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The Yale Fitness Intervention Trial in female cancer survivors: Cardiovascular and physiological outcomes

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Abstract

Background—Induced premature menopause and cardio-toxic therapy increase cardiovascular disease risk in female cancer survivors.

Objective—To compare the effects of a 12 month aerobic-resistance fitness center intervention to home based physical activity on cardiovascular function and metabolic risk factors.

Methods—Subjects (N = 154) who had completed primary and/or adjuvant chemotherapy (past 3 years) were randomized to a fitness center intervention or a home based group. The fitness center intervention was a structured thrice weekly aerobic (30 min brisk walking treadmill in target heart range) combined with resistance (30 min of lower body strength training) exercise program, supervised for the first 6 months. The home based group received national guidelines for 30 min moderate intensity exercise most days of the week. Fasting serum samples were collected at baseline, 6 and 12 months for insulin, glucose, lipids and hemoglobin A-1C. A graded exercise stress test was also performed at baseline and 6 months.

Results—The majority of subjects were white (85.7%), had breast cancer (83.1%) and the average age was 51.9 years. Subjects in the fitness center intervention had significantly improved time on treadmill ($p = .039$), improved heart rate recovery at 1 min ($p = .028$), greater MET minutes/week ($p = .0001$), a trend for improved insulin resistance ($p = .067$) and stable insulin levels ($p = .045$) compared to the home based physical activity group.

Conclusions—Exercise represents a potential cardiac risk reduction intervention for cancer survivors.

Clinical Trials.gov—NCT01102985.

Keywords

Breast cancer; Cardiovascular fitness; Heart rate recovery; Exercise; Insulin resistance

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Introduction

Cancer and cardiovascular disease are integrally related and the growing specialty of cardio-oncology has identified the need for interdisciplinary collaboration in clinical care and research.^{1,2} The menopausal transition increases cardiovascular disease risk.³ For women diagnosed with breast cancer, the known presence of cardiovascular risk factors (e.g. overweight, obesity, sedentary behavior), premature treatment induced menopause, cardiotoxicity associated with chemotherapy and targeted agents, deconditioning during treatment and aromatase inhibitor endocrine therapy have resulted in lower cardiovascular reserve and a predicted increased risk for cardiovascular disease.^{4–8} There are more than 3 million breast cancer survivors and due to advances in breast cancer treatment, all-cause mortality has now surpassed breast cancer specific mortality.⁹ Assessment of risk factors and risk reduction interventions are urgently needed. As one example, weight gain during and after breast cancer treatment is common,^{10–12} which is associated with an increased risk of recurrence and lower survival^{13–16} and represents a modifiable risk factor for tertiary prevention.^{17,18}

Healthy lifestyle behaviors are recognized as essential risk reduction interventions for cardiovascular health in women.^{1,19,20} Exercise has been shown to stabilize or prevent weight gain in healthy women²¹ improves insulin resistance,²² decreases the risk of diabetes²³ improves lipid profile^{24,25} and reduces overall cardiovascular disease risk.²⁶ For cancer survivors, physical activity has been shown to improve aerobic capacity, quality of life, strength, fatigue and depression, although there are wide variations in the exercise protocols in terms of duration, intensity, and types of delivery.^{27–31} The increased risk of cardiovascular disease among breast cancer survivors due to aging, presence of cardiovascular risk factors and/or cardiotoxicity from cancer treatment^{32–34} in the context of prolonged cancer survival rates supports an ongoing need to evaluate lifestyle behaviors as a cardiovascular risk reduction strategy. The purpose of the Yale Fitness Intervention Trial (Yale FIT), a randomized controlled trial (RCT), was to determine the effect of a 12-month aerobic-resistance exercise intervention compared to a home based physical activity group on cardiovascular function and metabolic risk factors in female cancer survivors. The hypothesis of the trial was that the aerobic-resistance exercise intervention would have significantly improved cardiovascular fitness outcomes and a better metabolic profile compared to the home based physical activity group at 6 and 12 months.

