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ORIGINAL PAPER

Effects of an exercise and hypocaloric healthy eating program on biomarkers associated with long-term prognosis after early-stage breast cancer: a randomized controlled trial

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Abstract Excess body weight at diagnosis and weight gain after breast cancer are associated with poorer long-term prognosis. This study investigated the effects of a lifestyle intervention on body weight and other health outcomes influencing long-term prognosis in overweight women (BMI > 25.0 kg/m^2) recovering from early-stage (stage I–III) breast cancer. A total of 90 women treated 3–18 months previously were randomly allocated to a 6-month exercise and hypocaloric healthy eating program ($n = 47$, aged 55.6 ± 10.2 year) or control group ($n = 43$, aged 55.9 ± 8.9 year). Women in the intervention group received three supervised exercise sessions per week and individualized dietary advice, supplemented by weekly nutrition seminars. Body weight, waist circumference, waist/hip ratio [WHR], cardiorespiratory fitness, blood biomarkers associated with breast cancer recurrence and cardiovascular disease risk, and quality of life (FACT-B) were assessed at baseline and 6 months. Three-day diet diaries were used to assess macronutrient and energy intakes. A moderate reduction in body weight in the intervention group (median difference from baseline of -1.09 kg; IQR -0.15 to -2.90 kg; $p = 0.07$) was accompanied by significant reductions in waist circumference ($p < 0.001$), WHR ($p = 0.005$), total ($p = 0.021$) and saturated fat ($p = 0.006$) intakes, leptin ($p = 0.005$), total cholesterol ($p = 0.046$), and resting diastolic blood pressure ($p = 0.03$). Cardiopulmonary fitness ($p < 0.001$) and FACT-B quality of life ($p = 0.004$) also showed significant improvements in the intervention group. These findings suggest that an individualized exercise and a hypocaloric healthy eating program can positively impact upon health outcomes influencing long-term prognosis in overweight women recovering from early-stage breast cancer.

International Standard Randomized Controlled Trial Number: ISRCTN08045231 http://www.controlled-trials.com/

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Introduction

Excess body weight at diagnosis and weight gain after treatment have been associated with reduced quality of life [1, 2] and poorer survival in breast cancer survivors [3–5]. High percentage body fat levels can increase exposure to tumor-promoting sex hormones [6], growth-promoting factors (e.g., insulin-like growth factor [IGF] axis peptides) [7], and chronic low-grade systemic inflammation [8, 9], which could increase the risk of disease recurrence and other primary tumors [10, 11]. The accumulation of body fat also increases the risk of other chronic conditions, including diabetes mellitus and cardiovascular disease, which affects the quality of cancer survivorship and increases the risk of cardiovascular mortality [12].

Previous studies show that dietary energy restriction can evoke reductions in body weight in breast cancer survivors [13, 14] and reduce the risk of disease recurrence and mortality [15]. However, long-term maintenance of a healthy body weight is more commonly observed when hypocaloric diets are combined with regular exercise in overweight and obese individuals [16–18]. Preliminary evidence suggests that exercise in combination with dietary advice can evoke favorable body composition changes in breast cancer patients [19], and evidence from cohort studies shows that a physically active lifestyle after early-stage breast cancer treatment is associated with improved survival [20–23], which may be independent of weight loss [20, 21]. Additionally, regular exercise participation can positively impact upon cancer-related fatigue, physical fitness, and quality of life in breast cancer survivors [24, 25].

Very few studies to date have investigated the health benefits of combined exercise and dietary interventions in women recovering from breast cancer, and none have been conducted in the early recovery phase after treatment. Hence, the aim of this study was to investigate the effectiveness of a 24-week lifestyle intervention, involving supervised aerobic exercise and personalized dietary advice, on body weight and other key health outcomes influencing the quality of cancer survivorship and long-term prognosis in overweight women 3–18 months after primary treatment for early-stage breast cancer.

Methods

Participant recruitment

A total of 90 overweight women with a BMI > 25 kg/m^2 who had completed surgery, chemotherapy, and radiotherapy for early-stage breast cancer (stage I–III) 3–18 months previously were recruited to the study. Patients receiving adjuvant endocrine treatments were eligible, and those yet to complete a 1-year course of adjuvant trastuzumab were also included, subject to acceptable cardiac function determined by a multi-gated acquisition (MUGA) scan and consultant approval. Exclusion criteria included concomitant HRT or oral contraceptives; metastatic or active loco-regional disease; physical or psychiatric impairment limiting physical mobility; severe nausea, anorexia, or other conditions precluding participation in exercise, following alternative/complementary diets or taking high-dose antioxidant supplements; and currently engaged in regular exercise. Patients were recruited from the Cancer Clinical Trials Centre at Weston Park Hospital, Sheffield, UK, or through local cancer support services, the local media, or word of mouth. The routes by which patients were recruited to the trial and reasons for exclusion are shown in Fig. 1. Ethics approval was obtained from the South Sheffield Research Ethics Committee, and all participants provided written informed consent prior to the first assessment visit.

