



Long-Term Favorable Effects of Physical Exercise on Burdensome Symptoms in the OptiTrain Breast Cancer Randomized Controlled Trial

Integrative Cancer Therapies
Volume 19: 1–14
© The Author(s) 2020
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/1534735420905003
journals.sagepub.com/home/ict


Fleur Wiggeraad, MD¹ , Kate A. Bolam, PhD¹, Sara Mijwel, PhD¹,
Elsken van der Wall, MD, PhD², Yvonne Wengström, OCN, PhD^{1,3},
and Renske Altena, MD, PhD^{1,3}

Abstract

Purpose: We evaluate longitudinal changes in symptom clusters and core burdensome symptoms in breast cancer patients who participated in the OptiTrain trial. **Methods:** 240 women were randomized to 16 weeks of supervised exercise (RT-HIIT or AT-HIIT) or usual care (UC) during adjuvant chemotherapy. Symptom clusters were composed using the Memorial Symptom Assessment Scale (MSAS), assessed at baseline, 16 weeks and 12 months later. Three symptom clusters were formed. **Results:** Three symptom clusters were identified: “emotional,” “treatment-related toxicity,” and “physical,” with core burdensome symptoms present over time. At 16 weeks, the reported burdens of “feeling sad” (RT-HIIT vs UC: effect size [ES] = -0.69; AT-HIIT vs UC: ES = -0.56) and “feeling irritable” (ES = -0.41 RT-HIIT; ES = -0.31 AT-HIIT) were significantly lower in both intervention groups compared with UC. At 12 months, the AT-HIIT group continued to have significantly lower scores for the core burdensome symptoms “feeling sad” (ES = -0.44), “feeling irritable” (ES = -0.44), and “changes in the way food tastes” (ES = -0.53) compared with UC. No between-group differences were found for physical symptoms. **Conclusion:** We identified 3 symptom clusters in breast cancer patients during and after adjuvant chemotherapy, composed of “emotional,” “treatment-related toxicity,” and “physical” symptoms. After treatment completion up to 12 months post-baseline, patients in the physical exercise groups reported lower symptom burden scores for emotional symptoms, compared with UC. Our findings indicate a preserved and long-term beneficial effect of physical exercise on self-reported emotional well-being in chemotherapy-treated breast cancer patients.

Keywords

breast cancer, physical exercise, adjuvant chemotherapy, long-term effects, symptom burden, symptom cluster

Submitted September 30, 2019; revised December 3, 2019; accepted January 10, 2020

Introduction

Breast cancer is the most frequent form of female cancer worldwide, with a steadily rising incidence over the past decades.¹ Most patients are diagnosed with primary, resectable breast cancer, and a relevant part is treated with systemic therapies to decrease the risk for relapse and improve breast cancer-related survival. Systemic therapies, such as chemotherapy and endocrine therapy, cause considerable side effects and decline in functional status and health-related quality of life (HR-QoL).^{2,3}

Throughout chemotherapy treatment, most breast cancer patients report multiple burdensome physical and psychological symptoms, related to the disease itself and to respective

treatments. Symptom burden is defined as the subjective, quantifiable prevalence, frequency, and severity of symptoms, placing a physiological burden on patients and producing multiple negative, physical, and emotional patient responses.⁴ The burdensomeness of symptoms can be assessed with

¹Karolinska Institutet, Stockholm, Sweden

²University Medical Center Utrecht, Utrecht, Netherlands

³Karolinska University Hospital, Stockholm, Sweden

Corresponding Author:

Renske Altena, Department of Oncology and Pathology Cancer Center Karolinska, Karolinska Institutet, K7 Onkologi-Patologi, K7 OnkPat Bergh, Stockholm 171 77, Sweden.
Email: Renske.altena@ki.se



various questionnaires, for example, the Memorial Symptom Assessment Scale (MSAS), where the patient grades the self-perceived severity of the respective symptoms. Such burdensome symptoms can be described individually, as well as be grouped into clusters. Symptom clusters can be defined as 2 or more concurrent symptoms that are related to each other, for example, by etiology or affected domain.^{5,6} This clustering as well as reporting the burden of symptoms has a larger impact on clinical outcomes and HR-QoL than individual symptoms.⁷⁻¹⁴ Grouping self-reported symptoms into clusters adds to our understanding of the coherence of individual symptoms and can help identify shared pathophysiological factors. Moreover, it enables estimation of their burdensomeness and assessment of the combined effect of certain symptoms on HR-QoL. This information helps clinicians design effective interventions targeting the most burdensome symptoms and identify factors promoting self-support measures.

A number of studies have described burdensome symptoms and/or symptom clusters in patients with early-stage breast cancer. To our knowledge, only 2 longitudinal studies reported on changes in both symptom clusters and burdensome symptoms during and after adjuvant systemic treatment, assessed by self-reported symptoms from the MSAS.^{15,16} Both studies revealed clusters of burdensome symptoms involved in emotional, gastrointestinal, and physical symptomatology and showed dynamics in the composition of symptoms within the clusters over time. In addition, core symptoms within these clusters contributed the most to the burdensomeness experienced by patients. Core symptoms were based on the symptoms within a cluster with the highest internal correlations.¹³

The prospective, randomized controlled OptiTrain study that included breast cancer patients receiving adjuvant chemotherapy showed beneficial effects of 16 weeks of both resistance and high-intensity interval training (RT-HIIT) and moderate-intensity aerobic and high-intensity interval training (AT-HIIT) on total symptoms and symptom burden as measured by the MSAS, while detrimental effects were found for the usual care (UC) group.¹⁷ To date, the effects of a physical exercise intervention during chemotherapy on clusters of burdensome symptoms are not known. Moreover, it is not known which domains and core burdensome symptoms within those clusters are most affected by physical exercise.

In the current analysis, we aim to describe longitudinal changes in symptom clusters in the RT-HIIT, AT-HIIT, and UC groups in the OptiTrain cohort. We will also assess the effect of RT-HIIT and AT-HIIT on core burdensome symptoms within these symptom clusters.

Patients and Methods

This study is a secondary analysis of data collected as part of the longitudinal prospective, randomized controlled OptiTrain breast cancer trial.

Participants

Recruitment to the study took place at the Karolinska University Hospital (Solna, Sweden) from March 2013 to July 2016. Inclusion criteria were women aged between 18 and 70 years, diagnosed with I to IIIa stage breast cancer, and scheduled to receive adjuvant chemotherapy consisting of anthracyclines, taxanes, or a combination of both. Exclusion criteria included cardiac disease (assessed by routine electrocardiogram and a questionnaire), major psychiatric disorders, or other concurrent malignant diseases. The participants were randomly allocated to either (1) RT-HIIT, (2) AT-HIIT, or (3) a control group receiving UC prior to baseline testing. The intervention groups (RT-HIIT and AT-HIIT) commenced the exercise training 3 days after the second chemotherapy session and ended the intervention 3 weeks following the last chemotherapy session. Details of the randomization and blinding process have been published previously.¹⁸ The OptiTrain study (NCT02522260) was approved by the Regional Ethical Review Board in Stockholm (Dnr 2012/1347-31/1, 2012/1347-31/2, 2013/632-32, 2014/408 32).¹⁷ All participants gave written informed consent prior to enrollment.

Outcome Measures

Study assessments took place at baseline (1 week prior to participants' second chemotherapy session), at 16 weeks (postintervention), and 12-month post-baseline (follow-up). Neither participants nor testers were blinded to study group allocation.

Memorial Symptom Assessment Scale

Patients completed the 32-item MSAS at home.^{19,20} The scale includes occurrence, frequency, severity, and distress associated with each symptom using 4- and 5-point rating scales. Symptom burden was calculated as the average of frequency, severity, and distress of each symptom. Higher scores indicated higher symptom burden.