Methods

Subject recruitment

Subject recruitment, enrollment, attrition and intervention design has been previously described in detail.³⁵ Briefly, eligible subjects (breast, colorectal, gynecologic cancer or lymphoma diagnosis; ≥ 3 years since completion of non-endocrine cancer therapy; menopausal [peri or early postmenopausal, the latter defined as ≥ 5 years since last menstrual period], no resistance exercise ≥ 3 times/week; physically able to participate [physician permission]) were recruited predominantly from two hospital tumor registries supplemented by physician or self referrals from clinical sites. After baseline data were collected, we used

a stratified randomization of blocks of 6 to help control the wave enrollment. We also stratified based on cancer site, as most subjects were expected to have a diagnosis of breast cancer. The study was approved by the Yale University Human Subjects Review Committee.

Exercise intervention protocol

The exercise intervention was an aerobic-resistance intervention delivered by trained research interventionists at community fitness centers (matched to where women lived or worked) 3 times per week, supervised for the first 6 months and unsupervised the last 6 months. The first 4 weeks were designed as progressive training to achieve the intervention target of 30 min of aerobic activity in the subject's target heart rate goal (65%–75%) through brisk walking on a treadmill and approximately 30 min of lower body resistance exercises including lunges, squats and 8 repetitions, specifically with leg press, toe press, leg extension, leg curl up and bent knee sit ups. The BORG Rating of Perceived Exertion Scale³⁶ was reviewed with subjects on beta blockers with the goal by the end of the four week training to have subjects exercising at 13–16 perceived exertion rating. Warm up and cool down stretching exercises were performed before and at the end of each exercise session. Subjects were encouraged to perform aerobic activity on other days of the week. For the subjects randomized to the home based group, national guidelines for physical activity for adults (30 min moderate level activity most days of the week) were provided and reviewed, supported by the American Cancer Society's "Smart Steps" booklet which describes examples of moderate intensity activities. Both the intervention and home-based groups received the American Cancer Society Nutrition Guidelines for cancer survivors.³⁷

Metabolic data acquisition

Data were collected at the Yale Center for Clinical Investigation's Hospital Research Unit (HRU) at baseline, 6 and 12 months in the morning after a 12 h fast. Serum was collected for insulin, glucose, Hemoglobin A1-C, total cholesterol, triglycerides, and high density and low density lipoprotein. Insulin resistance was determined by the homeostatic model of assessment (HOMA) index (fasting plasma glucose [in millimoles per liter] X fasting plasma insulin [in microunits per millimeter] divided by 22.5).³⁸ Weight was recorded on a balance beam scale with light clothing and no shoes to the nearest pound and height measured to the nearest inch.

Hemodynamic monitoring and exercise testing

The study research nurse took blood pressure after a 10 min period of complete rest (supine) with a mercury sphygmomanometer. The mean of three resting BP readings taken 1 min apart was used as the resting blood pressure reading. A graded exercise treadmill test was performed at the Yale New Haven Hospital, Cardiovascular Nuclear Imaging and Exercise Laboratory at baseline and 6 months using a standard modified Bruce protocol with progressive 3 min stages of exercise.³⁹ A modified twelve lead electrocardiogram was obtained prior to exercise and recorded continuously throughout the stress protocol and monitored continuously for a minimum of 5 min post exercise. Heart rate and blood pressure were recorded in each stage of exercise.⁴⁰ Patients were evaluated for the change in total exercise treadmill time at 6 months and change in heart rate from peak exercise to one and 5

min post exercise was assessed as an index of autonomic function and predictor of cardiovascular outcome as previously applied in the general population.^{41,42}

Monitoring physical activity

The International Physical Activity Questionnaire (IPAQ)^{43,44} was administered by a research assistant to document leisure, moderate and vigorous activity which summarizes all the types of physical activity to yield a score, reported as MET minutes per week. MET minutes per week were calculated in subscales of walking, moderate intensity, and vigorous intensity as the product of MET level, minutes per episode, and time spent per week. The total MET minutes per week was the sum of the three subscales, which represented to total amount of physical activity.

Statistical analysis

Data analysis was performed with SAS version 9.3. Chi-square test, Cochran-Armitage trend test and t-tests were used to examine baseline equivalence in demographic and clinical variables between two groups. The change of cardiac outcomes physical activity were estimated using a general linear model (GLM) and least square means (LS-mean) were estimated after controlling for age and baseline outcome. To examine the improvements in metabolic risk factors, the changed scores at 6 and 12 months from baseline between two groups were estimated using mixed effect model with a within-subject correlation structure. LS-means of change score were estimated from group-time interaction term after controlling for age, baseline BMI, and baseline score.

