Research Article

Cancer Epidemiology, Biomarkers & Prevention

Effect of Weight Loss with or without Exercise on Inflammatory Markers and Adipokines in Postmenopausal Women: The SHAPE-2 Trial, A Randomized Controlled Trial

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Abstract

Background: We investigated the effect of equivalent weight loss, by a hypocaloric diet or mainly exercise, on inflammatory markers and adipokines in overweight postmenopausal women.

Methods: Women were randomized to a diet ($n = 97$), mainly exercise ($n = 98$), or control group ($n = 48$). Goal of both interventions was to lose 5 to 6 kg bodyweight by a hypocaloric diet or an exercise program (4 hours/week) combined with a small caloric intake restriction. Outcomes after 16 weeks included serum high-sensitive C–reactive protein (hsCRP), IL6, adiponectin, and leptin.

Results: Both intervention groups achieved the target weight loss. Controls remained weight stable. Compared with control, hsCRP decreased with mainly exercise [treatment effect ratio (TER) = 0.64] and borderline statistically significant with diet (TER = 0.77). There was a suggestively larger effect of exercise, directly compared with diet (TER = 0.83). Leptin decreased with both interventions: mainly exercise (TER = 0.55) and diet (TER = 0.59), versus control. Effects attenuated and lost significance after adjusting for change in body fat percentage, and to a lesser extent when adjusting for fitness. No effects were seen on IL6 and adiponectin.

Conclusions: A 16-week randomized intervention inducing comparable weight loss by a hypocaloric diet or mainly exercise, resulted in favorable effects on serum hsCRP and leptin. We found a possible more beneficial effect on hsCRP with mainly exercise versus diet. These effects of exercise were established by changes in body fat percentage and physical fitness.

Impact: A modest amount of weight loss in postmenopausal women reduces hsCRP and leptin levels which might be associated with a lower breast cancer risk. *Cancer Epidemiol Biomarkers Prev; 25(5); 799–806. ©2016 AACR.*

Introduction

Postmenopausal women who are overweight or obese and have an inactive lifestyle are at increased risk of breast cancer (1–3). Evidence suggests that hormone pathways, as sex hormones and insulin, inflammation markers, and adipokines play a key role in the link between these lifestyle-related factors and breast cancer risk (4, 5).

Obesity is strongly associated with a chronic low-grade inflammatory state. Fat tissue can be seen as an endocrine organ that secretes multiple inflammatory factors and adipokines (5).

High levels of IL6, C–reactive protein (CRP), and leptin have been associated with a higher risk of several cancers, including potentially postmenopausal breast cancer (6–10), whereas adiponectin, an adipokine inversely associated with obesity, seems to be protective for breast cancer development (11, 12). Leptin is an adipokine involved in the regulation of hunger and satiety and acts proinflammatory. Levels are increased in obese individuals (11). IL6 is mainly produced in adipose tissue, but also by leukocytes and skeletal muscle (13). CRP is an acute phase protein which is produced by the liver in reaction to inflammation and production is upregulated in direct response to IL6.

Weight loss in overweight and obese women, by diet or exercise, may normalize levels of the above mentioned inflammatory markers and adipokines (14, 15). It has been argued that exercise may have beneficial effects on these markers, irrespective of concurrent weight loss (4, 16). However, empirical data for this hypothesis are still scarce.

The aim of the current study is to determine the effect of equivalent weight loss, with or without exercise, on markers of inflammation and adipokines in postmenopausal women. We hypothesize that weight loss induces favorable effects on these biomarkers, and that effects are more pronounced in the mainly exercise group as compared with the hypocaloric diet group.

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Clinical trial registration: NCT01511276 (clinicaltrials.gov).

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doi: 10.1158/1055-9965.EPI-15-1065

Materials and Methods

Design overview

The Sex Hormones And Physical Exercise (SHAPE)-2 study is a randomized controlled trial designed to investigate the effects of a comparable amount of weight loss reached with or without exercise, on markers of postmenopausal breast cancer risk, in healthy, inactive, and overweight/obese postmenopausal women (17). The primary outcome was changed in serum sex hormone levels (18). Here, we report on inflammatory markers [high-sensitive (hs)CRP, IL6] and adipokines (leptin and adiponectin). The study design and protocol are described elsewhere (17). The study was approved by the Medical Ethics Committee of the University Medical Center Utrecht (Utrecht, the Netherlands). All participants signed informed consent.