Randomization and allocation concealment

Following the assessment of outcome variables at baseline, patients were randomly allocated (1:1 ratio) to one of two groups: (1) lifestyle intervention or (2) control group. The control group received a healthy eating booklet, *Eat Well* (Food Standards Agency, UK), which also included brief advice on keeping active. Minimization was used to balance the potentially confounding variables of chemotherapy and treatment with tamoxifen, aromatase inhibitors, or no hormone therapy. Randomization was performed by an independent researcher at the Clinical Trials Research Unit, University of Leeds. The randomization sequence was not disclosed until patients had completed their baseline assessments.

Power calculation

Change in body weight was chosen as the primary outcome variable for calculation of sample size. Utter et al. [26] reported an 8.1 ± 0.6 kg (9 %) reduction in body weight in obese women recruited to a 12-week lifestyle intervention, incorporating moderate dietary energy restriction in conjunction with aerobic exercise. This amount of weight loss is associated with improved physical and mental health in obese women [27, 28] and is much greater than that associated with improved survival (-2.3 kg) over a median of 5-year follow-up in early-stage breast cancer patients who reduced their dietary fat intake versus controls who gained weight [15]. Using these data, we estimated that recruitment of 90 women (45 in each group) would give us

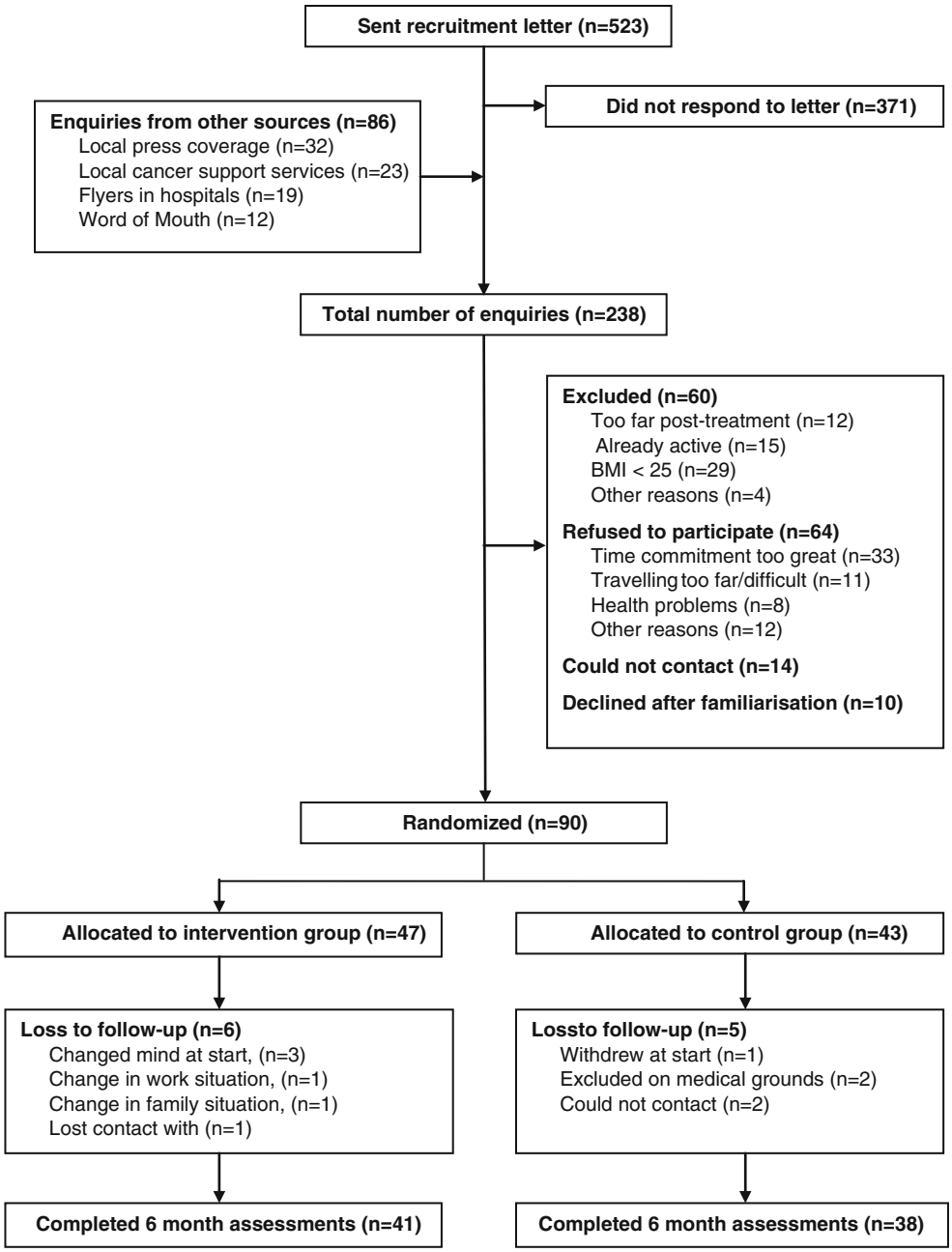

Fig. 1 Flow of patients through the trial

90 % power to detect a clinically meaningful reduction in body weight between the groups at the two-sided α level of 0.05.

Pragmatic lifestyle intervention

The 24-week lifestyle intervention combined three weekly supervised exercise sessions and an individually tailored hypocaloric healthy eating program. Exercise sessions comprised 30 min of aerobic exercise (65–85 % age-predicted maximum heart rate) using treadmill, cross-trainer, cycle ergometer, and/or rowing ergometer, followed by 10–15 min of muscle-strengthening exercises using resistance bands, hand weights, and stability balls. Each participant also received one-to-one individualized dietary advice and written information ("Weight Loss On A Plate," Scottish Dietetic Association). The written information included information on portion sizes from common foods in each food group and a healthy eating plan. The goal was to reduce the patient's total daily calorie intake to 600 kcal below their calculated energy requirements, thereby inducing an estimated steady weight loss of

up to 0.5 kg each week. Additional weekly small-group nutrition education seminars included topics such as dietary fat intake, hydration, achieving a healthy balanced diet, and alcohol consumption.

Assessments and outcome measures