Results

From 1264 potential subjects identified from the tumor registries and 81 referrals, 672 were screened, and of those, 308 were determined eligible, and 154 (76 in the fitness center and 78 in the home-based group) women were enrolled.³⁵ There were four women who never started the exercise program, and over the first six months, four who were lost to follow-up and seven withdrew for non-study injuries or illness conditions leaving 139 women (67 in gym exercise vs. 72 in home-based activity) evaluable (Fig. 1).

The sample consisted of primarily White women (85.7%) who were married (70%), employed either full or part time (82.8%), had a breast cancer diagnosis (83.1%) and an average age of 51.9 years (SD = 6.1). Half of the subjects had received adjuvant chemotherapy (52.7%) and 69.4% were on adjuvant endocrine therapy with either tamoxifen or an aromatase inhibitor.³⁵ Comparison of baseline characteristics for cardiac, body composition, physical activity level and metabolic risk factors between the fitness center intervention and home based group are shown in Table 1. Lower triglycerides ($p = .0129$) and higher peak heart rate ($p = .0187$) in exercise intervention subjects compared to home-based physical activity subjects were observed at baseline. None of the other baseline characteristics were significantly different between the two groups.

Cardiovascular fitness

Cardiovascular fitness outcomes improved in the fitness center exercise intervention group compared to the home based physical activity group. Both groups improved time on treadmill at 6 months ($<.001$) (Fig. 2) but the fitness center group had significantly greater improvement ($P = .039$).

We evaluated change from peak heart rate to 1 min post exercise an established index of autonomic function and cardiovascular fitness. After controlling for peak heart rate and age at baseline, the fitness center group had significantly improved heart rate recovery (HRR) at 1 min compared to the home based group ($p = .028$) (Table 2).

HRR during a cool-down period of 5 min after peak exercise was positively associated with time on treadmill ($r = .225$, $p = .006$). There were no significant differences in blood pressure between groups. Significantly greater improvement in total MET minutes per week was observed in the fitness center group compared to the home based group ($p < .0001$).

Metabolic risk factors

After controlling for age, baseline BMI, and baseline values, Table 3 shows the least square mean and 95% confidence interval of changed metabolic outcomes from baseline. There was a trend for improved insulin resistance in the fitness center intervention group at 6 months ($p = .067$) and insulin was significantly increased in the home-based group compared to no change in the fitness center group at 12 months ($p = .0450$).

When cholesterol levels were analyzed by type of adjuvant endocrine therapy (30% aromatase inhibitor [AI], 31% tamoxifen, 39% no endocrine therapy) (Table 4), women on AI therapy had increased cholesterol levels over time. Those in the home-based group had a statistically significant greater increase compared to the exercise group ($p = .0378$). Among women on tamoxifen, the home-based group had significantly higher insulin resistance ($p = .0486$) compared to the fitness center group (Table 4).

Baseline BMI was an important predictor of increased insulin ($p = .0020$), insulin resistance ($p = .0188$), and LDL cholesterol ($p = .0469$). As weight is also a known factor in metabolic outcomes, weight was categorized as a loss (> 5 lbs), stable (within ± 5 lbs) or gain (> 5 lbs). Of 130 evaluable subjects with weight data at baseline and 12 months, 20% lost weight, 30% gained and 50% were weight stable. There was no change in weight by fitness center or home based group (data not shown) but women who gained weight had significantly higher insulin ($p = .0434$), and insulin resistance ($p = .0194$), with no significant changes in other metabolic variables after controlling for age, baseline BMI, and baseline score (Table 5).

In summary, cardiac autonomic function as reflected by post exercise HRR was significantly improved for subjects in the fitness center intervention compared to the home based group. The aerobic-resistance fitness center intervention also stabilized insulin and insulin resistance for women on AI and Tamoxifen endocrine therapies compared to the observed increases for subjects in the home based group. Baseline BMI was a predictor of increased insulin and insulin resistance and subjects who gained weight during the year of the study also had significant increases in insulin and insulin resistance.