Setting and participants

The study was conducted in eight municipalities in the Netherlands, surrounding two research sites. Women, ages 50 to 69 years, were recruited via mass mailings and media attention.

Eligible women were insufficiently active [<2 hours/week of at least moderate intensive activities (≥4 metabolic equivalent, MET)], overweight-to-obese [body mass index (BMI): 25–35 kg/m^2], and postmenopausal (>12 months cessation of menses). Main exclusion criteria were: use of sex hormones, smoking, diagnosed with breast cancer (past or present) or other cancers in the past 5 years or diabetes mellitus. The recruitment and inclusion procedure is depicted in Fig. 1.

Run-in period

All participating women started with a 4- to 6-week run-in period wherein a standardized diet was prescribed (50%–60% carbohydrate, 15%–20% protein, and 20%–35% fat, and maximum one unit of alcohol/day) on the basis of the National Guidelines for Healthy Nutrition (19). The goal of this diet was to keep their bodyweight stable and achieve a comparable diet composition among study participants. The diet was prescribed by a study dietitian, after exploring the individuals' dietary history, body weight, and physical activity level to assess energy needs (20).

Randomization and interventions

After the run-in period, women were randomized by computer, stratified for municipality to a diet-induced weight loss group (diet group), weight loss mainly induced by exercise (mainly exercise group), or stable weight control group (control group; ratio interventions vs. control; 2:2:1). Both weight loss intervention programs aimed for 5 to 6 kg weight loss. The programs were delivered by physiotherapists and/or dietitians, who also closely monitored body weight by supervised weighing. When participants reached the target weight loss, or after a maximum of 14

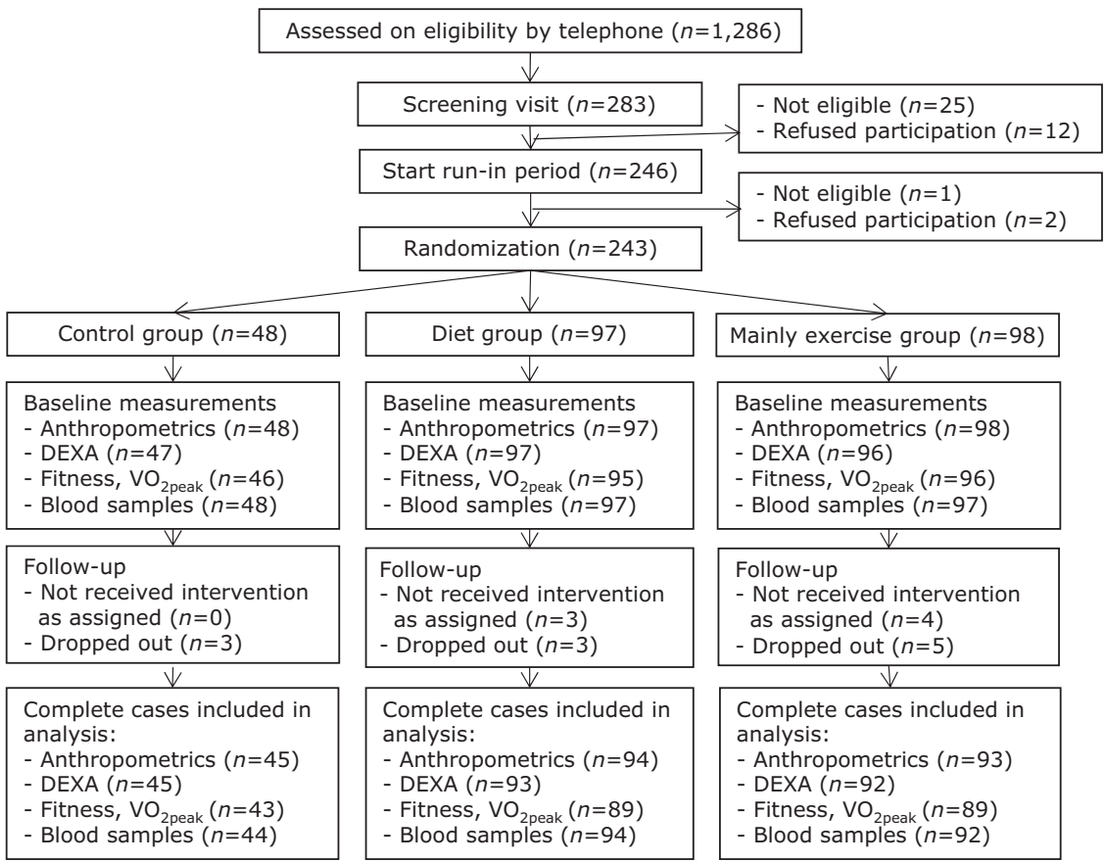

Figure 1.
Flow chart of the inclusion, random assignment, and follow-up of the SHAPE-2 study participants. DEXA, dual-energy X-ray absorptiometry.

weeks, they entered a period of weight maintenance (of 2–6 weeks) wherein diet was adapted to stabilize body weight.

