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Effects of supervised exercise during adjuvant endocrine therapy in overweight or obese patients with breast cancer: The I-MOVE study

Harm L. Ormel [a], Carolina P. Schröder [a], Gabriela G.F. van der Schoot [a], Nico-Derk L. Westerink [a], Annette W.G. van der Velden [b], Boelo Poppema [c], Aline H. Vrieling [d], Jourik A. Gietema [a], Annemiek M.E. Walenkamp [a], Anna K.L. Reyners [a, *]

[a] Department of Medical Oncology, University Medical Centre Groningen, University of Groningen, Groningen, the Netherlands
[b] Department of Internal Medicine, Martini Hospital Groningen, Groningen, the Netherlands
[c] Department of Internal Medicine, Ommelander Hospital Group, Scheemda, the Netherlands
[d] Department of Rehabilitation Medicine, University Medical Centre Groningen, University of Groningen, Groningen, the Netherlands

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ABSTRACT

Background: Adjuvant endocrine therapy (ET) in patients with breast cancer (BC) increases the risk of becoming less physically active. Physical inactivity is associated with a higher risk of treatment-related side effects and mortality. This study investigated whether supervised exercise increased the proportion of patients adhering to the national physical activity (PA) guideline during adjuvant ET in overweight or obese BC patients.

Methods: This multicentre single-arm clinical trial included patients with BC participating in a 12-week supervised exercise intervention. An accelerometer measured moderate to vigorous PA (MVPA) at baseline (T0), after 12 (T1) and 26 weeks (T2). The primary endpoint was change in the proportion of patients with weekly ≥150 min of MVPA at T1 compared to T0. Secondary endpoints were adherence to PA guideline at T2, metabolic syndrome (MetS), body composition, health-related quality of life (HRQoL) and BC-specific functioning and symptoms, self-reported PA, self-efficacy, exercise motivation and satisfaction with life.

Results: 141 patients with a median age of 61 years and a mean BMI of 31.3 participated. Adherence to the PA guideline increased from 38.3% at T0, to 40.4% at T1 ($p = .112$) and 44.7% at T2 ($p = .003$). MetS, body composition, HRQoL, BC-specific functioning and symptoms (i.e. fatigue, dyspnoea), self-reported PA, self-efficacy, exercise motivation and satisfaction with life improved significantly over time.

Conclusions: Supervised exercise increased the proportion of BC patients adhering to the PA guideline over time. Furthermore, MetS, body composition, HRQoL and symptoms improved. Our findings highlight the clinical relevance of supervised exercise during ET in overweight BC patients.

Clinical trial information: (NCT02424292).

1. Introduction

Breast cancer is the leading cause of mortality among women worldwide, with approximately 2.1 million newly diagnosed cases in 2018 [1]. Mounting evidence reveals the potential risk of being overweight (body mass index (BMI) of ≥25 kg/m^2) or obese (BMI ≥30 kg/m^2) for the development of cancer and impaired cancer outcome [2]. A large survey among all women in the Netherlands in 2000 revealed that 51% (>40 years of age) were overweight or obese [3]. Patients who are overweight or obese are at an increased risk of recurrent disease, and of worse breast cancer-specific and overall survival outcome compared to patients with a BMI <25 kg/m^2 [2,4]. Adverse lifestyle habits, such as physical inactivity and sedentary behaviour, are common in patients with breast cancer who are overweight or obese [5,6]. This is particularly the case during adjuvant endocrine treatment, as it can cause arthralgia, and can be associated with weight gain and cancer-related fatigue [7].

* Corresponding author.
E-mail address: a.k.l.reyners@umcg.nl (A.K.L. Reyners).

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Also, a cluster of cardiovascular risk factors known as metabolic syndrome (MetS) can develop, which is related to poor outcome in these patients during adjuvant endocrine therapy [8,9].