Patients were assessed at baseline and after the 24-week intervention (and at the same time points in the control group) by a trained technician who was blinded to group allocation.

Primary outcomes

Body weight and body composition (body mass index [BMI], waist circumference, waist/hip ratio [WHR]) were measured using standard techniques. Percentage body fat was estimated from bioimpedence (Bodystat 1500, Bodystat Ltd., UK).

Secondary outcomes

Aerobic fitness was measured using a submaximal, 8-min, single-stage walking test on a treadmill [29]. Resting systolic and diastolic blood pressures were measured with a mercury sphygmomanometer using the auscultatory technique. The Functional Assessment of Cancer Therapy-General (FACT-G), including the breast subscale (FACT-B) [30], was used to measure quality of life. Three-day diet diaries were analyzed for total energy and macronutrient intake (NetWisp 3: Tinuviel Software Systems, Cheshire, UK).

Blood analysis

Blood samples were available for 43 women in the intervention group and 40 women in the control group. Blood samples (15–20 mL) were drawn from an antecubital vein between 8:30 and 10:00 am in the morning following a 12-h overnight fast for measurement of blood markers associated with cancer recurrence and cardiovascular disease risk. Plasma samples were stored at -80° C until analysis, and duplicate baseline and postintervention samples were analyzed in the same batch. Testosterone, sex hormone-binding globulin (SHBG), glucose, high-sensitivity C-reactive protein (*hs*-CRP), and blood lipid lipoproteins (total cholesterol and high-density lipoprotein [HDL]) were assayed in the Department of Clinical Chemistry at Sheffield Teaching Hospitals NHS Foundation Trust. Estrone, estradiol, insulin, insulin-like growth factor-1 (IGF-1) and its binding proteins (IGFBP-1 and IGFPB-3), and leptin were analyzed in the Biomedical Research Centre at Sheffield Hallam University using commercially available high-sensitivity enzyme-linked immunosorbent assays (IGF-1, IGFBP-3, leptin: R&D Systems, Oxon, UK, intraassay and interassay coefficients of variation [CVs] ranged from 3.3 to 5.0 % and 5.4 to 8.3 %, respectively; IGFBP-1: Diagnostic Systems Laboratories Inc., USA, intraassay and interassay CVs of 4.6 and 7.6 %, respectively; estradiol, estrone, insulin: DRG Diagnostics, Germany, intraassay and interassay CVs ranged from 5.3 to 8.5 % and 6.0 to 12.9 %, respectively). Assay sensitivities for estradiol and estrone were 1.3 and 6.2 pg/mL, respectively. Values below the assay sensitivity for estradiol ($n = 13$ for the intervention group and $n = 8$ for the control group) and estrone ($n = 1$ for each group) were set to 1 unit below the detection limit. The homeostasis model assessment (HOMA) was used as a surrogate measure of whole-body insulin resistance and calculated as the product of fasting glucose (mM) and insulin (mU/L) levels divided by 22.5 [31].