Discussion

The findings of the Yale FIT study confirm the importance of exercise in a high risk cancer survivor population related to cardiovascular outcomes. Both time on treadmill and HRR were significantly improved for subjects in the Yale FIT aerobic-resistance intervention group. Improvement in HRR is clinically important as it is a prognostic predictor,^{41,45} an indicator of cardiac autonomic function⁴⁶ and overall cardiovascular fitness has been reported to reduce cancer mortality, independent of adiposity.⁴⁷ As two-thirds of the subjects in Yale FIT were overweight or obese, improvement in fitness supports the cardiovascular health benefits of exercise in an at risk population of cancer survivors.

Being overweight, obese and weight gain after treatment is common among breast cancer survivors,^{10–12,48} weight gain in non-obese healthy postmenopausal women is associated with insulin resistance,⁴⁹ and higher fasting insulin levels and insulin resistance are associated with poorer outcomes for cancer survivors.^{50–52} Thus, investigators have evaluated the effect of exercise on insulin levels and insulin resistance.^{42,53–56} While two studies showed a decrease in insulin levels in the exercise intervention group,^{53,56} it was not significantly different compared to the control group in either study ($p = .08$ and $p = .07$ respectively). The findings of Yale FIT demonstrated stabilization of fasting insulin levels in the exercise group compared to statistically increased insulin levels in the home based group and a trend for improvement in insulin resistance for the exercise group, but only at 12 months. Two of the previous cited studies were only of 4 months⁵⁶ or 6 months duration⁵³ and perhaps longer sustained exercise is needed to alter these metabolic outcomes. Weight did influence insulin and insulin resistance with women with stable weight or who lost weight having significantly lower levels, which is similar to a recently published weight loss trial in breast cancer survivors.⁵⁷ There was no significant change in triglycerides by group or type of adjuvant therapy. The effect of AI and Tamoxifen endocrine therapy on lipids is mixed⁵⁸ and it is unknown even if there are favorable changes in lipids, if that translates into a clinical benefit.⁵⁹ However, endocrine therapy is now recommended for up to 10 years and the cardiovascular effects are yet to be fully identified.

BMI has been reported to be a predictor of increased cardiovascular disease⁸ and increased recurrence rate and decreased survival.^{16,48,51} In Yale FIT, long term cancer outcomes could not be evaluated but baseline BMI was a predictor of increased insulin and insulin resistance. The relationship of BMI and insulin on breast cancer progression is complex^{60,61} but a comprehensive risk reduction approach related to cardiovascular disease, diabetes, cancer specific and all-cause mortality is needed.⁶¹ The effect of weight reduction for women who are overweight or obese at diagnosis on disease free and overall survival is unknown as we await results of ongoing trials.⁶⁰ However, what is known are the health benefits of regular sustained exercise as a non-pharmacologic intervention for cardiovascular and overall health of women who are cancer survivors.^{14,17,18} The combination of aerobic plus resistance exercise is recommended for all women >50 years of age and resistance exercise has the potential to decrease chronic illness risks associated with central adiposity, increased fat mass, and elevated waist circumference in normal, overweight and obese breast cancer survivors.^{62,63}

Limitations of the study are the sample size, especially for the sub-analyses by type of adjuvant endocrine therapy, the lack of a cardiovascular assessment at 12 months and the downward drift in level of physical activity in the intervention group during the last nonsupervised 6 months. Also, the average age of the subjects was relatively young across the age spectrum of women with cancer and perhaps the intervention would have greater impact on older age survivors with known cardiovascular risk factors.^{7,8}

In summary, we demonstrated that a 12-month aerobic-resistance exercise intervention delivered at a fitness center resulted in significantly better cardiovascular fitness and metabolic risk factors compared to a national guideline home-based physical activity group. We had a 77.4% adherence rate to the supervised thrice weekly exercise intervention at the fitness centers across the first 6 months.³⁵ However, based on the MET minutes/week, there was a decline in physical activity in the last six months when women were not being supervised and there was little change in physical activity among the home-based group. A major challenge is how to motivate, engage and sustain cancer survivors in physical activity to achieve a risk reduction benefit. Text messaging, feedback with accelerometers and peer coaching offer potential strategies to promote adherence over time. Innovative and cost effective interventions are needed to increase physical activity and prevent weight gain in order to decrease co-morbid health risks.