Furthermore, physical activity (PA) levels tend to deteriorate after a breast cancer diagnosis, especially among overweight and obese patients [10]. In the Netherlands, the national PA guideline "Nederlandse Norm Gezond Bewegen (NNGB)" recommendation is to perform aerobic and resistance exercises, and avoid sedentary behaviour [11]. The aerobic PA guideline recommends engaging in moderate to vigorous physical activity (MVPA) for ≥150 min per week, e.g. brisk walking (5–7 km/h) [11]. The resistance PA guideline recommends performing resistance exercises twice per week [11]. However, most patients do not follow in these recommendations [12]. When adherence to the PA guideline is gradually met in 5 years after a breast cancer diagnosis compared to being physically inactive at baseline, all-cause- and cancer mortality risks could potentially be reduced with hazard ratios of 0.76 and 0.89, respectively [13]. Participation in supervised exercise to improve PA behaviour could be beneficial during adjuvant endocrine therapy in patients with breast cancer. It can render health gain, as it can potentially endorse a physically active lifestyle, limit weight gain, improve parameters of MetS and improve health-related quality of life (HRQoL) [14,15].

Therefore, this study aimed to investigate whether supervised exercise increased the proportion of patients adhering to the Dutch national aerobic PA guideline during adjuvant endocrine therapy in overweight or obese patients with breast cancer. Additionally, MetS, HRQoL and breast cancer-specific functioning and symptoms, body composition, self-reported PA, self-efficacy, exercise motivation and overall satisfaction with life were investigated.

2. Methods

2.1. Study design and patients

In this multicentre, single-arm clinical trial, the I-MOVE study, patients treated with endocrine therapy with curative intent for hormone receptor-positive, stage I-III breast cancer, regardless of other treatment modalities, were prospectively included. Overweight (BMI ≥25 to <30 kg/m^2) or obese (BMI ≥30 kg/m^2) female patients between the age of 18 and 75 years who did not previously participate in an oncologic rehabilitation program were eligible. Exclusion criteria were uncontrolled heart disease, dementia, ongoing side effects of previous chemotherapy, or other contraindications to exercise. Written informed consent was obtained from all included patients. The protocol was approved by the local medical ethics committee of the University Medical Centre Groningen and registered in ClinicalTrials.gov (NCT02424292).

2.2. Recruitment and study procedures

Eligible patients were identified through hospital medical records. Recruitment occurred between August 2015 to February 2019 at the University Medical Centre Groningen, Martini Hospital Groningen and Ommelander Hospital Group Scheemda in the Netherlands. After informed consent, a detailed medical history was obtained and anthropometric measures were performed. After overnight fasting blood samples were drawn at the local hospital laboratory to determine fasting blood glucose and lipid profile. Baseline questionnaires were provided, and patients were instructed to wear an accelerometer. Patients underwent assessments at baseline (T0), post-intervention after 12 weeks (T1) and follow-up 26 weeks after T0 (T2).

Table 1
Baseline characteristics of patients participating in the I-MOVE study (n = 141).

Characteristics, mean (SD (±)), median [range], no. (%)	(n = 141)
Demographic characteristics	
Age at inclusion (years)	61 [34 to 74]
Marital status	
Married/relationship (living together)	103 (73.0%)
Single/divorced/widowed/relationship (not living together)	38 (27.0%)
Education	
Low-medium (elementary-, primary- or secondary school/ lower- or secondary vocational education)	100 (70.9%)
High (higher vocational-, college- or university education)	40 (28.4%)
Missing	1 (0.7%)
Employment status	
Paid work/work as a volunteer	38 (27.0%)
Sickness leave/re-integration process	33 (23.4%)
Unemployed/retirement/housewife	64 (45.4%)
Other	6 (4.3%)
Behavioural characteristics	
Smoking habits (yes)	
Current smoker	19 (13.5%)
Former smoker	80 (56.7%)
Non-smoker	42 (29.8%)
Pack years (years)	17 [0 to 75]
Alcohol consumption (yes)	65 (46.1%)
Medical oncologist or treating physician advised exercise (yes)	82 (58.2%)
Medical characteristics	
BMI (kg/m^2)	31.3 ± 4.4
BMI (categorised)	
Overweight (≥25–29.9 kg/m^2)	69 (48.9%)
Obese (≥30–39.9 kg/m^2)	66 (46.8%)
Morbid obese (≥40 kg/m^2)	7 (4.3%)
Antihypertensive drug treatment (yes)	52 (36.9%)
Tumour stage	
I	65 (46.1%)
II	58 (41.1%)
III	18 (12.8%)
Radiation therapy (yes)	111 (78.7%)
Chemotherapy (yes)	73 (51.8%)
Endocrine therapy (type)	
Aromatase inhibitor	54 (38.3%)
SERM	83 (58.9%)
LHRH-analogue combined with aromatase inhibitor or SERM	4 (2.8%)
Duration of endocrine therapy (months)	15 [0 to 96]