Data analysis

Intention-to-treat analysis was used to compare patients in the groups to which they were randomly assigned with missing data being imputed using the SPSS expectation maximization procedure. Shapiro–Wilk's tests were used to check the normality of the data prior to data analysis. As body weight, BMI, and the blood markers were non-normally distributed, change scores between the groups were analyzed using the Mann–Whitney U test and the results presented as median (interquartile range [IQR]). Normally distributed data were analyzed using analysis of covariance (ANCOVA), with baseline values used as the covariate. Normally distributed data are presented as mean $\pm$ SD or as adjusted mean differences with 95 % confidence intervals (CI). Categorical data were analyzed using chi-squared tests (χ^2). The strength and direction of bivariate associations between changes in body weight/waist circumference and the blood markers were explored using Spearman's rank correlation coefficient (ρ). Statistical significance throughout was taken at the two-sided 5 % level ($p < 0.05$). All data were analyzed using SPSS v17.0 (IBM, Somers, USA).

Results

Patient characteristics, loss to follow-up, and compliance

Of the 90 patients recruited to the study, 47 (52.2 %) were randomized to the intervention group and 43 (47.8 %) to the comparison group. Their mean age was 55.7 years (SD 9.5 years, range 36–77 years), with most women being postmenopausal ($n = 61$, 67.7 %). Of the remainder, eight

(8.9 %) were premenopausal, twelve (13.3 %) were perimenopausal, and menopausal status was not recorded for a further nine (10 %) women. The two groups were reasonably well matched on most variables at baseline, including hormone treatments and chemotherapy (Table 1). A higher proportion of women in the intervention group underwent mastectomy (versus breast conserving surgery), and this was statistically significant ($p = 0.0002$). However, a subgroup analysis showed that this had no effect on response to the intervention. Six women (12.8 %) from the intervention group and five women (11.6 %) from the control group were lost to follow-up, with missing data points imputed as described above. Imputation of these missing data points gave similar results to the available case analyses. Compliance to the supervised exercise and dietary seminar sessions was very good, with women completing, on average, 80 % of the sessions offered to them. There were no adverse events arising from the intervention.

Primary outcomes

A modest reduction in body weight of borderline statistical significance was observed in the intervention group versus controls at 24 weeks (median difference from baseline of −1.09 kg; IQR −0.15 to −2.90 kg vs. −0.40 kg; IQR 0.70 to −1.80 kg, respectively; $p = 0.07$), with 57 % ($n = 26$) of women in the intervention group and 31 % ($n = 13$) in the control group losing at least 1 kg of body weight ($\chi^2 = 3.03$, $df = 1$, $p = 0.08$). Upon removal of two outlying weight change values that were >3 SD from the mean (one from the intervention group and another from the control group), there was a significant reduction in body weight in the intervention group versus controls (median difference from baseline of −1.25 kg; IQR −0.26 to −2.93 kg vs. −0.40 kg; IQR 0.73 to −1.72 kg, respectively; $p = 0.03$). A modest reduction in BMI of borderline statistical significance was also observed in the intervention group versus controls at 24 weeks