Diet group. Women allocated to the diet group were prescribed a caloric deficit of 3,500 kcal/week, compared with the estimated individuals' caloric needs (the standardized run-in diet). Participants were asked to maintain their habitual physical activity level. Two half-hour individual consultations and five one-hour group sessions were scheduled at the dietitian's office. Nutritional education, self-management training, and behavior change techniques were provided. Furthermore, telephone consultations were scheduled biweekly for monitoring and motivation.

Mainly exercise group. This group followed an intensive 4 hours/week combined endurance and strength exercise program with an average energy expenditure of approximately 2,530 kcal/week (17, 19). These women were also prescribed a relatively small caloric intake restriction of 1,750 kcal/week to ensure the 5 to 6 kg weight loss goal within 14 weeks (21–23). The total targeted weekly energy deficit from exercise and diet in the mainly exercise group was, therefore, approximately 4,280 kcal/week. Since in this group, the main focus was on exercise, we refer to this group as "mainly exercise-induced weight loss" in short "mainly exercise" group.

The exercise program included two 1-hour group sessions of combined strength and endurance training at the physiotherapy center and two 1-hour sessions of moderate-to-vigorous Nordic walking per week. The intensity of the endurance training was gradually increased from 60% to 90% of the heart rate reserve [HRR; intensity%*(maximum heart rate − resting heart rate)+ resting heart rate; ref.24]. Strength training was performed in circuits of 20 to 25 repetitions per exercise and comprised all major muscle groups. In addition, 2 hours/week Nordic walking at 60%–65% HRR were performed individually or, preferably, in supervised classes. Furthermore, women were instructed to increase their energy expenditure in daily activities, for example, by taking the bike for shopping and by climbing stairs. Participants kept an exercise log that was regularly checked by the physiotherapist.

Control group. The control group was requested to maintain their habitual physical activity level and continue the standardized run-in diet. Participants in the control group were offered an alternative weight loss program after study completion.

Outcome measurements

The primary outcomes of the current analysis were serum hsCRP, IL6, adiponectin, and leptin. Blood samples were collected at baseline and after 16 weeks, women were instructed not to exercise in the 48 hours preceding blood sampling. Samples were directly centrifuged and stored at −80°C. After trial completion, the samples were sent to the laboratory for analysis all at once. Multiple samples of each individual were analyzed in the same batch to minimize random error due to batch-to-batch variation. Laboratory assays were performed at "Labor Nord-West" in Nordhorn, Germany. High-sensitivity CRP was measured by an immunoturbidimetric assay (CRP Gen.3, Cobas Roche). ELISA were used to measure IL6 (HS-600B, R&D Systems), leptin (ME E-0300, LDN), and adiponectin (RD195023100, BioVendor). Intra-assay coefficients of variation were 3.3% for hsCRP, 2.4% for IL6, 2.5% for leptin, and 3.6% for adiponectin.

Secondary outcomes included anthropometrics, measured according to standard procedures (17), and lean and fat mass by dual-energy X-ray absorptiometry (DEXA, Lunar Prodigy). Cardiorespiratory fitness (VO_{2peak}) was measured by a maximal cycle exercise test with respiratory gas analysis. Physical activity was objectively measured during seven consecutive days by the ActiGraph activity monitor (GT3X+ Tri-Axis). In addition, habitual physical activity was measured by the SQUASH questionnaire (25).

Statistical analysis

Sample size calculations were based on the primary outcome of the SHAPE-2 trial, that is, serum estradiol. The current sample size provides >80% power to detect a minimal difference of 0.4 mg/L between two study groups on hsCRP. Considering multiple testing, P values <0.025 and <0.05 were considered significant for the comparisons of both interventions versus control, and mainly exercise versus diet, respectively. Matching 97.5% confidence intervals (CI) were given for the comparisons with control and 95% CIs for the comparison mainly exercise versus diet.