SD, standard deviation; BMI, body mass index; LHRH, luteinizing hormone-releasing hormone; SERM, selective oestrogen receptor modulator.

2.3. Study intervention

Patients were referred to a facility-based supervised exercise intervention. In case patients were unable to participate in such a program due to barriers like travel distances or time constraints, they were allowed to attend a home-based supervised exercise intervention at a physiotherapy practice near their home with the same exercise prescriptions.

Patients were prescribed three supervised exercise sessions per week and consisted of a combination of supervised aerobic exercise training (AET) three times a week and resistance exercise training (RET) twice a week for twelve weeks. The AET and RET were fully tailored based on the patient's exercise capacity. The duration, frequency and intensity of the exercise program were following the American College of Sports Medicine recommendations [16]. The AET intensity of patients who participated in the facility-based supervised exercise was based on the training heart rate determined by performing a maximal cardiopulmonary exercise test as part of usual care. The AET intensity of the home-based supervised exercise was based on the training heart rate determined by the Karvonen formulae [17]. During week 1–6, AET was performed at a training heart rate of 40–60% and during week 7–12 at a training heart rate of 60 to 70–75%. The AET was performed on a bicycle- or

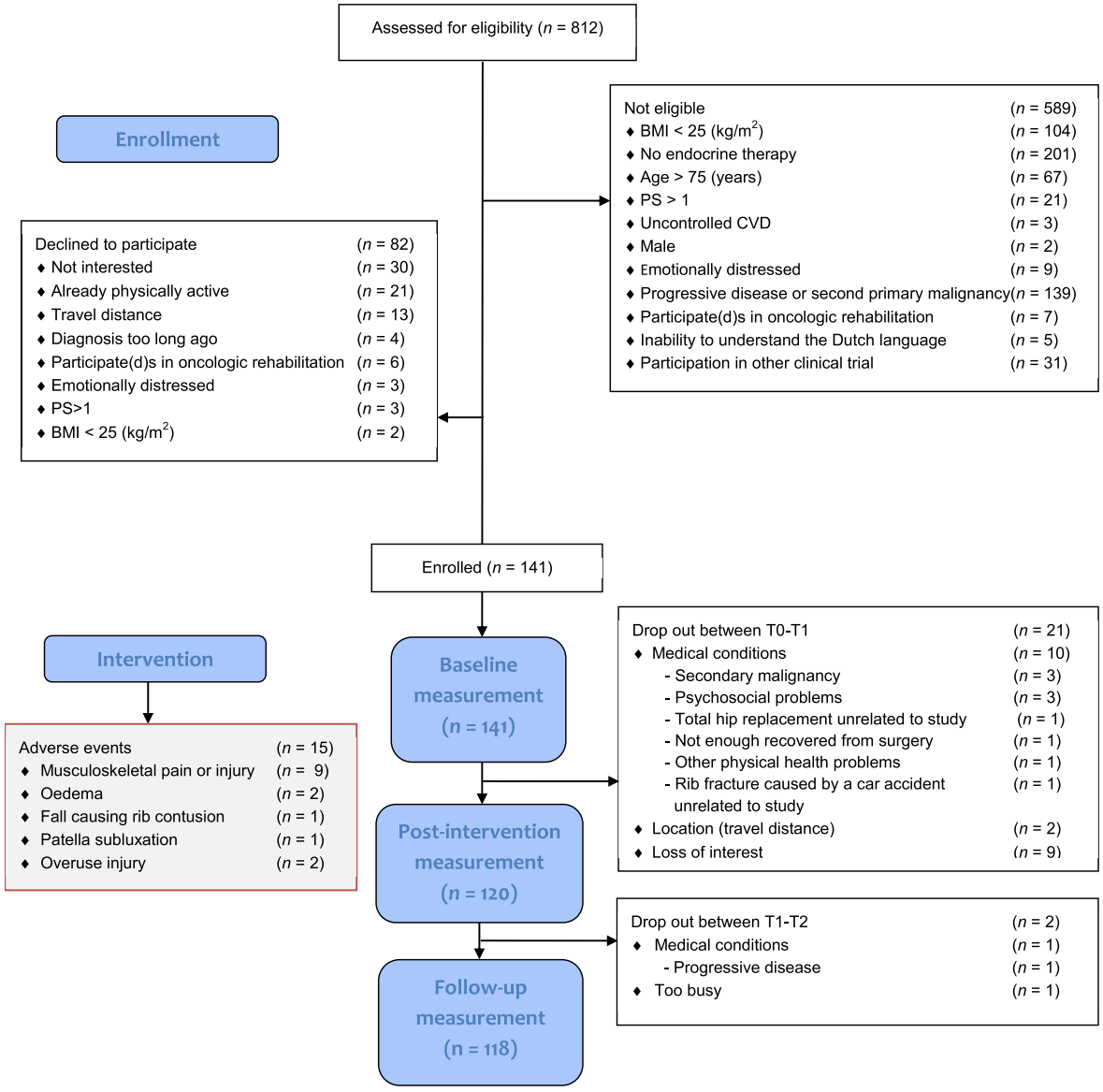

Fig. 1. CONSORT diagram of the I-MOVE study. PS, performance score; BMI, body mass index; CVD, cardiovascular disease; T0, baseline; T1, post-intervention (12 weeks); T2, follow-up (26 weeks).