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Fig. 1.
Enrollment.

Fig. 2. Increased time on treadmill at 6 months from baseline. Note. Mean of increased time on treadmill was calculated by the quartile of time at baseline.

Table 1

Baseline comparisons between fitness center and home based groups.

	Fitness center N = 76	Home-based N = 78	Baseline difference (P-value)
	Mean (SD)	Mean (SD)	
Body composition			
Weight (lb)	173.6 (42.8)	166.7 (41.0)	($\dagger$).2654
BMI	29.5 (6.8)	28.5 (6.8)	($\dagger$).2984
Waist circumference (cm)	87.1 (15.0)	85.5 (15.6)	($\dagger$).4611
Total fat (kg)	31.5 (11.2)	30.3 (11.9)	($\dagger$).3815
Total lean (kg)	44.1 (7.6)	42.8 (7.4)	($\dagger$).2832
Total mass (kg)	77.8 (17.4)	75.3 (18.3)	($\dagger$).3039
% Fat	39.6 (6.3)	39.1 (6.6)	.6154
Metabolic risk factors			
Insulin	13.9 (8.4)	14.1 (9.3)	($\dagger$).7403
Glucose	5.44 (0.98)	5.78 (1.79)	($\dagger$).1564
Hemoglobin A1c	0.056 (0.004)	0.058 (0.012)	($\dagger$).2247
Total lipid	187.6 (27.2)	185.5 (28.0)	.6411
Triglycerides	96.0 (41.3)	119.1 (66.3)	($\dagger$).0129
HDL-Cholesterol	53.6 (14.6)	50.6 (14.3)	.1978
LDL-Cholesterol	107.3 (22.6)	105.2 (23.0)	.5716
Cardiac variables			
Resting heart rate	75.6 (9.5)	76.3 (11.8)	.7072
Peak heart rate	166.6 (14.9)	160.6 (16.2)	.0187
Recovery heart rate	100.5 (15.0)	99.1 (16.8)	.6077
(*) Change heart rate in 1 min (%)	15.7 (5.5)	14.7 (6.0)	.3466
Resting Systolic Blood Pressure	116.7 (14.4)	119.9 (16.3)	.2182
Resting diastolic blood pressure	73.2 (8.4)	74.8 (9.5)	.2803
Level of physical activity			
MET minutes per week	1327 (1494)	1446 (1843)	($\dagger$).4218

Note. (*) % Change Heart Rate in 5 min = $100 \times (\text{Peak HR} - \text{Recovery HR}) / \text{Peak HR}$ (%). P-values were obtained from two-side *t*-test with log-transformed score when variables are skewed.

Table 2

Changes in heart rate reduction (HRR) over 6 months, blood pressure, and physical activity (MET minutes per week) between the fitness center intervention and home-based physical activity groups. (N = 139).

	Baseline mean (SD)	6 Month mean (SD)	Delta LS-mean (95% CI)	Comparison of delta (p-value)
Heart rate reduction at 1 min				
Fitness Center	15.7 (5.5)	16.9 (5.9)	1.30 (−0.45, 3.05)	.0286
Home-Based	14.7 (6.1)	13.3 (8.6)	−1.55 (−3.38, 0.29)	
Systolic blood pressure (mmHg)				
Fitness Center	116.7 (14.3)	115.0 (14.7)	−2.44 (−5.40, 0.52)	.5646
Home-Based	119.5 (16.7)	118.1 (14.4)	−1.22 (−4.14, 1.69)	
Diastolic blood pressure (mmHg)				
Fitness Center	73.3 (8.7)	71.3 (9.2)	−2.77 (−5.03, −0.52)	.2326
Home-Based	74.7 (9.8)	73.7 (9.3)	−0.85 (−3.06, 1.36)	
Total MET minutes per week				
Fitness Center	1309.7 (1512.9)	2816.8 (2538.6)	1482.4 (1038.9, 19025.9)	<.0001
Home-Based	1433.8 (1741.3)	1223.0 (870.3)	−173.6 (−591.5, 244.2)	

Note. Delta is the changed score during 6 months from baseline and least-square means (LS-Mean) were estimated from general linear regression model after controlling for baseline score and age.

Table 3

Least square mean changed metabolic outcomes at 6 and 12 months between fitness center and home based groups.