Intervention

The OptiTrain exercise protocol has been described previously.^{17,18} Briefly, both exercise groups trained twice per week for 16 weeks, and each session was approximately 60 minutes in duration. The exercise sessions were conducted at the exercise clinic at the Karolinska University Hospital and supervised by an exercise physiologist or oncology nurse. The RT-HIIT group performed high-load resistance exercises targeting the major muscle groups consisting of 2 to 3 sets of 8 to 12 repetitions, at an intensity of 70% to 80% of their estimated 1 repetition maximum. The RT-HIIT sessions concluded with 3 × 3 minute bouts of high-intensity

interval exercise at a rating of perceived exertion of 16 to 18, with each bout split by 1-minute recovery, on a cycle ergometer. The AT-HIIT group initiated each session with 20 minutes of moderate-intensity (rating of perceived exertion = 13-15) continuous aerobic exercise followed by the same high-intensity interval exercise as in RT-HIIT.

Usual Care

The UC group received printed written information on physical activity advice based on the American College of Sports Medicine for cancer survivors, directly after baseline testing.²¹

Statistical Methods

Cancer-related fatigue was the primary endpoint of the OptiTrain trial and was the basis for the power calculation.^{17,18} In the current study, descriptive statistics were used to summarize demographic and treatment data.

In each of the 3 arms of the OptiTrain trial (RT-HIIT, AT-HIIT, and UC), symptom burden scores were calculated for all 32 items on the MSAS, according to the MSAS manual. Symptom burden scores ranged between 0 and 4.¹⁹ Only symptom burden scores above 0.5 (high burden) were included for further analysis.¹⁶ The cutoff point of 0.5 was chosen based on findings from a previous study, where associations were found between the presence of symptom clusters among cancer patients and survival duration, independent of other prognostic factors.²² The symptom cluster analysis, with principal component analysis (PCA) as the extraction method and varimax rotation method with Kaiser normalization was conducted with the symptom burden scores for each of the 3 study arms. A fixed number of 3 components in the PCA was chosen, comparable to a previous study,¹⁶ as we expected that many symptoms would be assigned to the same component or symptom cluster. Furthermore, we argued that this would be helpful to determine core (burdensome) symptoms and perform between-group comparisons. Only symptoms with a factor loading ≥ 0.5 were included in a component. PCAs were performed at each measurement time (baseline, 16 weeks, and 12 months after baseline).

The most prominent burdensome symptom in a component was the symptom with the highest factor loading.

Core burdensome symptoms were defined as symptoms present in 1 of the 3 symptom clusters at most study assessments and in all 3 study arms. To explore differences in symptoms between the groups at 16 weeks and 12 months post-baseline, we used linear mixed models with Bonferroni correction, controlling for baseline values, menopausal status, and tumor receptor status. Data not normally distributed were log-transformed prior to linear mixed models analyses. Standardized effect sizes (ES) were calculated as

described previously.^{18,23} ES with scores of 0.2 to 0.5, 0.5 to 0.8, and >0.8 were considered small, medium, and large effects, respectively.²⁴ The results were considered statistically significant at the 5% level ($P < .05$). All calculations were done with the IBM SPSS version 25 statistical package for Windows.

Results

In total, 240 women were randomized into the OptiTrain study and 206 women completed baseline testing. The CONSORT study flow chart is shown in Figure 1. The demographic and clinical characteristics of the original patient sample for this secondary analysis are listed in Table 1. One hundred seventy-seven women completed the MSAS at all 3 time points and were included in the current analysis. There were no significant differences in baseline and treatment characteristics between those who completed the follow-up at 12 months compared with those who completed the 16-week time point measurements. No patients had died or had a recurrence at the 12-month time point. Attendance rates for participants in the RT-HIIT and AT-HIIT groups were 68% and 63%, respectively, and adherence to the training program was 83% in the RT-HIIT group and 75% in AT-HIIT group.^{18,25}

Formation of Symptom Clusters

Three symptom clusters were formed; these were labelled “emotional cluster,” “treatment-related toxicity cluster,” and “physical cluster” based on the burdensome symptoms that composed these clusters. Table 2 summarizes the respective symptoms and their factor loadings in the 3 clusters over time.

Longitudinal Changes in Symptom Clusters

Baseline. At baseline, 3 burdensome symptoms (eg, “I don’t look like myself,” “feeling irritable,” and “feeling sad”) were present in the emotional cluster in all 3 study arms. Only “nausea” and “sweats” overlapped in all 3 study arms in the treatment-related toxicity cluster and physical cluster, respectively. The absolute number of burdensome symptoms was more diverse between the 3 study arms in the treatment-related toxicity and physical clusters, summarized in Table 2.

Sixteen Weeks Post-Baseline. At 16 weeks, the symptom clusters of the 3 study arms were composed of different symptoms compared with the 3 study arms at baseline. Furthermore, the symptom clusters consisted of different overlapping symptoms between the 3 study arms compared with baseline. For the emotional cluster, “worrying” was the most prominent burdensome symptom in

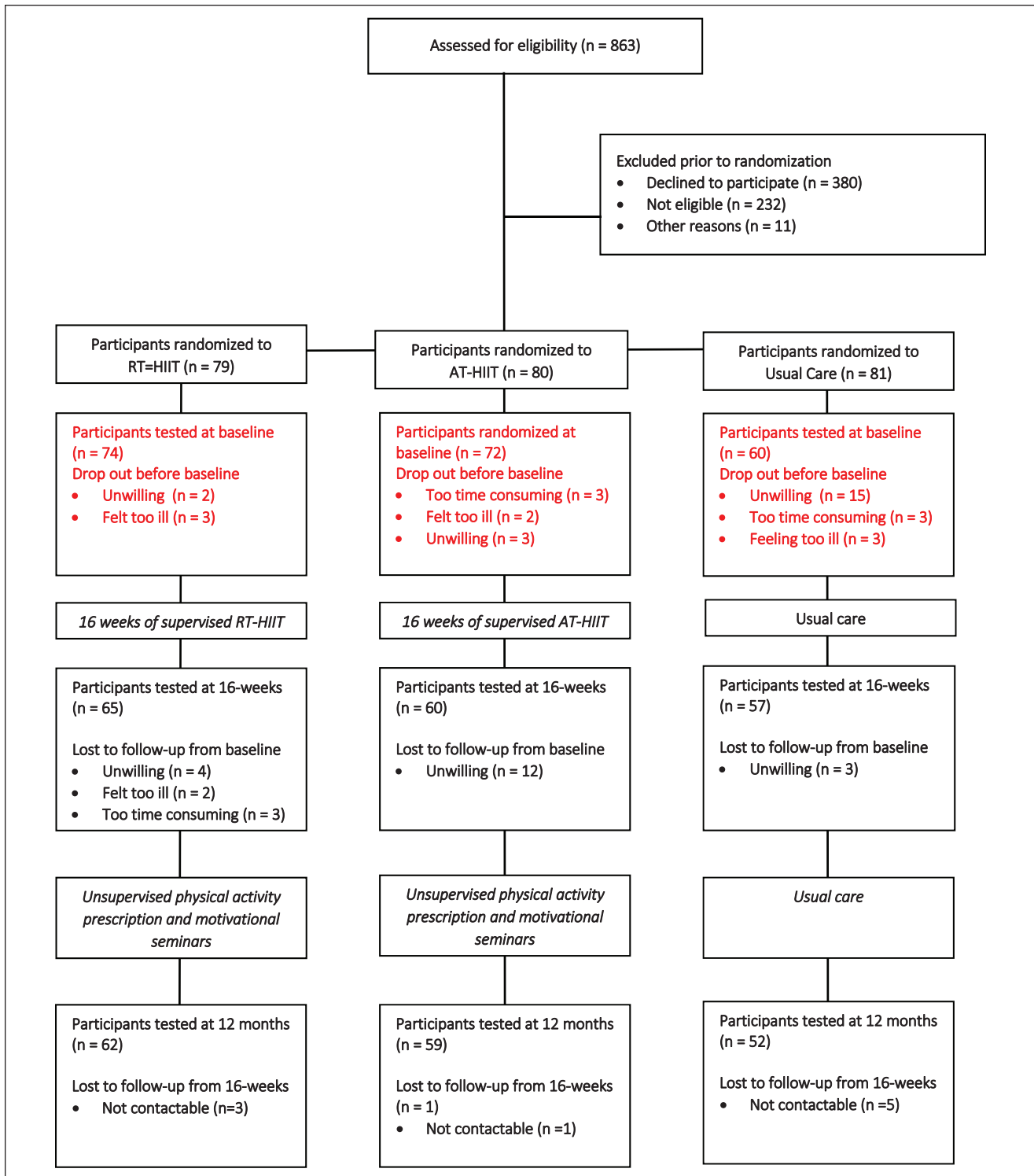


Figure 1. CONSORT diagram: participant flow through the OptiTrain study.

the RT-HIIT group and “feeling irritable” the most prominent burdensome symptom in the AT-HIIT and UC groups. The most prominent burdensome symptoms in the treatment-related toxicity cluster were “changes in the way food tastes” for the RT-HIIT and AT-HIIT groups,

and “lack of appetite” for the UC group. In the physical cluster “feeling bloated,” “lack of appetite,” and “difficulty sleeping” were the most prominent burdensome symptoms for the RT-HIIT, AT-HIIT, and UC groups, respectively.