row ergometer or treadmill for 30 min. The intensity of RET started at 50% of the one-repetition maximum during the first week and was progressively increased by 5–10%. The RET was performed for 20–30 min in a muscle strengthening circuit with a frequency of three series with twelve repetitions per exercise. Behavioural changing techniques were administered throughout the program with a focus on self-efficacy based on Social Cognitive Theory [18]. Patients were allowed to attend a dietician, occupational therapist, psychologist, labour consultant or to follow a quit-smoking program besides this intervention.

2.4. Outcome measures

Change in MVPA was objectively measured by wearing an GT3X-BT accelerometer (ActiGraph, Pensacola, FL, USA) continuously during one week on the hip or wrist to determine the primary endpoint, proportion of patients adhering to the aerobic PA guideline (≥150 min of MVPA per week), at T1. Secondary outcome measures were adherence to the PA guideline at T2, MetS, HRQoL and breast cancer-specific functioning and symptoms, body composition, self-reported PA, self-efficacy, exercise motivation and overall satisfaction with life.

The accelerometer measured high-frequency (60 Hz) raw acceleration in units of gravity, Euclidean norm minus 1 [19]. Raw data were downloaded from the accelerometer and converted into CSV files using Actilife Software version 6.13.4. Consecutively, the GGIR package version 1.6 in R' was used to process the CSV files [19]. Prior validated cut-points for MVPA were as follows: ≥100 mG (wrist-worn, non-dominant side), ≥110 mG (wrist-worn, dominant side) and ≥69 mG (hip-worn) [20,21]. A valid day of wearing time was defined as at least 8 h [22].

MetS was categorised as being present when three or more of the following criteria were met: waist circumference ≥88 cm; blood pressure (systolic ≥130 mmHg or diastolic ≥85 mmHg or drug treatment); triglycerides (≥150 mg/dL or drug treatment); high-density lipoprotein cholesterol (≤50 mg/dL or drug treatment) and fasting blood glucose (≥100 mg/dL or drug treatment) [23]. Also, the modified MetS *z*-score was calculated using