Table 1 Baseline demographic and clinical characteristics of the two groups

Characteristic	Intervention group ($n = 47$)	Control group ($n = 43$)	p values
Age, years	55.6 (10.2)	55.9 (8.9)	0.87[a]
Body mass, kg	78.0 (10.0)	83.2 (17.0)	0.22[b]
Body mass index, kg/m^2	29.6 (3.5)	31.1 (5.6)	0.27[b]
Waist circumference, cm	91.1 (10.1)	94.6 (13.6)	0.17[a]
Waist/hip ratio	0.83 (0.07)	0.83 (0.06)	0.95[a]
Percent body fat	42.0 (4.5)	43.6 (5.9)	0.15[a]
Dietary intakes			
Total energy, kcal	1,678.9 (417.2)	1,740.2 (389.6)	0.49[a]
Protein, g	72.2 (14.7)	79.1 (16.1)	0.04[a]
Carbohydrate, g	203.0 (51.7)	207.1 (49.3)	0.70[a]
Total fat, g	61.7 (23.1)	64.2 (21.7)	0.60[a]
Saturated fat, g	21.5 (8.8)	21.6 (8.1)	0.97[a]
Ethnicity			
White, no. (%)	46 (98)	42 (98)	0.95[c]
Marital status			
Married/cohabitating, no. (%)	31 (66)	30 (69.8)	0.70[c]
Single/windowed/divorced, no. (%)	16 (34)	13 (30.2)	0.70[c]
Education			
Secondary and A levels	18 (38)	12 (28)	0.30[c]
Degree	8 (17)	8 (19)	0.84[c]
Vocational qualifications	6 (13)	2 (5)	0.18[c]
Smokers, no. (%)	3 (6)	1 (2)	0.35[c]
Treatment			
Mastectomy, no. (%)	28 (60)	9 (21)	0.0002[c]
Breast conserving surgery, no. (%)	19 (40)	34 (79)	0.0002[c]
Chemotherapy, no. (%)	27 (57)	23 (54)	0.71[c]
Radiotherapy, no. (%)	40 (85)	35 (81)	0.64[c]
Tamoxifen, no. (%)	23 (49)	22 (51)	0.83[c]
Aromatase inhibitor, no. (%)	14 (30)	11 (26)	0.66[c]
Trastuzumab, no. (%)	4 (9)	6 (14)	0.41[c]
Lymphedema, no. (%)	10 (21)	15 (35)	0.15[c]

Data are presented as mean (SD) unless otherwise stated

p values shown for group comparisons: [a]ANOVA, [b]Mann–Whitney U test, [c]chi-square test

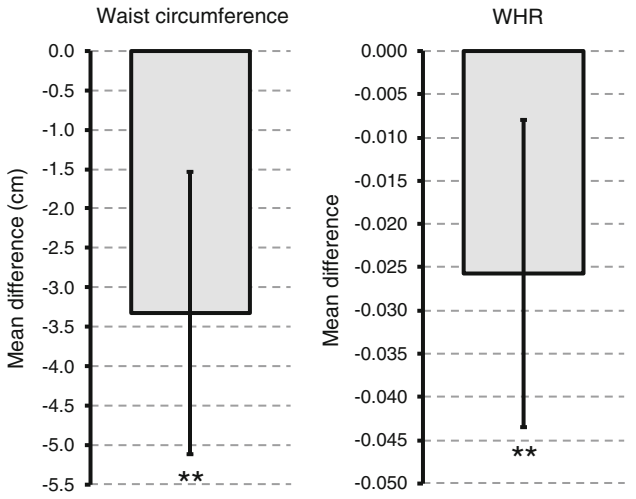

Fig. 2 Adjusted mean difference in waist circumference and WHR between the groups. *Error bars* indicate 95 % CI; ** $p < 0.01$

(median difference from baseline of −0.50 kg/m^2; IQR −0.10 to −1.10 kg vs. −0.20 kg; IQR 0.30 to −0.67 kg/m^2, respectively; $p = 0.05$). There was a greater reduction in waist circumference (adjusted mean difference of −3.32; 95 % CI −1.53 to −5.11 cm; $p < 0.001$) and WHR (adjusted mean difference of −0.026; 95 % CI −0.008 to −0.043; $p = 0.005$) in favor of the intervention group (Fig. 2). No change in bioimpedence percentage body fat was observed.

Secondary outcomes

Aerobic fitness, blood pressure, quality of life, and dietary intake

Women allocated to the intervention group showed a significantly greater improvement in cardiorespiratory fitness ($p < 0.001$) and diastolic blood pressure ($p = 0.03$) than the controls (Table 2). Greater increases in the FACT-B and breast cancer subscale scores were also observed in the intervention group (Table 3). The relative advantage was >6 points ($p = 0.004$) in FACT-B score and >2 points ($p = 0.007$) in the breast cancer subscale. Although there were no differences between the groups in total energy and protein or carbohydrate intake, the intervention group showed a significantly greater reduction in total fat (adjusted mean difference of −9.1 g, 95 % CI −1.4 to −16.7 g; $p = 0.021$) and saturated fat (adjusted mean difference of −4.1 g, 95 % CI −1.2 to −7.0 g; $p = 0.006$) versus controls.