Table 1. Baseline Participant Characteristics.

	Total, N = 206	RT-HIIT, N = 74	AT-HIIT, N = 72	UC, N = 60
Age (years), mean (SD)	53.3 (10.0)	52.7 (10.3)	54.4 (9.5)	52.6 (10.2)
BMI, mean (SD)	25.0 (4.3)	25.0 (4.3)	24.8 (4.4)	25.0 (4.2)
Married or partnered, n (%)	124 (62.9%)	43 (60.6%)	40 (59.7%)	41 (69.5%)
Level of education, n (%)				
University completed	131 (66.2%)	48 (67.6%)	44 (64.7%)	39 (66.1%)
Current smokers, n (%)	10 (5.1%)	3 (4.3%)	4 (5.9%)	3 (5.2%)
Employed, n (%)	159 (80.3%)	53 (74.6%)	59 (86.8%)	47 (79.7%)
Menopausal status, n (%)				
Premenopausal	84 (40.8%)	35 (47.3%)	26 (36.1%)	23 (38.3%)
Postmenopausal	122 (59.2%)	39 (52.7%)	46 (63.9%)	37 (61.7%)
Tumor profile, n (%)				
Triple negative	31 (15.0%)	12 (16.2%)	8 (11.1%)	11 (18.3%)
ER+/-, HER2+	49 (23.8%)	16 (21.6%)	22 (30.6%)	11 (18.3%)
ER+, HER2-	126 (61.2%)	46 (62.2%)	42 (58.3%)	38 (63.3%)
Positive lymph nodes, n (%)	78 (44.1%)	30 (48.4%)	24 (39.3%)	24 (44.4%)
Chemotherapy regimen, n (%)				
Anthracycline	83 (40.3%)	31 (41.9%)	27 (37.5%)	25 (41.7%)
Taxane	6 (2.9%)	2 (2.7%)	4 (5.6%)	0 (0.0%)
Combination (anthracycline + taxane)	117 (56.8%)	41 (55.4%)	41 (56.9%)	35 (58.3%)
Targeted therapy, n (%)				
Endocrine treatment	144 (78.7%)	55 (82.1%)	52 (81.3%)	37 (71.2%)
Aromatase inhibitor	79 (43.2%)	27 (40.3%)	31 (48.5%)	21 (40.3%)
Tamoxifen	65 (35.5%)	28 (41.8%)	21 (32.9%)	16 (30.7%)
Trastuzumab	46 (22.3%)	15 (20.3%)	15 (20.8%)	16 (26.7%)

Abbreviations: RT-HIIT, resistance and high-intensity interval training; AT-HIIT, moderate-intensity aerobic and high-intensity interval training; UC usual care; SD, standard deviation; BMI, body mass index; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2.

Twelve Months Post-Baseline. In all 3 study arms, the symptom clusters consisted of a lower absolute number of burdensome symptoms compared with baseline and 16 weeks. Moreover, the symptom clusters consisted of less overlapping symptoms between the 3 study arms compared with baseline and 16 weeks. The emotional cluster at 12 months was composed mostly of the same burdensome symptoms as those reported at baseline. In the emotional cluster, “feeling irritable,” “difficulty concentrating,” and “lack of energy” were the most prominent burdensome symptoms in the RT-HIIT, AT-HIIT, and UC groups, respectively.

The most prominent burdensome symptoms in the treatment-related toxicity cluster were “dry mouth” for the RT-HIIT and AT-HIIT groups and “numbness” for the UC group. In the physical symptom cluster, “sweats” was the most prominent burdensome symptom in the RT-HIIT and AT-HIIT groups and “dry mouth” the most prominent burdensome symptoms for the UC group.

Core Burdensome Symptoms Within the Respective Symptom Clusters

The emotional cluster consisted of 5 core burdensome symptoms in all 3 study arms at most time points: “feeling

nervous,” “feeling sad,” “problems with sexual interest or activity,” “feeling irritable,” and “I don’t look like myself.” The treatment-related toxicity cluster was composed of 5 core burdensome symptoms: “dry mouth,” “nausea,” “numbness or tingling in hands or feet,” “diarrhea,” and “changes in the way food tastes.” The physical cluster consisted of 2 core burdensome symptoms: “feeling drowsy” and “sweats.”

Longitudinal Differences in Core Symptoms in the Intervention Groups

The mean symptom burden scores at all 3 time points, between-group differences at 16 weeks and at 12 months, as well as ES for differences in core burdensome symptoms are shown in Table 3. Longitudinal changes in mean symptom burden score for those core burdensome symptoms in the different study groups are depicted in Figure 2.

At 16 weeks, patients in both exercise groups reported significantly lower symptom burden scores for “feeling sad” (RT-HIIT vs UC: ES = -0.69; AT-HIIT vs UC: ES = -0.56) and “feeling irritable” (ES = -0.41 RT-HIIT; ES = -0.31 AT-HIIT), compared with the UC group. At 12 months, the AT-HIIT group had significantly lower scores for “feeling

Table 2. Symptom Clusters With Burdensome Symptoms and Factor Loadings^a.

	Symptom Clusters	Symptoms	Factor Loadings			
<i>Baseline</i>						
RT-HIIT	Emotional	I don't look like myself	0.710			
		Feeling irritable	0.701			
		Hair loss	0.693			
	Treatment-related toxicity		Feeling sad	0.655		
			Problems with sexual interest or activity	0.631		
			Feeling drowsy	0.832		
			Worrying	0.832		
			Shortness of breath	0.766		
			Nausea	0.711		
			Changes in the way food tastes	0.681		
			Lack of energy	0.680		
			Difficulty concentrating	0.637		
			Lack of appetite	0.586		
			Dry mouth	0.511		
			Diarrhea	0.504		
			Physical		Sweats	0.728
					Pain	0.664
AT-HIIT	Emotional	Difficulty sleeping	0.522			
		Feeling irritable	0.775			
		Difficulty concentrating	0.760			
	Treatment-related toxicity		Feeling sad	0.730		
			I don't look like myself	0.641		
			Lack of energy	0.612		
			Feeling nervous	0.590		
			Nausea	0.791		
			Dry mouth	0.768		
			Constipation	0.753		
			Changes in the way food tastes	0.626		
			Physical		Worrying	0.804
					Feeling drowsy	0.794
UC	Emotional	Sweats	0.510			
		Feeling nervous	0.824			
		Lack of appetite	0.776			
		Feeling sad	0.714			
		Feeling irritable	0.670			
		Pain	0.642			
		Difficulty sleeping	0.596			
	Treatment-related toxicity		Shortness of breath	0.543		
			I don't look like myself	0.520		
			Lack of energy	0.811		
			Difficulty concentrating	0.741		
			Feeling bloated	0.739		
			Diarrhea	0.704		
			Worrying	0.650		
Physical		Feeling drowsy	0.650			
		Nausea	0.516			
		Hair loss	-0.533			
		Changes in the way food tastes	0.518			
16 weeks	RT-HIIT	Emotional	Sweats	0.511		
			Worrying	0.800		
			Feeling irritable	0.766		

(continued)

Table 2. (continued)