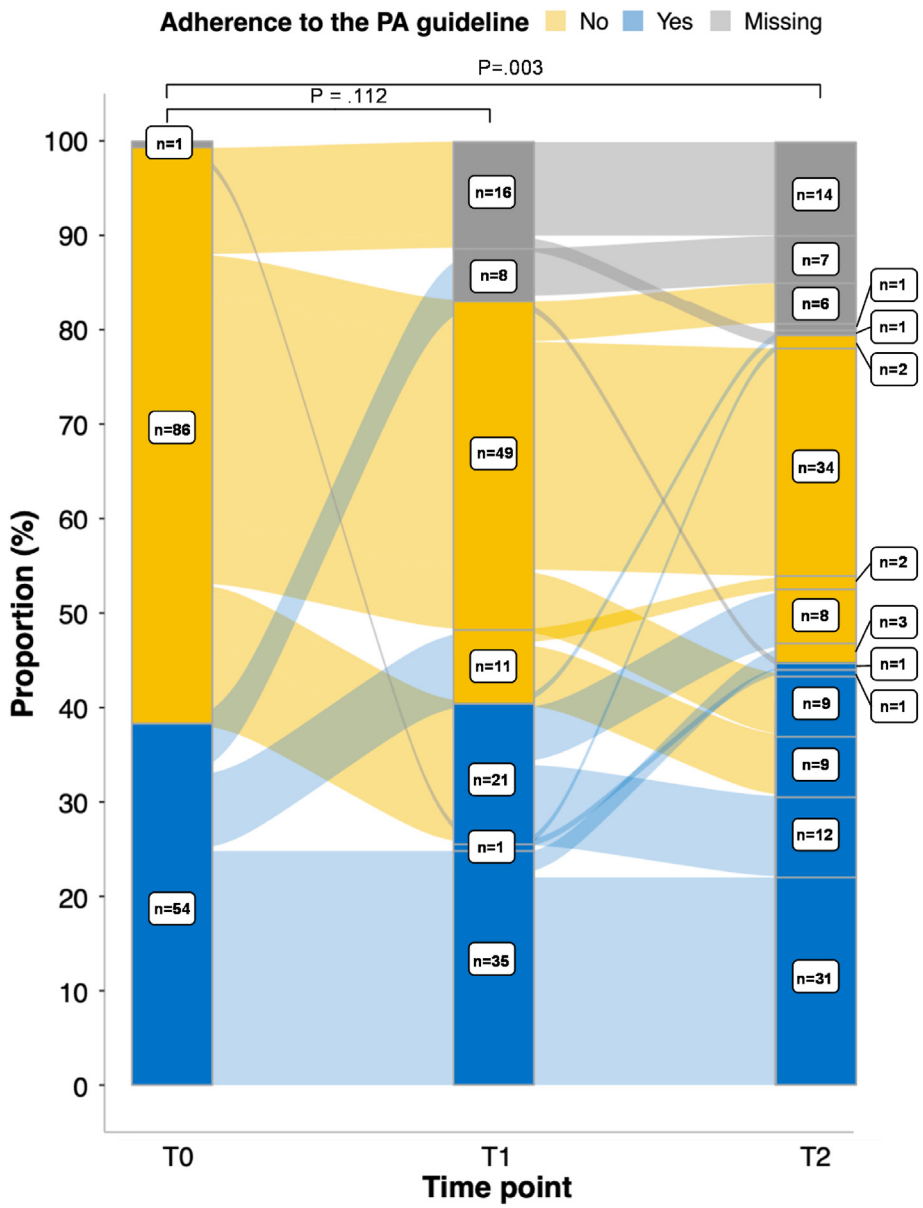

Fig. 2. Alluvial diagram of proportion of patients adhering to the PA guideline. Flows between the blocks represent changes in clusters of patients that adhere or do not adhere to the PA guideline over time. PA, physical activity; T0, baseline; T1, post-intervention (12 weeks); T2, follow-up (26 weeks).

individual patient data representing standardised data of metabolic variables [24]. Weight and height were used to calculate body mass index (kg/m^2). To calculate waist/hip ratio standard measuring tape was used to determine the waist, measured at midway between the lower rib and iliac crest, and hip circumference, measured around the widest portion of the buttocks. Fat percentage was measured by 4-site skinfold measurement using a Harpenden Skinfold Calliper [25]. A fasting (>8 h) blood sample was obtained. Blood pressure was measured after >5 min of sitting quietly using the arm of the unaffected breast.