The primary analysis was performed according to the intention-to-treat principle. Levels of all four biomarkers were log-transformed to obtain normal distributions. Between-group differences in the markers were assessed by ANCOVA models with correction for the baseline biomarker level. As the biomarkers were log-transformed, their coefficients with 97.5% CI or 95% CI from the ANCOVA models represent a treatment effect ratio (TER). The TER indicates how many times the level in one group is higher (TER>1) or lower (TER<1) compared with the reference group.

If an intervention effect was found, we explored whether change in body fat percentage or fitness (VO_{2peak}) mediated these effects, by adding each, separately, as a covariate to the model. All analyses were performed using SPSS version 21.

Results

A total of 243 women were included in the SHAPE-2 study (control, $n = 48$; diet, $n = 97$; mainly exercise, $n = 98$; Fig. 1). Baseline characteristics of the three study groups were comparable (see Table 1). On average, participants were 60 years, had a BMI of 29 kg/m^2, a body fat percentage of 44%, and a mean VO_{2peak} of 21.9 mL/kg/minute. At 16 weeks follow-up, blood samples were available for 231 participants (95%). In five samples, IL6 and hsCRP values were below the limit of detection, that is, <0.11 pg/mL, $n = 2$ and <0.2 mg/L, $n = 3$, respectively. The value of the lower limit of detection was assigned to these samples. hsCRP values >25 mg/L were excluded from analysis ($n = 1$ at follow-up), as has also been done by others (26, 27), as these may indicate a clinical inflammation or infection. In clinical practice, a cutoff of 10 mg/L is mostly used in the diagnosis of an acute infection. However, overweight to obese women often have higher levels of CRP due to a chronic low-grade inflammation (28, 29) and levels above 10 mg/L, therefore, do not necessarily represent an acute infection. Women in the diet group had a median attendance of four of five group sessions. The mainly exercise group showed a median attendance of 84% of all offered exercise hours.

Body composition and fitness

The results of the SHAPE-2 trial on body composition and fitness are published separately (18). To summarize, both groups

Table 1. Baseline characteristics of the SHAPE-2 study population

	Control group ($n = 48$)	Diet group ($n = 97$)	Mainly exercise group ($n = 98$)
		Mean (SD)	
Age (years)	60.0 (4.9)	60.5 (4.6)	59.5 (4.9)
Time since last menses (years)	11.4 (7.8)	10.7 (6.1)	10.9 (7.7)
Education[a], number (%)			
Low	15 (31.3%)	27 (27.8%)	33 (33.6%)
Middle	15 (31.3%)	27 (27.8%)	20 (20.4%)
High	18 (37.5%)	42 (43.3%)	44 (44.9%)
First-degree family member with breast cancer, number (%)	9 (18.8%)	23 (23.7%)	24 (24.5%)
Weight (kg)	80.9 (10.0)	80.0 (8.6)	80.4 (9.0)
BMI (kg/m^2)	29.5 (2.6)	29.3 (2.5)	29.0 (2.9)
Body fat percentage (%)	43.6 (5.0)	44.1 (3.8)	43.8 (4.0)
Total body fat (kg)	34.2 (7.4)	33.9 (5.7)	33.9 (6.2)
Lean mass (kg)	43.4 (3.9)	42.7 (4.0)	43.1 (4.1)
VO_{2peak}, relative (mL/kg/min)	22.1 ± 4.7	21.9 ± 4.0	21.8 ± 3.7
VO_{2peak} (mL/min)	1,751 ± 363	1,742 ± 310	1,749 ± 293
Physical activity, activity monitor[b] (min/day)		Median (interquartile range)	
Sedentary	652 (600–691)	637 (606–685)	630 (593–678)
Light	179 (164–226)	194 (175–214)	197 (157–229)
Moderate	35 (25–39)	35 (22–46)	33 (27–46)
Vigorous	0.33 (0.17–0.61)	0.35 (0.17–0.53)	0.29 (0.14–0.47)
SQUASH questionnaire, moderate and vigorous activity[c] (min/week)	270 (120–495)	184 (115–420)	248 (90–465)
Alcohol (g/day)	3.7 (0.0–11.7)	5.7 (0.0–10.0)	4.3 (0.0–10.0)
		Geometric mean (95% CI)	
hsCRP (mg/L)	1.83 (1.40–2.40)	2.04 (1.67–2.49)	1.81 (1.49–2.19)
IL6 (pg/mL)	1.31 (1.12–1.52)	1.41 (1.27–1.55)	1.41 (1.25–1.59)
Adiponectin (ng/mL)	9.34 (8.38–10.41)	9.68 (9.06–10.34)	9.53 (9.10–9.99)
Leptin (ng/mL)	27.4 (23.1–32.5)	28.5 (25.5–32.0)	31.4 (28.1–35.2)