	Symptom Clusters	Symptoms	Factor Loadings	
AT-HIIT	Treatment-related toxicity	Feeling sad	0.741	
		Difficulty sleeping	0.640	
		Feeling nervous	0.635	
		I don't look like myself	0.544	
		Changes in the way food tastes	0.791	
		Dry mouth	0.730	
		Lack of appetite	0.504	
		Numbness	0.500	
		Physical	Feeling bloated	0.786
			Shortness of breath	0.689
	Swelling of arms or legs		0.688	
	Lack of energy		0.677	
	Feeling drowsy		0.652	
	Emotional	Pain	0.545	
		Feeling irritable	0.732	
		Sweats	0.675	
		Feeling bloated	0.548	
		Problems with sexual interest or activity	0.530	
	Treatment-related toxicity	Difficulty sleeping	0.512	
		Changes in the way food tastes	0.894	
Dry mouth		0.869		
Numbness		0.816		
Pain		0.622		
Feeling sad		0.605		
I don't look like myself		0.555		
Worrying		0.525		
Physical		Lack of energy	0.512	
		Lack of appetite	0.785	
	Feeling nervous	0.698		
	Feeling drowsy	0.619		
	Changes in skin	0.592		
UC	Emotional	Difficulty concentrating	0.569	
		Shortness of breath	0.517	
		Feeling irritable	0.743	
		Swelling of arms or legs	0.718	
		Problems with sexual interest or activity	0.651	
	Treatment-related toxicity	Sweats	0.607	
		Feeling bloated	0.569	
		Feeling sad	0.517	
		Worrying	0.509	
		Numbness	0.508	
		Lack of appetite	0.709	
		Dry mouth	0.704	
		Changes in the way food tastes	0.673	
		Changes in skin	0.639	
		Physical	Difficulty sleeping	0.772
Feeling drowsy	0.734			
I don't look like myself	0.714			
Difficulty concentrating	0.649			
Lack of energy	0.617			
<i>1 year</i>	Emotional	Feeling irritable	0.851	
RT-HIIT		Difficulty concentrating	0.818	

(continued)

Table 2. (continued)

	Symptom Clusters	Symptoms	Factor Loadings	
AT-HIIT	Treatment-related toxicity	Feeling sad	0.810	
		Lack of energy	0.747	
		Feeling nervous	0.589	
		Dry mouth	0.874	
		Pain	0.626	
		Sweats	0.890	
	Physical	Difficulty sleeping	0.743	
		Difficulty concentrating	0.854	
	Emotional	Feeling nervous	0.695	
		Feeling sad	0.583	
		Treatment-related toxicity	Dry mouth	0.746
			Numbness	0.720
Lack of energy			0.599	
Physical		Pain	0.597	
	Sweats	0.784		
	Feeling irritable	0.717		
UC	Emotional	Difficulty sleeping	0.640	
		Lack of energy	0.839	
		Feeling nervous	0.829	
		Feeling sad	0.827	
		Difficulty concentrating	0.806	
		Feeling irritable	0.684	
	Treatment-related toxicity	Pain	0.647	
		Numbness	0.828	
		Sweats	0.825	
	Physical	Dry mouth	0.840	
		Difficulty sleeping	0.765	

Abbreviations: RT-HIIT, resistance and high-intensity interval training group; AT-HIIT, moderate-intensity aerobic and high-intensity interval training; UC, usual care.

^aSymptom burden scores above 0.5 (high burden) were included in the principle component analysis. This eliminated 11 symptoms at baseline (“cough,” “numbness or tingling in hands or feet,” “problems with urination,” “vomiting,” “itching,” “dizziness,” “difficulty swallowing,” “mouth sores,” “weight loss,” “swelling of arms or legs,” and “changes in skin”), 11 symptoms at 16 weeks (“cough,” “nausea,” “problems with urination,” “vomiting,” “diarrhea,” “itching,” “dizziness,” “difficulty swallowing,” “mouth sores,” “weight loss,” and “constipation”), and 22 symptoms at 1 year (“cough,” “nausea,” “feeling drowsy,” “feeling bloated,” “problems with urination,” “vomiting,” “shortness of breath,” “diarrhea,” “worrying,” “problems with sexual interest or activity,” “itching,” “lack of appetite,” “dizziness,” “difficulty swallowing,” “mouth sores,” “change in the way food tastes,” “weight loss,” “hair loss,” “constipation,” “swelling of arms or legs,” “I don’t look like myself,” and “changes in skin”).

sad” (ES = -0.44), “feeling irritable” (ES = -0.44), and “changes in the way food tastes” (ES = -0.53), compared with the UC group.

No adverse events were reported as a result of the testing or the exercise sessions.

Discussion

The most important finding from the current analysis was that patients in the OptiTrain cohort who were randomized to AT-HIIT and RT-HIIT reported significantly lower symptom burden scores for “feeling sad” and “feeling irritable” at 16 weeks, compared with UC. This beneficial effect of physical exercise was persistently present in the AT-HIIT group at 12 months post-baseline. Results from this analysis

provide important new insights in alleviating symptom burden through physical exercise interventions and offer potential self-care strategies in this relatively large subgroup of cancer patients.

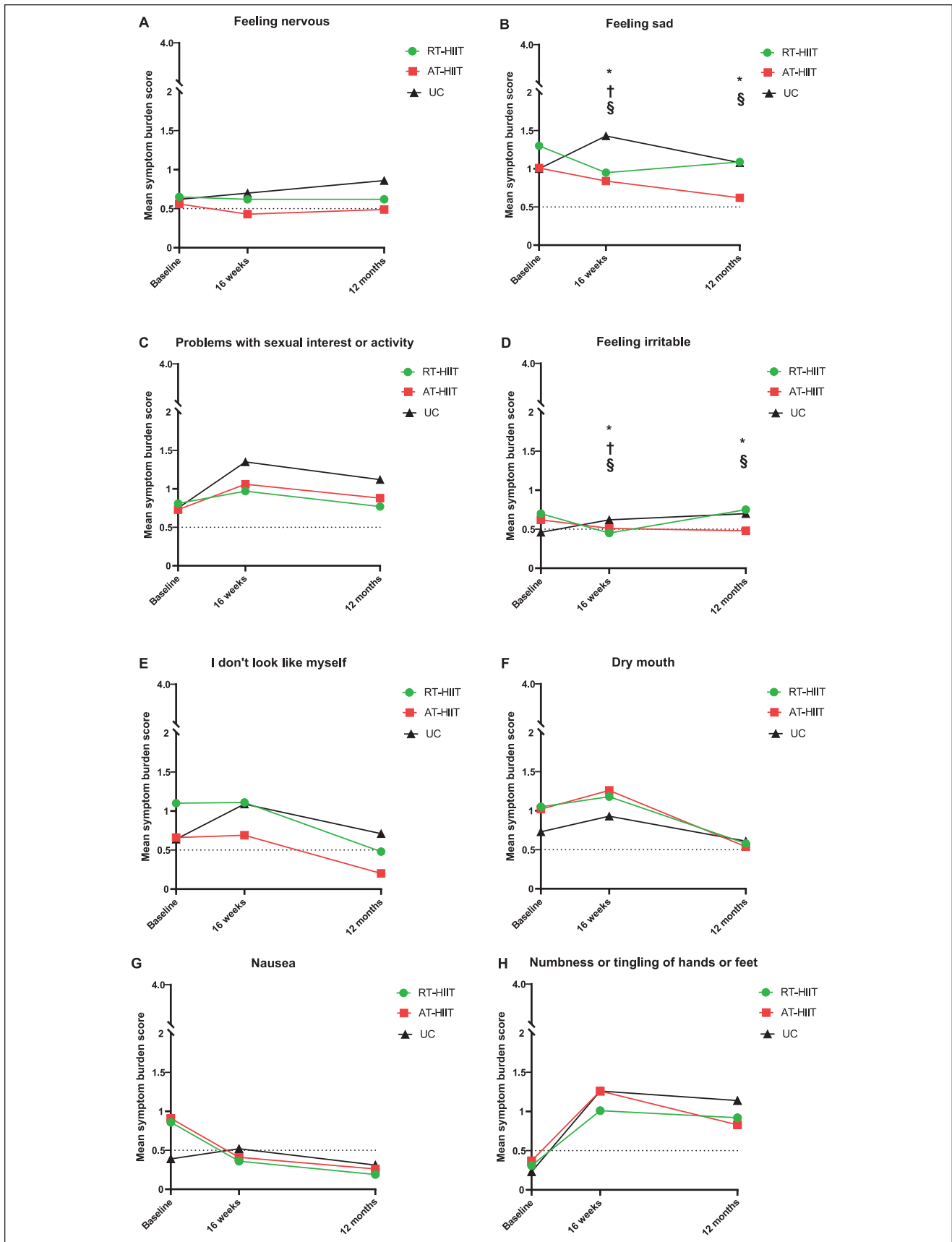
The symptom clusters were labelled after the main origin of symptoms in the respective clusters, that is, emotional, treatment-related toxicity, and physical symptoms. The symptoms included in the emotional and physical symptom clusters in our patient cohort are largely overlapping with those in previous studies in patients with breast cancer.^{10,13,15,16,26} In the current study, the treatment-related toxicity symptom cluster consisted of various symptoms, for example, “changes in the way food tastes,” “dry mouth,” and “nausea,” that were partially overlapping with previously reported gastrointestinal symptom clusters.^{15,16}