Patient-reported HRQoL and (breast) cancer-specific functioning and symptoms were measured with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (QLQ-C30) and Breast cancer module (QLQ-BR23) [26,27].

Self-reported PA was measured with the Physical Activity Scale for the Elderly (PASE) questionnaire [28]. Patient-reported self-efficacy was measured using the validated Dutch version of the General Self-Efficacy Scale [29]. Exercise motivation was measured by using the Transtheoretical model stage of behavioural change and patients were categorised as non-regular exerciser or as regular exerciser [30]. Satisfaction with life was measured by using a Likert scale (1-10). Exercise adherence was calculated by the number of attended divided by the prescribed exercise sessions (36 sessions in total).

2.5. Sample size calculation and statistical analyses

It was assumed that at baseline, approximately 30% of the eligible patients would adhere to the PA guideline and an increase of 20% from T0 to T1 was considered to be clinically relevant [12,31,32]. Enrolment of 120 patients provided 80% power to detect a 20% difference at T1, with a two-sided alpha of $p < .05$. Assuming 15% dropout and using the exact McNemar test, 141 patients were

Table 2
Changes in metabolic syndrome.

MetS outcome	(T0)	(T1)	(T2)	Δ Mean change from T0 with 95% CI or (%)			
				(Δ T0-T1)		(Δ T0-T2)	
Mean (SD (±)), no. (%)	(n = 141)	(n = 120)	(n = 117)	(n = 120)	P^a	(n = 117)	P^a
MetS risk factors							
WC (cm)	100.0 ± 11.9	97.7 ± 11.8	97.2 ± 11.6	−2.1 (−3.0 to −1.3)	.000	−2.6 (−3.5 to −1.7)	.000
SBP (mm HG)	141.5 ± 19.4	136.3 ± 18.4	135.0 ± 18.8	−5.6 (−8.4 to −2.9)	.000	−6.4 (−9.7 to −3.1)	.000
DBP (mm HG)	84.4 ± 9.5	80.7 ± 9.1	80.5 ± 10.0	−3.7 (−5.4 to −2.0)	.000	−3.9 (−6.0 to −1.9)	.000
HDL-C (mg/dL)	59.8 ± 15.4	59.3 ± 14.3	60.2 ± 13.8	−1.1 (−2.7 to 0.4)	.147	−0.7 (−2.3 to 0.8)	.340
TGs (mg/dL)	141.3 ± 65.4	138.8 ± 67.2	135.1 ± 57.6	−0.7 (−9.8 to 8.4)	.882	−4.4 (−13.4 to 4.6)	.338
FBG (mg/dL)	106.6 ± 14.4	105.7 ± 12.2	104.1 ± 10.4	0.5 (−1.0 to 1.9)	.524	−1.1 (−2.9 to 0.8)	.244
Presence of MetS (yes)	98 (69.5%)	66 (46.8%)	73 (51.8%)	−13.0 (−9.2%)	.001	−7.0 (−5.0%)	.189
MetS z-score	1.4 ± 3.5	0.4 ± 3.4	0.1 ± 3.7	−0.7 (−1.1 to −0.4)	.000	−1.0 (−1.4 to −0.6)	.000

MetS, metabolic syndrome; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density-lipoprotein cholesterol; TGs, triglycerides; FBG, fasting blood glucose; SD, standard deviation; CI, confidence interval.
[a] Differences within-group were assessed by general linear models repeated measures analysis of variance when data was continuous and normally distributed with planned comparisons using paired samples *t*-tests and by the Cochran's Q test with planned comparisons using McNemar test when data was categorical with two-sided p values.

needed to be included.

All variables were checked for normality. Across time comparisons for dichotomous dependent variables were performed using Cochran's Q test. When statistically significant, comparisons were performed without adjustment for multiple testing using the exact McNemar test with T0 as the reference value. Across time comparisons for continuous variables were performed using general linear models repeated-measures analysis of variance. When statistically significant, comparisons were performed using the paired *t*-test with T0 as the reference value. All data across time-points T0, T1, T2 were analysed using SPSS (version 23.0) and R (version 3.6.2). All data stated are median with ranges unless indicated otherwise.