NOTE: Data on family history of breast cancer were available for $n = 241$ (99.2%) women; DEXA scan (body fat mass, lean mass), $n = 240$ (98.8%); VO_{2peak}, $n = 237$ (97.5%); alcohol intake, $n = 226$ (93.0%); accelerometer data, $n = 161$ of 215 women in total (74.9%); SQUASH questionnaire, $n = 236$ (97.1%); blood samples for risk markers, $n = 242$. All other data were available for all 243 women.

[a]Education: low, primary school and technical/professional school; middle, college degree; high, university degree.

[b]GT3X+ ActiGraph activity monitor. Minutes/day of activity spent in each activity category.

[c]Activities performed ≥4 metabolic equivalents (MET).

attained the weight loss goal. Women in the diet group lost −4.9 kg (−6.1%) and women in the mainly exercise group −5.5 kg (−6.9%; Table 2). Compared with control, total body fat (mass and percentage) decreased significantly in both intervention groups, with a significant larger loss with mainly exercise compared with diet. Lean mass was preserved with mainly exercise, and lost with diet, compared with control. Physical fitness and activity assessed by VO_{2peak} and the SQUASH questionnaire, respectively, increased with mainly exercise only, versus both control and diet.

Markers of inflammation and adipokines

We found a statistically significant decrease in circulating levels of hsCRP in the mainly exercise group (TER = 0.64; 97.5% CI, 0.44–0.95; Table 3) compared with control. We found a borderline statistically significant reduction in hsCRP in the diet group compared with control (TER = 0.77; 97.5% CI, 0.53–1.14, considering $P < 0.025$ in the comparison with control). Also leptin decreased statistically significant in both the mainly exercise group (TER = 0.55; 97.5% CI, 0.43–0.72) and diet group (TER = 0.59; 97.5% CI, 0.46–0.77) compared with control. Although changes were in favor of the intervention groups, no statistically significant effects were found for circulating IL6 and adiponectin levels. When directly comparing mainly exercise with diet, CRP showed a TER suggestive for a larger effect in the mainly exercise group, but just failed to reach statistical significance (TER = 0.83; 95% CI, 0.69–1.01). For leptin, no statistically significant differences were observed between the two intervention groups.

After adjusting for change in body fat percentage, intervention effects on hsCRP attenuated and lost statistical significance. Effects on leptin also attenuated, but remained statistically significant in the diet group (Table 4). Adjustment for VO_{2peak} showed that effects in the mainly exercise group attenuated for hsCRP but not for leptin (Table 4).

Discussion

Weight loss of 6% to 7%, mainly achieved by exercise or by a hypocaloric diet only, resulted in favorable changes in serum levels of hsCRP and leptin in healthy overweight postmenopausal women. For hsCRP, an indication was found for a possible more beneficial effect of exercise compared with diet, which appear to be mediated by changes in body fat and physical fitness. The effects on leptin appear to be mediated by body fat, predominantly in the mainly exercise group and to a lesser extent in the diet group, and not by fitness.

Our results on hsCRP are in line with several previous diet or exercise weight loss studies in healthy postmenopausal women (14, 27, 30–34). Results of exercise-only interventions in a comparable population are mixed. Some trials observed beneficial effects on CRP and IL6 by exercise (35, 36). However, other trials reported no effect (26, 37) or they observed beneficial effects

Table 2. Baseline and 16-week differences in body composition measures between study groups