Table 3. Core Symptoms With Mean Symptom Burden Scores and Between-Group Differences.

		Baseline			Baseline to 16 Weeks			Baseline to 12 Months			
		Mean	SD	Mean ± SD	Mean	SD	Mean ± SD	Mean (95% CI)	Effect Size	Mean (95% CI)	Effect Size
		Between-Group Differences, Mean (95% CI)			Between-Group Differences, Mean (95% CI)			Between-Group Differences, Mean (95% CI)			
Emotional	Feeling nervous	0.65 ± 1.03		0.62 ± 0.88		0.62 ± 0.97	RT-HIIT vs UC	-0.08 (-0.21 to 0.42)	-0.10	-0.02 (-0.15 to 0.11)	-0.25
	AT-HIIT	0.56 ± 0.83		0.43 ± 0.85		0.49 ± 0.80	AT-HIIT vs UC	0.11 (-0.05 to 0.26)	-0.21	-0.09 (-0.23 to 0.04)	-0.32
	UC	0.62 ± 1.10		0.70 ± 1.00		0.86 ± 1.02					
Feeling sad	RT-HIIT	1.30 ± 1.13		0.95 ± 1.05		1.09 ± 1.20	RT-HIIT vs UC	-0.18 (-0.27 to -0.08)*	-0.69	-0.10 (-0.20 to 0.006)	-0.26
	AT-HIIT	1.01 ± 1.02		0.84 ± 1.01		0.62 ± 0.82	AT-HIIT vs UC	-0.13 (-0.23 to -0.03)*	-0.56	-0.21 (-0.33 to -0.10)*	-0.44
	UC	1.00 ± 1.11		1.43 ± 1.54		1.08 ± 1.17					
Problems with sexual interest or activity	RT-HIIT	0.81 ± 1.27		0.97 ± 1.31		0.77 ± 1.19	RT-HIIT vs UC	0.02 (-0.14 to 0.16)	-0.37	-0.17 (-0.35 to 0.01)	-0.34
	AT-HIIT	0.73 ± 1.20		1.06 ± 1.21		0.88 ± 1.22	AT-HIIT vs UC	-0.08 (-0.21 to 0.05)	-0.23	-0.07 (-0.22 to 0.08)	-0.19
	UC	0.75 ± 1.01		1.35 ± 1.41		1.12 ± 1.34					
Feeling irritable	RT-HIIT	0.70 ± 1.03		0.45 ± 0.59		0.75 ± 1.01	RT-HIIT vs UC	-0.22 (-0.36 to -0.08)*	-0.41	-0.15 (-0.31 to 0.01)	-0.20
	AT-HIIT	0.62 ± 0.88		0.51 ± 0.55		0.48 ± 0.79	AT-HIIT vs UC	-0.20 (-0.34 to -0.07)*	-0.31	-0.23 (-0.37 to -0.08)*	-0.44
	UC	0.46 ± 0.87		0.62 ± 0.76		0.70 ± 1.04					
I don't look like myself	RT-HIIT	1.10 ± 1.31		1.11 ± 1.24		0.48 ± 0.96	RT-HIIT vs UC	-0.06 (-0.20 to 0.08)	-0.37	-0.08 (-0.30 to 0.14)	-0.57
	AT-HIIT	0.66 ± 1.02		0.69 ± 1.12		0.20 ± 0.55	AT-HIIT vs UC	-0.04 (-0.21 to 0.13)	-0.40	-0.10 (-0.38 to 0.18)	-0.50
	UC	0.64 ± 1.08		1.09 ± 1.91		0.71 ± 1.12					
Treatment-related toxicity	Dry mouth	1.05 ± 1.12		1.18 ± 1.62		0.58 ± 0.91	RT-HIIT vs UC	0.07 (-0.07 to 0.21)	-0.06	-0.05 (-0.21 to 0.12)	-0.35
	AT-HIIT	1.02 ± 1.00		1.26 ± 1.84		0.54 ± 0.89	AT-HIIT vs UC	-0.02 (-0.16 to 0.11)	0.05	0.03 (-0.14 to 0.20)	-0.38
	UC	0.73 ± 0.85		0.93 ± 1.13		0.61 ± 0.96					
Nausea	RT-HIIT	0.86 ± 1.11		0.36 ± 0.75		0.19 ± 0.49	RT-HIIT vs UC	-0.10 (-0.29 to -0.09)	-0.63	0.08 (-0.17 to 0.33)	-0.60
	AT-HIIT	0.91 ± 1.08		0.41 ± 0.79		0.26 ± 0.56	AT-HIIT vs UC	-0.20 (-0.18 to 0.22)	-0.65	-0.07 (-0.29 to 0.16)	-0.59
	UC	0.39 ± 0.85		0.52 ± 0.96		0.31 ± 0.65					
Numbness or tingling of hands or feet	RT-HIIT	0.31 ± 0.79		1.01 ± 1.28		0.92 ± 1.14	RT-HIIT vs UC	0.03 (-0.32 to 0.27)	-0.49	0.02 (-0.29 to 0.32)	-0.45
	AT-HIIT	0.37 ± 0.67		1.26 ± 2.55		0.83 ± 1.01	AT-HIIT vs UC	0.02 (-0.26 to 0.29)	-0.23	-0.04 (-0.30 to 0.22)	-0.74
	UC	0.23 ± 0.54		1.26 ± 1.38		1.14 ± 1.18					
Diarrhea	RT-HIIT	0.51 ± 0.78		0.30 ± 0.72		0.24 ± 0.47	RT-HIIT vs UC	0.12 (-0.07 to 0.32)	-0.07	0.08 (-0.13 to 0.29)	-0.05
	AT-HIIT	0.57 ± 1.28		0.68 ± 0.96		0.33 ± 0.68	AT-HIIT vs UC	0.12 (-0.07 to 0.29)	0.23	0.07 (-0.14 to 0.28)	-0.01
	UC	0.50 ± 0.87		0.35 ± 0.67		0.27 ± 0.66					
Changes in the way food tastes	RT-HIIT	0.91 ± 1.14		0.78 ± 1.08		0.10 ± 0.45	RT-HIIT vs UC	0.08 (-0.10 to 0.26)	-0.49	-0.10 (-0.42 to 0.22)	-0.35
	AT-HIIT	1.03 ± 1.16		1.33 ± 2.46		0.01 ± 0.07	AT-HIIT vs UC	0.09 (-0.07 to 0.25)	-0.09	-0.82 (-1.37 to -0.27)*	-0.53
	UC	0.75 ± 1.04		1.16 ± 1.18		0.32 ± 0.83					
Physical	Feeling drowsy	0.76 ± 1.02		0.67 ± 1.05		0.50 ± 0.75	RT-HIIT vs UC	-0.12 (-0.26 to -0.02)	-0.49	-0.12 (-0.27 to -0.04)	-0.22
	AT-HIIT	0.62 ± 0.85		0.69 ± 0.85		0.38 ± 0.67	AT-HIIT vs UC	-0.09 (-0.23 to -0.05)	-0.35	-0.12 (-0.29 to 0.04)	-0.22
	UC	0.60 ± 0.93		0.99 ± 1.05		0.56 ± 0.77					
Sweats	RT-HIIT	0.77 ± 1.01		1.17 ± 1.19		1.35 ± 1.17	RT-HIIT vs UC	-0.10 (-0.25 to 0.06)	-0.21	-0.04 (-0.20 to 0.11)	-0.11
	AT-HIIT	0.81 ± 1.03		1.17 ± 1.23		1.42 ± 1.12	AT-HIIT vs UC	-0.09 (-0.24 to 0.07)	-0.25	-0.12 (-0.27 to 0.03)	-0.08
	UC	0.61 ± 0.90		1.21 ± 1.19		1.30 ± 1.22					

Abbreviations: SD, standard deviation; CI, confidence interval; RT-HIIT, resistance and high-intensity interval training group; UC, usual care; AT-HIIT, moderate-intensity aerobic and high-intensity interval training.