Cardiac Variables	Intervention	6 months		12 months	
		LS-mean difference (95% CI)	p-value	LS-mean difference (95% CI)	p-value
Insulin	Fitness Center Home-based	1.30 (−0.33, 2.94) 2.61 (0.97, 4.24)	.2702	1.29 (−0.41, 2.99) 3.72 (2.08, 5.35)	.0450
HOMA	Fitness Center Home-based	0.09 (−0.45, 0.64) 0.82 (0.27, 1.36)	.0673	0.02 (−0.55, 0.58) 0.71 (0.17, 1.25)	.0843
HbA1c	Fitness Center Home-based	−0.01 (−0.09, 0.07) −0.03 (−0.10, 0.05)	.7459	−0.09 (−0.02, −0.01) −0.07 (−0.14, 0.01)	.7144
Total Cholesterol	Fitness Center Home-based	1.51 (−4.44, 7.46) 1.85 (−3.82, 7.53)	.9347	6.71 (0.61, 12.80) 8.27 (2.57, 13.98)	.7132
Triglyceride(†)	Fitness Center Home-based	−0.05 (−0.13, 0.03) −0.00 (−0.08, 0.07)	.4092	−0.02 (−0.11, 0.06) 0.03 (−0.04, 0.11)	.3187
HDL Cholesterol	Fitness Center Home-based	1.76 (−0.41, 3.93) 2.11 (0.04, 4.17)	.8221	4.76 (2.53, 6.98) 3.79 (1.72, 5.87)	.5381
LDL Cholesterol	Fitness Center Home-based	3.82 (−1.01, 8.66) 1.27 (−3.34, 5.88)	.4551	7.90 (2.96, 12.84) 8.00 (3.37, 12.62)	.9775

Note. Least square mean (LS-mean) and 95% confidence intervals were estimated after controlling for age, baseline BMI, and baseline score. (†) triglyceride was log-transformed to hold a normal assumption of residuals.

Least square mean of changed metabolic outcomes at 6 and 12 months between the fitness center and home-based groups by adjuvant endocrine therapy type.