	Baseline mean	16 Weeks mean	Change 16 weeks	% Change 16 weeks	Treatment effect[a] (97.5% CI): intervention vs. control	P^b	Treatment effect[a] (95% CI): mainly exercise vs. diet	P^c
Body weight, (kg)								
Control	80.4	80.4	0.06	0.07				
Diet	80.3	75.4	−4.89	−6.09	−4.95 (−6.10 to −3.80)	<0.001		
Mainly exercise	80.4	74.9	−5.52	−6.87	−5.58 (−6.73 to −4.44)	<0.001	−0.63 (−1.23 to −0.04)	0.037
Body fat percentage (%)								
Control	43.5	43.7	0.22	0.50				
Diet	44.0	41.5	−2.54	−5.76	−2.82 (−3.94 to −1.71)	<0.001		
Mainly exercise	43.9	39.8	−4.11	−9.38	−4.38 (−5.50 to −3.27)	<0.001	−1.56 (−2.14 to −0.98)	<0.001
VO_{2peak} (mL/min)								
Control	1,761	1,682	−78.6	−4.46				
Diet	1,752	1,707	−44.9	−2.56	32.0 (−64.1 to 128.0)	0.310		
Mainly exercise	1,766	1,885	119	6.72	198 (103–294)	<0.001	166 (117–216)	<0.001
SQUASH moderate and vigorous activity (min/week)[d]								
Control	270	300	30.0	11.1				
Diet	184	170	−14.0	−7.6	−82.6 (−363.8 to 198.8)	0.370		
Mainly exercise	248	495	247	99.6	221.7 (55.8–499.3)	0.015	304.3 (157.9–450.7)	<0.001

NOTE: Complete cases, that is, women with both baseline and follow-up measurements, are presented. Therefore, baseline values may differ from the values as presented in Table 1. Complete case data of weight was available for 232 (95.5%) women; fat percentage, $n = 230$ (94.7%); VO_{2peak}, $n = 219$ (90.1%). NB, the results on body composition in this table are presented in more detail in an additional publication on hormone result (18).

[a]Treatment effect: the regression coefficient of a linear regression analysis with a 97.5% or 95% CI.

[b]$P < 0.025$ is considered significant for the comparison of both intervention groups versus control, a matching 97.5% CI is presented.

[c]$P < 0.05$ is considered significant for the comparison mainly exercise versus diet, a matching 95% CI is presented.

[d]On the basis of the SQUASH physical activity questionnaire, activities performed ≥4 metabolic equivalents.

that seem to be mainly explained by accompanied weight loss (26, 27, 38).

There are few trials that studied the effects of comparing diet- and exercise-induced weight loss in postmenopausal women (27, 34, 39). Of these, only the NEW trial is of a comparable size and scope. In this 12-month trial, 406 inactive and overweight-to-obese postmenopausal women were randomized to a reduced calorie diet, exercise, a combined diet, and exercise intervention or control (27). The NEW trial did not aim for equal weight losses across the intervention groups and there was no run-in period to standardize diet. Both interventions that included diet, resulted in more loss of body weight than the interventions in our study (−10.8% and −8.5% vs. −6%). In these groups of the NEW trial, CRP and IL6 both decreased to an extent comparable with our study. They did not find significant decreases in CRP or IL6 for the exercise only group, wherein weight loss was −2.4%. Their results implicate that greater weight loss has greater effects on CRP and IL6, and that

Table 3. Baseline and 16-week differences in risk markers between study groups and treatment effects

	Baseline geometric mean	16 Weeks geometric mean	% Change 16 weeks	TER[a] (97.5% CI): intervention vs. control	P^b	TER[a] (95% CI): mainly exercise vs. diet	P^c
hsCRP (mg/L)							
Control	1.72	1.99	16.2				
Diet	1.99	1.75	−12.3	0.77 (0.53–1.14)	0.042		
Mainly exercise	1.85	1.37	−26.1	0.64 (0.44–0.95)	<0.001	0.83 (0.69–1.01)	0.064
IL6 (pg/mL)							
Control	1.32	1.53	15.9				
Diet	1.44	1.40	−2.80	0.88 (0.65–1.19)	0.192		
Mainly exercise	1.42	1.34	−5.74	0.85 (0.63–1.14)	0.092	0.96 (0.83–1.12)	0.631
Adiponectin (ng/mL)							
Control	9.16	8.95	−2.29				
Diet	9.81	9.78	−0.32	1.03 (0.96–1.10)	0.241		
Mainly exercise	9.59	9.76	1.79	1.05 (1.03–1.18)	0.049	1.02 (0.98–1.06)	0.313
Leptin (ng/mL)							
Control	26.2	26.5	1.13				
Diet	29.3	17.3	−41.0	0.59 (0.46–0.77)	<0.001		
Mainly exercise	31.1	17.10	−45.1	0.55 (0.43–0.72)	<0.001	0.94 (0.82–1.07)	0.351

NOTE: Complete cases, that is, women with both baseline and follow-up measurements, are presented. Therefore, baseline values may differ from the values as presented in Table 1. Complete case data of CRP was available for $n = 229$ (94.2%) women, 1 woman was excluded because of an abnormal CRP value at follow-up (>25 mg/L). IL6, adiponectin, leptin, $n = 231$ [control, $n = 44$ (91.7%); diet, $n = 94$ (96.9%); mainly exercise, $n = 93$ (94.9%)].