* $P < .05$.



(continued)

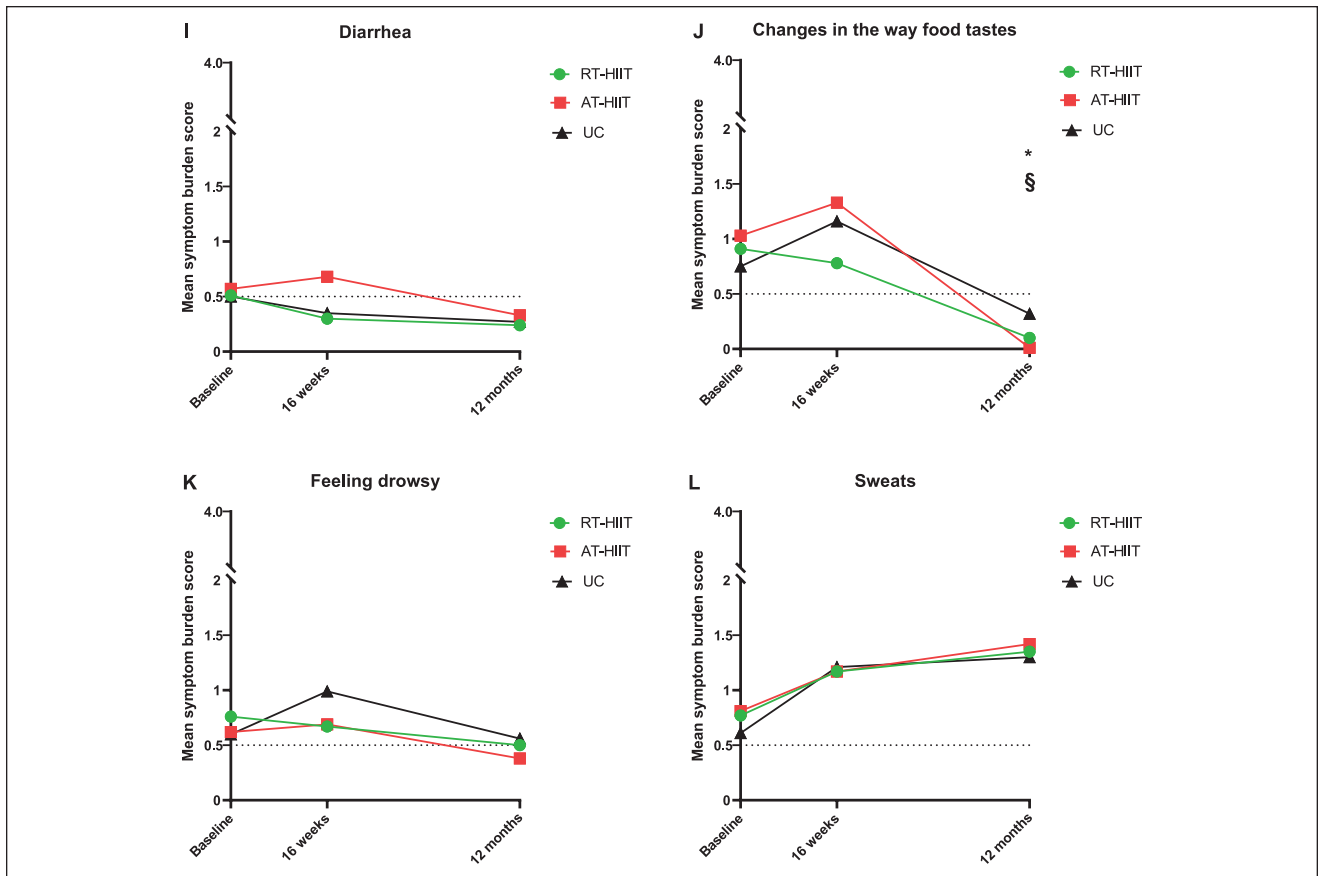


Figure 2. Core symptoms and change in mean symptom burden score over time.

Abbreviations: RT-HIIT, resistance and high-intensity interval training group; AT-HIIT, moderate-intensity aerobic and high-intensity interval training; UC, usual care.

Core symptoms and change in mean symptom burden score over time for (A-E) emotional symptoms cluster, (F-J) treatment-related toxicity symptom cluster, and (K and L) physical symptom cluster. Symptom burden scores ranged between 0 and 4. * $P < .05$, † $P < .05$ RT-HIIT between UC, § $P < .05$ AT-HIIT between UC.

Participants in the current study had already received 1 course of chemotherapy, contrary to the study by Browall et al,¹⁶ and thereby were already experiencing a range of treatment-induced side effects at baseline. This can be an explanation for the (partial) difference in symptoms present in the cluster, compared with other studies.¹⁶ All symptom clusters showed a number of consistently present individual core burdensome symptoms, as well as several symptoms entering and exiting the clusters at the respective study assessments.^{15,16} These changes have also been observed in the other longitudinal studies assessing symptom clusters in patients with (early-stage) breast cancer and reflect the dynamic nature of symptom clusters.^{15,16} This can be explained by differences in the treatment phase at the 3 study assessment time points, the use of high symptom burden scores (>0.5) as cutoff for the PCA, as well as the low absolute number of symptoms in the symptom clusters at the 12-month post-baseline assessment.

In the emotional symptom cluster, at 16 weeks post-baseline, a beneficial effect in both exercise groups was found for the core burdensome symptoms “feeling sad” and “feeling irritable,” compared with UC; and this effect was preserved at the 12-month post-baseline assessment in the AT-HIIT group.

Several physiological as well psychological mechanisms may contribute to this positive effect of physical exercise on emotional well-being. Elevated serum endorphin concentrations, released by intensive aerobic exercise, have been associated with changes in mood state (eg, euphoria), altered pain perception, and responses to several hormones, such as cortisol.^{27,28} Previous findings from the OptiTrain study showed that patients in the RT-HIIT group reported significantly lower pain sensitivity than those in the UC group at 16 weeks post-baseline.²⁵ In addition, a number of psychological hypotheses can explain these results. The “distraction hypothesis” describes that exercise provides distraction from negative and worrying thoughts, leading to

a “mental time-out,” which can, in turn, cause a mood-lifting effect.²⁹ Furthermore, the “mastery hypothesis” implies that the effects of completing an effortful task, such as exercise, could bring out a feeling of mastery which, in itself, elevates mood.²⁷ Supporting the mastery hypothesis, beneficial effects were previously found for “role functioning” in the RT-HIIT group at 16 weeks.¹⁸ Moreover, the “self-efficacy hypothesis” highlights the importance of self-regulation and self-empowerment. Patients are more likely to maintain adherence to self-set goals when they experience a higher level of perceived self-efficacy.³⁰

This positive effect of physical exercise on emotional well-being might also be linked to increased activity levels after completion of the intervention. A study in breast cancer patients demonstrated that patients who participated in a physical exercise intervention (consisting of various resistance and flexibility exercises) during chemotherapy had higher levels of physical activity 60 months after completing the intervention, and it reported a more positive mood state than those in the control group.³¹ In the OptiTrain cohort, the majority of patients in all 3 groups reported being more physically active at 12 months compared with baseline testing, even though no significant between-group differences were found.¹⁷