Blood analysis

The intervention had minimal effect on the blood biomarkers associated with disease recurrence and cardiovascular risk (Tables 4, 5), with the exception of leptin ($p = 0.005$), total cholesterol ($p = 0.046$), and HDL ($p = 0.015$). Given that 57 % ($n = 26$) of women in the intervention group and 31 % ($n = 13$) in the control group lost at least 1 kg of body weight, data from the two groups were pooled to investigate bivariate associations between changes in body weight/waist circumference and blood biomarkers. Change in body weight and waist circumference were positively correlated with changes in leptin ($p < 0.01$) and *hs*-CRP ($p < 0.01$) and negatively associated with SHBG ($p < 0.01$; Table 6). The change in body weight was also positively correlated with changes in IGFBP-3 ($p < 0.05$) and total cholesterol ($p < 0.05$), whereas the change in waist circumference was negatively associated with the change in IGF-1 ($p < 0.01$; Table 6).

Table 2 Cardiorespiratory variables at baseline and follow-up

Characteristic	Time	Intervention group ($n = 47$)	Control group ($n = 43$)	ANCOVA p value
Resting heart rate, beats/min	Baseline	78 (12)	74 (11)	
	24 weeks	75 (10)	74 (11)	
	Change	−3 (8)	0 (9)	0.16
Systolic blood pressure, mmHg	Baseline	138 (19)	137 (19)	
	24 weeks	131 (19)	133 (17)	
	Change	−7 (13)	−3 (11)	0.24
Diastolic blood pressure, mmHg	Baseline	90 (11)	88 (14)	
	24 weeks	84 (9)	87 (10)	
	Change	−5 (10)	−1 (10)	0.03
Predicted VO_2 max, mL/kg/min	Baseline	23.6 (4.0)	23.8 (5.1)	
	24 weeks	31.2 (5.2)	27.3 (5.8)	
	Change	7.6 (4.8)	3.5 (4.1)	<0.001

Data are presented as mean (SD)

Table 3 Quality of life variables at baseline and follow-up

Characteristic	Time	Intervention group ($n = 47$)	Control group ($n = 43$)	ANCOVA p value
FACT-B	Baseline	105.7 (17.5)	108.9 (14.8)	
	24 weeks	119.0 (12.8)	114.1 (14.6)	
	Change	13.3 (14.8)	5.1 (10.7)	0.004
Breast subscale	Baseline	21.9 (5.6)	21.7 (4.6)	
	24 weeks	26.0 (4.7)	23.5 (4.7)	
	Change	4.1 (5.1)	1.9 (4.2)	0.007

Data are presented as mean (SD)

Discussion

This study reports for the first time the effects of a combined exercise and dietary intervention on body weight and

Table 4 Sex steroid hormones, SHBG and HOMA at baseline and follow-up

Variable	Time point	Intervention group ($n = 43$)	Control group ($n = 40$)	Mann–Whitney p value
Estradiol, pg/mL	Baseline	6.7 (1.4, 14.8)	5.0 (2.4, 12.7)	
	24 weeks	6.4 (1.0, 24.8)	6.0 (1.2, 13.0)	
	Change	−0.5 (−4.5, 6.1)	−1.0 (−4.1, 2.4)	0.58
Estrone, pg/mL	Baseline	92.3 (64.3, 150.7)	102.6 (65.2, 167.7)	
	24 weeks	105.5 (48.4, 176.1)	101.6 (48.1, 171.9)	
	Change	5.1 (−13.1, 21.0)	−0.9 (−11.9, 6.4)	0.08
Testosterone, nmol/L	Baseline	1.8 (1.4, 2.2)	1.6 (1.3, 2.1)	
	24 weeks	1.7 (1.3, 2.2)	1.6 (1.3, 2.0)	
	Change	0.0 (−0.3, 0.3)	0.1 (−0.2, 0.3)	0.44
SHBG, nmol/L	Baseline	43.6 (32.1, 69.3)	51.4 (30.2, 76.3)	
	24 weeks	42.6 (35.3, 64.3)	50.0 (33.6, 73.9)	
	Change	2.2 (−2.2, 4.8)	−0.8 (−5.7, 3.4)	0.13
HOMA	Baseline	1.33 (0.87, 1.93)	1.91 (1.28, 2.67)	
	24 weeks	1.49 (1.09, 2.12)	2.08 (1.59, 2.93)	
	Change	0.07 (−0.39, 0.55)	0.25 (−0.40, 0.70)	0.86

Data are presented as median (interquartile range). Analyses for intervention group versus control group

Table 5 Blood-borne biomarkers associated with long-term outcome at baseline and follow-up