[a]TER: the treatment effect ratio (and 97.5% or 95% CI) represents the overall intervention effect on change in biomarker (adjusted for baseline biomarker level), estimated by linear regression analysis. The linear regression models were based on log-transformed biomarker data, therefore, the treatment effect is a ratio that indicates how many times the biomarker level is, on average, higher (TER>1) or lower (TER<1) in (i) the intervention group compared with the control group, or (ii) mainly exercise compared with the diet group. For example, TER = 0.9 indicates that the biomarker level in the intervention group is on average 10% lower compared with the control group.

[b]$P < 0.025$ is considered significant for the comparison of both intervention groups vs. control, a matching 97.5% CI is presented.

[c]$P < 0.05$ is considered significant for the comparison mainly exercise vs. diet, a matching 95% CI is presented.

Table 4. Treatment effects on biomarkers adjusted for change in fat percentage or change in VO_{2peak} (mL/min)

	TER[a] (97.5% CI): intervention vs. control	*P*[b]	TER[a] (95% CI): mainly exercise vs. diet	*P*[c]
Adjustment for change in fat percentage				
hsCRP (mg/L)				
Diet	0.87 (0.57–1.32)	0.296		
Mainly exercise	0.77 (0.48–1.24)	0.091	0.89 (0.72–1.09)	0.243
IL6 (pg/mL)				
Diet	0.94 (0.68–1.32)	0.604		
Mainly exercise	0.93 (0.64–1.37)	0.601	0.99 (0.84–1.17)	0.919
Adiponectin (ng/mL)				
Diet	1.02 (0.95–1.10)	0.367		
Mainly exercise	1.04 (0.96–1.14)	0.149	1.02 (0.98–1.06)	0.335
Leptin (ng/mL)				
Diet	0.83 (0.64–1.07)	0.023		
Mainly exercise	0.93 (0.69–1.25)	0.469	1.13 (0.99–1.28)	0.061
Adjustment for change in $VO_{2\ peak}$				
hsCRP (mg/L)				
Diet	0.78 (0.53–1.16)	0.057		
Mainly exercise	0.71 (0.47–1.08)	0.014	0.91 (0.73–1.13)	0.384
IL-6 (pg/mL)				
Diet	0.92 (0.67–1.25)	0.385		
Mainly exercise	0.87 (0.62–1.20)	0.183	0.95 (0.80–1.12)	0.514
Adiponectin (ng/mL)				
Diet	1.02 (0.95–1.09)	0.473		
Mainly exercise	1.04 (0.96–1.12)	0.103	1.02 (0.99–1.07)	0.230
Leptin (ng/mL)				
Diet	0.58 (0.45–0.76)	<0.001		
Mainly exercise	0.56 (0.42–0.75)	<0.001	0.96 (0.83–1.11)	0.574

[a]TER: Treatment effect ratio (and 97.5% or 95% CI). See footnote of Table 3 for the interpretation.
[b]$P < 0.025$ is considered significant for the comparison of both intervention groups versus control, a matching 97.5% CI is presented.
[c]$P < 0.05$ is considered significant for the comparison mainly exercise versus diet, a matching 95% CI is presented.

exercise only, without concurrent substantial weight loss, does not show effects on inflammatory markers.

Another trial by You and colleagues, randomized 34 obese but healthy women to a hypocaloric diet with and without exercise (34). Larger decreases in both CRP as IL6 occurred in the diet plus exercise group (8.5% weight loss) versus diet alone (5% weight loss).

We found an indication for a possible more beneficial effect of exercise on hsCRP when compared with diet. This effect is partly mediated by the larger amount of fat loss that was experienced in the mainly exercise group and probably also by other exercise-induced pathways.