Previous articles, a literature review in breast cancer patients and a randomized controlled trial in a geriatric population, confirmed that specifically aerobic exercise preserves emotional well-being.^{32,33} The underlying mechanisms that support the specific positive effect of aerobic exercise on emotional well-being are unclear. There might be a connection with the neurobiological mechanisms, mediated by factors such as brain-derived neurotrophic factor, insulin-like growth factor 1 (IGF-1), and vascular endothelial growth factor, but there are no hard data supporting this hypothesis.³⁴⁻³⁶

Notably, patients in all 3 study arms reported the core burdensome symptom “problems with sexual interest or activity” consistently high throughout all study assessments. Sexual dysfunction in breast cancer patients is a clinically relevant problem that is known to increase during chemotherapy, persists long after completion of oncological treatment,^{37,38} and can lead to changes in body image with a negative impact on quality of life.^{39,40} However, it is a topic not regularly brought up by either physicians or patients, due to various personal and cultural reasons.⁴¹

Our data highlight the long-term beneficial effects of physical exercise interventions on the burdensomeness of emotional symptoms. These findings underscore the need for awareness of physicians and nurses involved in care for breast cancer patients for such emotional symptoms, including mood disturbances and sexual dysfunction, and confirm that physical exercise can be an effective self-care strategy to ameliorate such problems.

In the treatment-related toxicity cluster, a significant beneficial effect of AT-HIIT was recorded for “changes in

the way food tastes” at 12 months post-baseline, with a medium effect size. Chemotherapy, particularly taxane-based chemotherapies, affect gustatory function through various mechanisms and cause temporary taste changes.⁴² Studies show that taste changes usually recover within 6 months of chemotherapy completion.^{42,43} This is in line with the trajectory of “changes in the way food tastes” that we observed in our cohort, where patients in all 3 study arms reported lower symptom burden scores at the 12 months post-baseline study assessment. The reason why patients in the AT-HIIT group reported lower symptom burden of taste changes is not known, but it might relate to more successful coping strategies¹⁵ that results in a lower rate of self-perceived complaints.

The physical cluster consists, in part, of various menopausal symptoms patients experience during treatment, either caused by chemotherapy-induced menopause and/or side effects from endocrine therapy.⁴⁴ The physical exercise intervention showed no significant effect on “feeling drowsy” and “sweats” in the RT-HIIT and AT-HIIT group at 16 weeks and 12 months. This is in line with a previous study, where no statistically significant effects of physical exercise on endocrine symptoms were found.⁴⁵

A recent review underscored the need for establishing efficacious interventions for alleviating various symptom clusters in cancer patients.⁴⁶ Up to now, only mind-body and cognitive-behavioral strategies interventions showed limited beneficial effects on symptom clusters⁴⁷⁻⁴⁹; all studies demonstrated beneficial effects on pain, fatigue, and emotional symptoms,^{47,48} and one of the studies also found beneficial effects on gastrointestinal symptoms.⁴⁹ The present analysis is, to our knowledge, the first to explore the effect of (2 different) physical exercise interventions on the presence of symptom clusters, as well as on core burdensome symptoms within these clusters.

Physical exercise can be promoted in the clinical setting as an effective supportive self-care intervention for women with early breast cancer,⁵⁰ and our study confirms that such an intervention can lead to improved emotional well-being.

The main strengths of this analysis are a long follow-up period and the detailed description of clusters of burdensome symptoms in 2 types of supervised exercises regimens. Limitations of this analysis include that the first study assessment was performed after 1 course of chemotherapy that influenced symptom burden in our analysis due to acute side effects of chemotherapy treatment.

Conclusion

In conclusion, the current analysis showed that RT-HIIT, AT-HIIT, and UC displayed “emotional,” “treatment-related toxicity,” and “physical” symptom clusters with a dynamic composition over time. Furthermore, both participants in the resistance or aerobic training combined with high-

intensity interval training groups experienced an amelioration of burdensome emotional symptoms, such as “feeling sad” and “feeling irritable.” This effect was seen directly after chemotherapy completion and persisted up to 12 months post-baseline for the AT-HIIT group, which underscores the potential value of physical exercise during curative breast cancer treatments as a way to improve and maintain emotional well-being in patients with breast cancer.

Acknowledgments

The authors would like to thank the participants in the OptiTrain Trial, Karolinska University Hospital, for the use of their facilities, and Malin Backman for the collection of questionnaire data and supervision of the exercise sessions.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the Swedish Cancer Society (130452, CAN 2016/334 to YW), the Cancer Society of Stockholm (131242 161262 to YW), the Swedish Cancer and Traffic Accident Foundation (F-C-001225 to YW), the Strategic Area in Health Care Sciences at Karolinska Institutet (Fellowship to KAB), and the Swedish Society for Medical Research (SLS 50514 to Helene Rundqvist). The funders have no role in the study design, data collection or analysis, decision to publish, or preparation of the article.

ORCID iD

Fleur Wiggenraad  <https://orcid.org/0000-0001-8780-7058>

References

1. Global Burden of Disease Cancer Collaboration; Fitzmaurice C, Akinyemiju TF, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 cancer groups, 1990 to 2016: a systematic analysis for the Global Burden of Disease Study. *JAMA Oncol*. 2018;4:1553-1568.
2. Montazeri A, Vahdaninia M, Harirchi I, Ebrahimi M, Khaleghi F, Jarvandi S. Quality of life in patients with breast cancer before and after diagnosis: an eighteen months follow-up study. *BMC Cancer*. 2008;8:330.
3. Partridge AH, Burstein HJ, Winer EP. Side effects of chemotherapy and combined chemohormonal therapy in women with early-stage breast cancer. *J Natl Cancer Inst Monogr*. 2001;(30):135-142.
4. Gapstur RL. Symptom burden: a concept analysis and implications for oncology nurses. *Oncol Nurs Forum*. 2007;34:673-680.
5. Kim HJ, McGuire DB, Tulman L, Barsevick AM. Symptom clusters: concept analysis and clinical implications for cancer nursing. *Cancer Nurs*. 2005;28:270-284.
6. Dodd MJ, Miaskowski C, Paul SM. Symptom clusters and their effect on the functional status of patients with cancer. *Oncol Nurs Forum*. 2001;28:465-470.
7. Kim HJ, Abraham IL. Statistical approaches to modeling symptom clusters in cancer patients. *Cancer Nurs*. 2008;31:E1-E10.
8. Kim HJ, Barsevick AM, Beck SL, Dudley W. Clinical subgroups of a psychoneurologic symptom cluster in women receiving treatment for breast cancer: a secondary analysis. *Oncol Nurs Forum*. 2012;39:E20-E30.
9. Kim HJ, Barsevick AM, Tulman L, McDermott PA. Treatment-related symptom clusters in breast cancer: a secondary analysis. *J Pain Symptom Manage*. 2008;36:468-479.
10. Phligbua W, Pongthavornkamol K, Knobf TM, Junda T, Viwatwongkasem C, Srimuninnimit V. Symptom clusters and quality of life in women with breast cancer receiving adjuvant chemotherapy. *Pacific Rim Int J Nurs Res*. 2013;17:249-267.
11. Albusoul RM, Berger AM, Gay CL, Janson SL, Lee KA. Symptom clusters change over time in women receiving adjuvant chemotherapy for breast cancer. *J Pain Symptom Manage*. 2017;53:880-886.
12. Sanford SD, Beaumont JL, Butt Z, Sweet JJ, Cella D, Wagner LI. Prospective longitudinal evaluation of a symptom cluster in breast cancer. *J Pain Symptom Manage*. 2014;47:721-730.
13. Molassiotis A, Wengström Y, Kearney N. Symptom cluster patterns during the first year after diagnosis with cancer. *J Pain Symptom Manage*. 2010;39:847-858.
14. Dodd MJ, Cho MH, Cooper BA, Miaskowski C. The effect of symptom clusters on functional status and quality of life in women with breast cancer. *Eur J Oncol Nurs*. 2010;14:101-110.
15. Sarenmalm EK, Browall M, Gaston-Johansson F. Symptom burden clusters: a challenge for targeted symptom management. A longitudinal study examining symptom burden clusters in breast cancer. *J Pain Symptom Manage*. 2014;47:731-741.
16. Browall M, Brandberg Y, Nasic S, et al. A prospective exploration of symptom burden clusters in women with breast cancer during chemotherapy treatment. *Support Care Cancer*. 2017;25:1423-1429.
17. Wengström Y, Bolam KA, Mijwel S, et al. Optitrain: a randomised controlled exercise trial for women with breast cancer undergoing chemotherapy. *BMC Cancer*. 2017;17:100.
18. Mijwel S, Backman M, Bolam KA, et al. Adding high-intensity interval training to conventional training modalities: optimizing health-related outcomes during chemotherapy for breast cancer: the OptiTrain randomized controlled trial. *Breast Cancer Res Treat*. 2018;168:79-93.
19. Portenoy RK, Thaler HT, Kornblith AB, et al. The Memorial Symptom Assessment Scale: an instrument for the evaluation of symptom prevalence, characteristics and distress. *Eur J Cancer*. 1994;30A:1326-1336.
20. Browall M, Sarenmalm EK, Nasic S, Wengström Y, Gaston-Johansson F. Validity and reliability of the Swedish version of the Memorial Symptom Assessment Scale (MSAS): an