Variable	Time point	Intervention group ($n = 43$)	Control group ($n = 40$)	Mann–Whitney p value
IGF-1, ng/mL	Baseline	60.0 (51.3, 87.6)	65.1 (48.2, 82.6)	
	24 weeks	57.2 (47.1, 80.7)	61.1 (50.8, 69.9)	
	Change	−1.7 (−11.2, 5.9)	−1.3 (−11.7, 6.7)	0.84
IGFBP-1, ng/mL	Baseline	48.4 (22.8, 59.9)	29.1 (17.6, 49.4)	
	24 weeks	45.9 (22.3, 67.0)	32.0 (22.9, 51.6)	
	Change	5.7 (−9.4, 16.1)	1.5 (−4.5, 9.8)	0.22
IGFBP-3, ng/mL	Baseline	2,457 (2,025, 3,070)	2,445 (1,851, 2,956)	
	24 weeks	2,326 (1,894, 2,887)	2,359 (2,011, 2,796)	
	Change	−166 (−323, 86)	−66 (−344, 403)	0.21
Leptin, pg/mL	Baseline	28,114 (22,549, 42,008)	27,264 (16,911, 47,177)	
	24 weeks	26,019 (16,489, 40,530)	30,853 (22,360, 43,096)	
	Change	**−3,351 (−9,088, 2,057)**	**4,553 (−4,342, 10,085)**	**0.005**
hs-CRP, mg/L	Baseline	1.37 (0.64, 2.53)	2.12 (0.67, 5.22)	
	24 weeks	1.52 (0.78, 3.37)	2.18 (0.82, 6.17)	
	Change	0.10 (−0.36, 0.63)	0.03 (−0.43, 0.70)	0.80
Total cholesterol, mmol/L	Baseline	5.70 (4.90, 6.50	5.00 (4.10, 6.15)	
	24 weeks	5.50 (4.70, 6.40)	5.15 (4.53, 5.95)	
	Change	**−0.20 (−0.50 0.10)**	**0.10 (−0.30, 0.58)**	**0.046**
HDL, mmol/L	Baseline	1.60 (1.36, 1.80)	1.47 (1.19, 1.74)	
	24 weeks	1.60 (1.33, 1.78)	1.48 (1.29, 1.80)	
	Change	**0.00 (−1.00, 1.00)**	**0.09 (−0.03, 0.22)**	**0.015**

Data are presented as median (interquartile range)

Significantly different changes between the groups are shown in bold text

other health outcomes associated with long-term outcome in overweight women during the early recovery phase (3–18 months) after stage I–III breast cancer treatment. Minimization ensured that the groups were well balanced on key variables such as chemotherapy and hormone treatments that could influence weight gain after breast cancer treatment. Although more women in the intervention group underwent mastectomy, this had no effect on response to the intervention. The ANCOVA of parametric data and comparison of change variables between groups for non-normally distributed data ensured that any slight variations between the groups at baseline were accounted

Table 6 Spearman's rank correlation coefficients (ρ) showing associations between changes in blood biomarkers, body weight, and waist circumference

	Δ Body weight	Δ Waist circumference
Estradiol	−0.11	−0.14
Estrone	0.07	−0.13
Testosterone	0.09	0.06
SHBG	**−0.29****	**−0.31****
HOMA	0.21	0.12
IGF-1	−0.08	**−0.39****
IGFBP-1	−0.06	−0.14
IGFBP-3	**0.27***	0.14
Leptin	**0.36****	**0.35****
hs-CRP	**0.33****	**0.31****
Total cholesterol	**0.23***	0.19
HDL cholesterol	0.06	−0.01

Data from the two groups were pooled before analysis

Δ indicates change from baseline

* $p < 0.05$; ** $p < 0.01$

Significant correlations are shown in bold text

for. Weight loss was modest in the intervention group and was only significantly different from the controls when two outlying weight change values were removed from the analysis. However, women in the intervention group experienced a significantly greater reduction in central adiposity (waist circumference) and an improvement in aerobic fitness in comparison with the controls.

The modest amount of weight loss was similar to that reported previously in some [19, 32–36] but not all studies [13, 26, 37, 38] of overweight cancer and non-cancer populations following combined exercise and dietary interventions lasting 2–12 months. Previous studies have used a wide variety of intervention formats, including home-based and supervised components, different behavioral strategies, and varying levels of psychosocial support, and those that provided more intensive support for dietary change have generally resulted in greater levels of weight loss [13, 26, 37]. The clinical importance of this modest reduction in body weight is unknown, but previous research has reported a progressive increase in body weight of 1–3 kg per year in women recovering from early-stage breast cancer [39], which can be accompanied by the accumulation of potentially hazardous central adiposity [40]. Observational evidence suggests that each 5 kg of weight gain after breast cancer diagnosis is associated with a 12 % increased risk of all-cause mortality and 13 % increased risk of breast cancer-specific mortality [4]. Conversely, interim data from the WINS study showed a 24 % improvement in 5-year relapse-free survival associated with an average weight loss of 2.3 kg 1 year after diagnosis in early-stage breast cancer patients versus controls who gained weight [15]. Considered together, this evidence suggests that a modest amount of weight loss (1–2 kg) over a time period of 24 weeks in the early recovery phase after treatment could be clinically important, particularly if this trend could be maintained to counteract an increased susceptibility to weight gain. This is supported by the reduction in circulating leptin concentration in the intervention group. Leptin promotes human breast cancer proliferation in vitro [41], and elevated levels were shown to be associated with adverse prognostic events in early-stage breast cancer survivors over long-term periods of follow-up (median of 12.1 years) [42].