In contrast to the above mentioned studies (27, 34), we did not observe significant reductions of IL6. Effects have been shown to be less robust for IL6 than for CRP (14). A review suggested that a minimum weight loss of 8%, which was not the target in our study, is required to establish notable effects (40). We defined our target based on expected change in sex hormone levels, the primary endpoint of the SHAPE-2 trial. Another explanation for our null finding on IL6 could be that substantial effects are more difficult to reach in a healthy population. This is supported by a trial showing that CRP and IL6 only improved in women with metabolic syndrome at baseline (39).

Both our interventions show beneficial and comparable effects on leptin (−41% and −45%). Two smaller RCTs also found a decrease in leptin after 12 weeks weight loss, but exercise did not add to this effect (41, 42). Also the NEW trial reported reductions in leptin (43): up to −40% in both intervention groups including a diet component. It has been hypothesized that exercise may decrease leptin levels irrespective of weight or fat loss. Insulin stimulates leptin secretion (44), and exercise may lower leptin levels by reducing insulin (45, 46). It may be that longer exercise duration is needed to show any effects as the NEW trial found a significant 13% reduction with exercise only.

We found in the diet intervention group reduced serum leptin levels that persisted after adjustment for change in body fat. Therefore, it seems that a hypocaloric diet affects leptin also irrespective of fat loss. For adiponectin, most weight loss trials including the SHAPE-2 do not observe significant improvements. Reviews suggest that at least 7.5% to 10% weight loss is needed to induce effects (40, 47).

Markers of inflammation and adipokines seem to be able to increase cancer risk through several pathologic mechanisms (11, 48, 49). Large cohort and cross-sectional studies observed associations with higher levels of inflammatory markers or adipokines and an increased cancer risk (9, 10, 50). Two meta-analyses on the effects of CRP on all-cancer risk found significant HRs of 1.10 per log unit increase in CRP (6, 7). The evidence was weaker but also suggestive for an increase in breast cancer risk. Another meta-analysis found that postmenopausal breast cancer risk was significantly increased with elevated levels of leptin (8). Our decreases in CRP and leptin, therefore, imply that cancer risk can be positively influenced by a modest amount of weight loss.

Strengths of the SHAPE-2 study include the unique design with the aim for a comparable weight loss either obtained by a hypocaloric diet or mainly with an exercise program. Another strength of the design is the run-in period with the standardized diet which minimizes inequalities in dietary intake of different food components that may influence the outcome. In addition,

adherence to the study protocol was high and the drop-out rate was low (5%).

A limitation to our study is that despite the fact that the weight loss target was achieved by both intervention groups, the mainly exercise group lost 0.6 kg more than the diet group. Although, this is a clinically small difference, it might have affected our results slightly. Another limitation is that only one blood sample was taken at baseline and follow-up. Validity of the outcomes could be improved by repeated blood sampling as natural day-to-day variability and extraneous effects can affect inflammatory markers and adipokines (51–54). Therefore, random misclassification might have diluted our effects. To reduce influences of extraneous effects, we instructed women not to exercise in the 48 hours prior to the blood sampling. Moreover, our observed effects on hsCRP and leptin were larger than reported intraindividual variations (51, 52).

Conclusions

We found that comparable weight loss (6%–7%) by either a hypocaloric diet or mainly exercise, significantly reduced circulating levels of the inflammatory marker hsCRP and leptin. For hsCRP, an indication was found for a possible more beneficial effect of exercise when compared with diet. Body fat and fitness appeared to be mediators in this association.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The support from the sponsors was unconditional, and the data collection, design, management, analysis, interpretation, and reporting were performed without their interference. The role of the sponsors was limited to approving the scientific proposal of the study; covering salary costs of study personnel, costs for the data collection, and costs for biochemical analyses.

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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): W.A. van Gemert, A.M. May, A.J. Schuit, B.Y.M. Oosterhof, P.H. Peeters, E.M. Monninkhof

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Acknowledgments

The authors thank all persons who have collected data or contributed to the running of the study working at the Julius Center, Utrecht, Medical Spectrum Twente, Enschede, HU University of Applied Sciences, Utrecht, or SHO laboratory, Velp. Furthermore, we would greatly like to thank all the study participants and the participating dietitians, physiotherapists, and Nordic walking instructors in the vicinities of Utrecht and Enschede.

Grant Support

This work was supported by the Dutch Cancer Society (UU 2010-4843) and the Dutch Pink Ribbon Foundation (PR110032, PR110039). E.M. Monninkhof received these grants.

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Received October 6, 2015; revised February 8, 2016; accepted February 8, 2016; published OnlineFirst February 16, 2016.

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