- instrument for the evaluation of symptom prevalence, characteristics, and distress. *J Pain Symptom Manage*. 2013;46:131-141.
21. Garber CE, Blissmer B, Deschenes MR, et al; American College of Sports Medicine. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med Sci Sports Exerc*. 2011;43:1334-1359.
 22. Wikman A, Johar A, Lagergren P. Presence of symptom clusters in surgically treated patients with esophageal cancer: implications for survival. *Cancer*. 2014;120:286-293.
 23. Morris SB. Estimating effect sizes from pretest-posttest-control group designs. *Organ Res Methods*. 2008;11:364-386. doi:10.1177/1094428106291059
 24. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. 2nd ed. Hillsdale, NJ: Lawrence Erlbaum; 1988.
 25. Mijwel S, Backman M, Bolam KA, et al. Highly favorable physiological responses to concurrent resistance and high-intensity interval training during chemotherapy: the OptiTrain breast cancer trial. *Breast Cancer Res Treat*. 2018;169:93-103.
 26. Bender CM, Ergyn FS, Rosenzweig MQ, Cohen SM, Sereika SM. Symptom clusters in breast cancer across 3 phases of the disease. *Cancer Nurs*. 2005;28:219-225.
 27. Mikkelsen K, Stojanovska L, Polenakovic M, Bosevski M, Apostolopoulos V. Exercise and mental health. *Maturitas*. 2017;106:48-56.
 28. Harber VJ, Sutton JR. Endorphins and exercise. *Sport Med*. 1984;1:154-171. doi:10.2165/00007256-198401020-00004
 29. Bahrke MS, Morgan WP. Anxiety reduction following exercise and meditation. *Cogn Ther Res*. 1978;2:323-333. doi:10.1007/BF01172650
 30. McAuley E, Blissmer B, Katula J, Duncan TE, Mihalko SL. Physical activity, self-esteem, and self-efficacy relationships in older adults: a randomized controlled trial. *Ann Behav Med*. 2000;22:131-139.
 31. Mutrie N, Campbell A, Barry S, et al. Five-year follow-up of participants in a randomised controlled trial showing benefits from exercise for breast cancer survivors during adjuvant treatment. Are there lasting effects? *J Cancer Surviv*. 2012;6:420-430.
 32. Patsou ED, Alexias GD, Anagnostopoulos FG, Karamouzis MV. Effects of physical activity on depressive symptoms during breast cancer survivorship: a meta-analysis of randomised control trials. *ESMO Open*. 2017;2:e000271. doi:10.1136/esmoopen-2017-000271
 33. Penninx BWJH, Rejeski WJ, Pandya J, et al. Exercise and depressive symptoms: a comparison of aerobic and resistance exercise effects on emotional and physical function in older persons with high and low depressive symptomatology. *J Gerontol B Psychol Sci Soc Sci*. 2002;57:P124-P132. <https://academic.oup.com/psychsocgerontology/article-lookup/doi/10.1093/geronb/57.2.P124>. Accessed September 16, 2019.
 34. Barha CK, Galea LA, Nagamatsu LS, Erickson KI, Liu-Ambrose T. Personalising exercise recommendations for brain health: considerations and future directions. *Br J Sports Med*. 2017;51:636-639. doi:10.1136/bjsports-2016-096710
 35. Duman RS, Monteggia LM. A neurotrophic model for stress-related mood disorders. *Biol Psychiatry*. 2006;59:1116-1127.
 36. Phillips C. Brain-derived neurotrophic factor, depression, and physical activity: making the neuroplastic connection. *Neural Plast*. 2017;2017:7260130.
 37. Farthmann J, Hanjalic-Beck A, Veit J, et al. The impact of chemotherapy for breast cancer on sexual function and health-related quality of life. *Support Care Cancer*. 2016;24:2603-2609. doi:10.1007/s00520-015-3073-2
 38. Ochsenkühn R, Hermelink K, Clayton AH, et al. Menopausal status in breast cancer patients with past chemotherapy determines long-term hypoactive sexual desire disorder. *J Sex Med*. 2011;8:1486-1494.
 39. Partridge AH. Cancer survivorship and the young breast cancer patient: addressing the important issues. *Oncologist*. 2013;18:e19-e20.
 40. Runowicz CD, Leach CR, Henry NL, et al. American cancer society/American Society Of Clinical Oncology Breast Cancer Survivorship Care Guideline. *J Clin Oncol*. 2016;34:611-635.
 41. Sporn NJ, Smith KB, Pirl WF, Lennes IT, Hyland KA, Park ER. Sexual health communication between cancer survivors and providers: how frequently does it occur and which providers are preferred? *Psychooncology*. 2015;24:1167-1173.
 42. Steinbach S, Hummel T, Böhner C, et al. Qualitative and quantitative assessment of taste and smell changes in patients undergoing chemotherapy for breast cancer or gynecologic malignancies. *J Clin Oncol*. 2009;27:1899-1905.
 43. de Vries YC, Boesveldt S, Kelfkens CS, et al. Taste and smell perception and quality of life during and after systemic therapy for breast cancer. *Breast Cancer Res Treat*. 2018;170:27-34.
 44. Knobf MT. The menopausal symptom experience in young mid-life women with breast cancer. *Cancer Nurs*. 2001;24:201-211.
 45. Mutrie N, Campbell AM, Whyte F, et al. Benefits of supervised group exercise programme for women being treated for early stage breast cancer: pragmatic randomised controlled trial. *BMJ*. 2007;334:517.
 46. Miaskowski C, Barsevick A, Berger A, et al. Advancing symptom science through symptom cluster research: expert panel proceedings and recommendations. *J Natl Cancer Inst*. 2017;109(4). doi:10.1093/jnci/djw253
 47. Kwekkeboom KL, Cherwin CH, Lee JW, Wanta B. Mind-body treatments for the pain-fatigue-sleep disturbance symptom cluster in persons with cancer. *J Pain Symptom Manage*. 2010;39:126-138.
 48. Kwekkeboom K, Zhang Y, Campbell T, et al. Randomized controlled trial of a brief cognitive-behavioral strategies intervention for the pain, fatigue, and sleep disturbance symptom cluster in advanced cancer. *Psychooncology*. 2018;27:2761-2769.
 49. Charalambous A, Giannakopoulou M, Bozas E, Marcou Y, Kitsios P, Paikousis L. Guided imagery and progressive muscle relaxation as a cluster of symptoms management intervention in patients receiving chemotherapy: a randomized control trial. *PLoS One*. 2016;11:e0156911.
 50. Furmaniak AC, Menig M, Markes MH. Exercise for women receiving adjuvant therapy for breast cancer. *Cochrane Database Syst Rev*. 2016;(9):CD005001. doi:10.1002/14651858.CD005001.pub3