Table 4

Variables	Intervention	6 months		12 months		
		LS-mean (95% CI)	Difference p-value	LS-mean (95% CI)	Difference p-value	
Aromatase inhibitor (N = 41)						
Insulin	Fitness center Home-based	0.11 (-2.34,2.56)	1.35 (-1.04,3.74)	0.70 (-1.75,3.16)	3.46 (1.02,5.90)	.1338
HOMA	Fitness Center Home-based	0.12 (-0.59,0.82)	0.55 (-0.14,1.23)	0.07 (-0.63,0.77)	0.89 (0.19,1.59)	.1236
HbA1c	Fitness Center Home-based	0.12 (-0.15,0.19)	-0.02 (-0.17,0.13)	-0.04 (-0.21,0.12)	-0.10 (-0.25,0.06)	.6623
Total Lipid	Fitness Center Home-based	2.77 (-6.66,12.19)	5.87 (-2.83,14.58)	5.87 (-2.83,14.58)	17.78 (8.90,26.67)	.0378
Triglyceride(†)	Fitness Center Home-based	-0.03 (-0.19, 0.13)	-0.01 (-0.16, 0.14)	-0.15 (-0.32, 0.01)	0.07 (-0.08, 0.23)	.0589
HDL Cholesterol	Fitness Center Home-based	-0.95 (-5.94,4.03)	2.95 (-1.20,8.77)	3.78 (-1.20,8.77)	5.22 (0.54,9.90)	.6905
LDL Cholesterol	Fitness Center Home-based	7.78 (0.49,15.08)	4.00 (-2.75,10.75)	9.20 (1.91,16.50)	12.94 (6.05,19.83)	.4741
Tamoxifen (N = 42)						
Insulin	Fitness Center Home-based	0.61 (-3.34,4.56)	5.08 (1.34,8.82)	0.31 (-3.63,4.27)	5.43 (1.78,9.08)	.0655
HOMA	Fitness Center Home-based	-0.08 (-1.19,1.03)	1.16 (0.11,2.21)	-0.33 (-1.44,0.78)	1.21 (0.18,2.24)	.0486
HbA1c	Fitness Center Home-based	0.03 (-0.10,0.17)	0.03 (-0.15,0.10)	-0.02 (-0.16,0.11)	-0.08 (-0.21,0.04)	.5238
Total lipid	Fitness Center Home-based	-3.08 (-14.21,8.05)	-4.37 (-14.64,5.90)	2.13 (-9.00,13.26)	1.83 (-8.22,11.88)	.9684
Triglyceride(†)	Fitness Center Home-based	-0.01 (-0.16, 0.14)	0.05 (-0.09, 0.19)	0.03 (-0.13, 0.18)	0.07 (-0.07, 0.20)	.7058
HDL Cholesterol	Fitness Center Home-based	2.23 (-2.02,6.48)	0.33 (-3.58,4.25)	2.18 (-2.07,6.43)	1.92 (-1.91,5.75)	.9286
LDL Cholesterol	Fitness Center Home-based	0.00 (-9.40,9.40)	-1.86 (-10.47,6.75)	5.63 (-3.77,15.03)	2.55 (-5.93,11.03)	.6310
No hormone therapy (N = 52)						
Insulin	Fitness Center Home-based	3.30 (0.94,5.65)	1.36 (-1.03,3.76)	1.94 (-0.69,4.58)	2.34 (-0.05,4.74)	.8209
HOMA	Fitness Center Home-based	0.45 (-0.56,1.45)	0.56 (-0.47,1.58)	0.19 (-0.93,1.32)	-0.04 (-1.06,0.99)	.7608
HbA1c	Fitness Center Home-based	-0.03 (-0.16,0.10)	-0.07 (-0.20,0.06)	-0.15 (-0.29, -0.01)	-0.05 (-0.18,0.07)	.3023
Total lipid	Fitness Center Home-based	2.77 (-8.23,13.77)	8.75 (-1.94,19.45)	12.25 (0.66,23.84)	9.00 (-1.81,19.82)	.6816
Triglyceride(†)	Fitness Center Home-based	-0.09 (-0.21, 0.04)	-0.02 (-0.14, 0.10)	0.04 (-0.09, 0.18)	-0.03 (-0.16, 0.09)	.4214
HDL Cholesterol	Fitness Center Home-based	3.80 (0.79,6.80)	3.25 (0.37,6.13)	7.73 (4.50,10.95)	4.05 (1.12,6.98)	.0973
LDL Cholesterol	Fitness Center Home-based	2.30 (-6.75,11.34)	5.05 (-3.74,13.84)	8.83 (-0.68,18.33)	10.94 (2.05,19.82)	.7459

Note. Least square mean (LS-mean) and 95% confidence intervals were estimated after controlling for age, baseline BMI, and baseline score.

Table 5

Least square mean of changed metabolic outcomes at 12 months by weight gain over 12 months.

	Weight lose ($< -5\text{lb}$) N = 26 LS-Mean (95% CI)	Stable weight (within $\pm 5\text{lb}$) N = 65 LS-Mean (95% CI)	Weight gain ($> 5\text{lb}$) N = 39 LS-Mean (95% CI)	P-value
Metabolic outcomes				
Insulin	1.60 (−0.99, 4.19)	1.52 (−0.13, 3.18)	4.79 (2.71, 6.88)	.0434
HOMA	−0.07 (−0.79, 0.65)	0.12 (−0.34, 0.58)	1.07 (0.49, 1.65)	.0194
HbA1c	−0.20 (−0.32, −0.08)	−0.03 (−0.11, 0.04)	−0.06 (−0.16, 0.04)	.0717
Total lipid	6.02 (−3.14, 15.17)	11.14 (5.29, 16.98)	3.22 (−4.26, 10.70)	.2576
Triglyceride(†)	0.04 (−0.08, 0.16)	−0.02 (−0.10, 0.05)	0.41 (−0.05, 0.14)	.5057
HDL Cholesterol	6.70 (2.83, 10.57)	4.98 (2.51, 7.44)	1.82 (−1.32, 4.97)	.1228
LDL Cholesterol	4.04 (−3.10, 11.19)	11.83 (7.26, 16.40)	3.35 (−10.49, 9.20)	.0535

Note. Least square mean (LS-mean) and 95% confidence intervals were estimated after controlling for age, baseline BMI, and baseline score.