Women in the intervention group experienced a significant reduction in central adiposity (waist circumference and WHR). Central adiposity is linked to elevated leptin concentration [43] and insulin resistance syndrome, including low-grade systemic inflammation [9], which is associated with cardiovascular morbidity/mortality in women [44], postmenopausal breast cancer risk [45, 46], and poorer survival in early-stage breast cancer patients [47]. Evidence that insulin resistance syndrome and low-grade systemic inflammation are common occurrences in breast cancer survivors [48] suggests that interventions for reducing central adiposity could significantly impact upon long-term outcome and disease-free survival. This is supported by the positive association between change in waist circumference and circulating leptin levels in the pooled analysis (Table 6). Previous research has reported similar moderate correlations between reductions in body fat and circulating leptin levels following hypocaloric diets in overweight postmenopausal women [49, 50]. Change in waist circumference was also positively associated with the change in *hs*-CRP and negatively associated with the change in SHBG (which controls the bioavailability of sex steroid hormones), providing further support for the benefits of reducing central adiposity in the early recovery phase after breast cancer treatment. The previously reported evidence of a nonlinear relationship between IGF-1 and central adiposity in a large cohort of women aged 32–77 years [44] could explain the negative association between change in waist circumference and change in IGF-1 concentration in the pooled analysis.

The intervention group also showed an improvement in cardiopulmonary fitness, as well as reductions in diastolic blood pressure and total cholesterol in relation to controls, which could act to counter the elevated risk of cardiovascular mortality previously reported in breast cancer survivors [12]. Improvements in cardiopulmonary fitness could also provide functional benefits for older breast cancer patients who are reported to have more physical limitations than age-matched controls [51]. These enhancements of cardiopulmonary and cardiovascular function in the

intervention group were accompanied by a perceived improvement in quality of life. The observed change in the FACT-B breast cancer subscale was within the range of 2–3 points, representing a minimally important difference, whereas the change in FACT-B score was slightly under the minimally important difference estimate of 7–8 points [52]. This improvement in quality of life could be attributed to a number of factors, including the increase in cardiopulmonary fitness and/or level of physical activity, weight loss/body composition changes, and an improvement in diet quality, which is consistent with the previous data [1, 2, 53, 54]. However, it is also important to be mindful of attention effects on quality of life outcomes, as an improvement in FACT-B score was previously reported in the attention control arm of a short-term exercise trial in a similar cohort of early-stage breast cancer patients [55].

Study limitations included the short-term nature of the intervention and lack of longer-term follow-up of the key outcomes. A longer-duration intervention, which included a more comprehensive and supportive package of dietary guidance, may have improved the level of weight loss in the intervention group. In addition, follow-up of key outcomes beyond 24 weeks, such as body weight and body composition, would have yielded more robust evidence of the longer-term impact of the intervention on the primary and secondary outcomes. In addition, the assessment of body composition was undertaken using simple anthropometric techniques and bioimpedence. An assessment of body composition parameters using more sophisticated scanning techniques would have shed more light on changes in lean body mass and specific fat compartments, such as central (abdominal) adiposity.

In summary, this pragmatic lifestyle intervention evoked a modest reduction in body weight and BMI, and a significant reduction in potentially hazardous central adiposity in overweight women 3–18 months after treatment for early-stage breast cancer. Improvements in cardiopulmonary fitness, cardiovascular function, and quality of life were also observed. Such changes are solid foundations for optimizing recovery in this early period after breast cancer treatment, when many women are vulnerable to the potentially adverse health effects of weight gain and increased body fat. The intervention also evoked favorable changes in circulating leptin levels which could be linked to reductions in central adiposity. Future pragmatic weight loss intervention trials should include more intensive support for dietary change and include the long-term assessment of clinical end-points such as mortality and disease-free survival.

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Conflict of interest The authors declare that they have no conflict of interest.

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