1.32; 95% CI, 1.08–1.61; ref. 11). In a cohort of 4,209 women ages 55 years and older, women with CRP levels between 3 and 10 mg/L had a 60% increased risk of breast cancer (HR, 1.59; 95% CI, 1.05–2.41) compared with those with CRP less than 1 mg/L (9). A nested case–control study within the Women's Health Initiative observational cohort found that nonhormone users in the highest CRP quartile (>3.33 mg/L) had a greater than doubling of risk (HR, 2.29; 95% CI, 1.13–4.65) for endometrial cancer than in women in the lowest CRP quartile (<0.64 mg/L; ref. 12).

Strengths of this study include a large sample size, a randomized controlled trial design, 3 intervention arms, long duration of the intervention (12 months), high retention (91%), high adherence to intervention prescriptions, and multiple measures of inflammation.

There were several limitations. Our study sample was highly selected (e.g., inclusion criteria and intervention requirements), which may limit the generalizability. The trial sample of overweight and obese postmenopausal women was relatively homogeneous sample, which may limit the generalizability for other race or ethnic groups, for normal weight or younger women, or for men. However, our sample represents a large segment of the population who are at increased risk for several cancers. We tested only one dietary weight loss program and one exercise program and therefore cannot extend results to other dietary patterns or exercise modalities. However, our diet intervention was based on the known weight loss efficacy of the Diabetes Prevention Program (37) and Look AHEAD interventions (38). Thus, our findings provide critical evidence on the benefits of weight loss and exercise lifestyle change interventions for reducing inflammatory biomarkers in postmenopausal women.

In conclusion, our findings support weight loss through calorie reduction and increased exercise as a means for reducing inflammatory biomarkers and thereby potentially reducing cancer risk in overweight and obese postmenopausal women.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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