3. Results

3.1. Study sample

Baseline characteristics are depicted in Table 1. In total, 141 patients were included of which 124 attended a facility-based and 17 a home-based supervised exercise intervention. Patients were seen for baseline assessments at a median of 20.5 months [0 to 96] after diagnosis. Fig. 1 displays the CONSORT diagram. The dropout rate was 14.9% at T1 and 16.3% at T2. The adherence rate to supervised exercise was 72% (26 of the 36 sessions).

3.2. Adherence to the national PA guideline

Patients wore the accelerometer on the non-dominant wrist (n = 56), dominant wrist (n = 51), hip (n = 19) or combinations at different time points (n = 15). At T0, patients engaged in a median MVPA of 118 min [0 to 786] per week. Median MVPA per week increased to 137 min [0 to 838] at T1 and 163 min [2 to 652] at T2. In total, 54 patients (38.3%) adhered to the national aerobic PA guideline at T0 (see Fig. 2). The proportion increased to 57 patients (40.4%) at T1 and 63 patients (44.7%) at T2. The primary endpoint, the increase in proportion from T0 to T1, was statistically non-significant (p = .112). However, a statistically significant longitudinal effect was found for adherence to the PA guideline using Cochran's Q test [$\chi^2(2) = 8.977$, p = .011]. Comparisons using the exact McNemar test showed a statistically significant increase in adherence to the PA guideline from T0 to T2 (p = .003).

3.3. Secondary outcomes

At T0, MetS was present in 69.5% of the patients (see Table 2). The proportion of patients with MetS decreased statistically significantly over time to 46.8% at T1 and 51.8% at T2 [$\chi^2(2) = 9.923$, p = .007]. Also, a statistically significant decrease was found in MetS *z*-score as well as in two MetS variables: waist circumference and blood pressure. Changes in other secondary outcomes are shown in Table A1. The mean BMI and fat percentage at T0 were 31.3 kg/m^2 (SD 4.4) and 42.7% (SD 3.6) respectively. Both variables decreased statistically significantly over time points (Table A1). At T0, mean HRQoL was rated 70.3. HRQoL increased statistically significantly over time to 76.8 at T1 and 76.9 at T2 [F (2,224) = 14.813, p = .000]. Statistically significant improvements from T0 were also found in fatigue, dyspnoea, body image, future perspective, physical-, social-, emotional- and role functioning, insomnia, breast symptoms and systemic therapy side effects. Statistically significant improvements in HRQoL and breast cancer-specific functioning and symptoms are presented in Fig. 3A and B and Table B1. The PASE sum score, total minutes of PA and sedentary time statistically significantly improved over time. Changes in self-reported PA, self-efficacy, exercise motivation, satisfaction with life, and maximal cardiopulmonary exercise test outcome (facility-based sub-group) are provided in Table B1.

4. Discussion

During treatment with adjuvant endocrine therapy for breast cancer, the studied supervised exercise increased the proportion of patients adhering to the Dutch national aerobic PA guideline. This increase was statistically non-significant immediately after completion of the intervention but was statistically significant during follow-up. Moreover, the effectiveness of supervised exercise was accentuated by statistically significant improvements in presence of MetS, body composition, HRQoL, breast cancer-specific functioning and symptoms (e.g. fatigue, dyspnoea), self-efficacy, exercise motivation and satisfaction with life in these patients.

This is the first large clinical study to present the effect of supervised exercise on objectively measured MVPA and corresponding proportion of patients adhering to the national PA guideline during adjuvant endocrine therapy in overweight or obese patients with breast cancer. Over the past years, the role of endocrine treatment has become more dominant compared to chemo-endocrine therapy for oestrogen receptor-positive breast cancer [33]. The majority of studies have focused on the effects of exercise interventions during or after adjuvant chemotherapy instead of concentrating on endocrine therapy. The use of endocrine therapy renders this subgroup highly at risk for adverse effects, and those

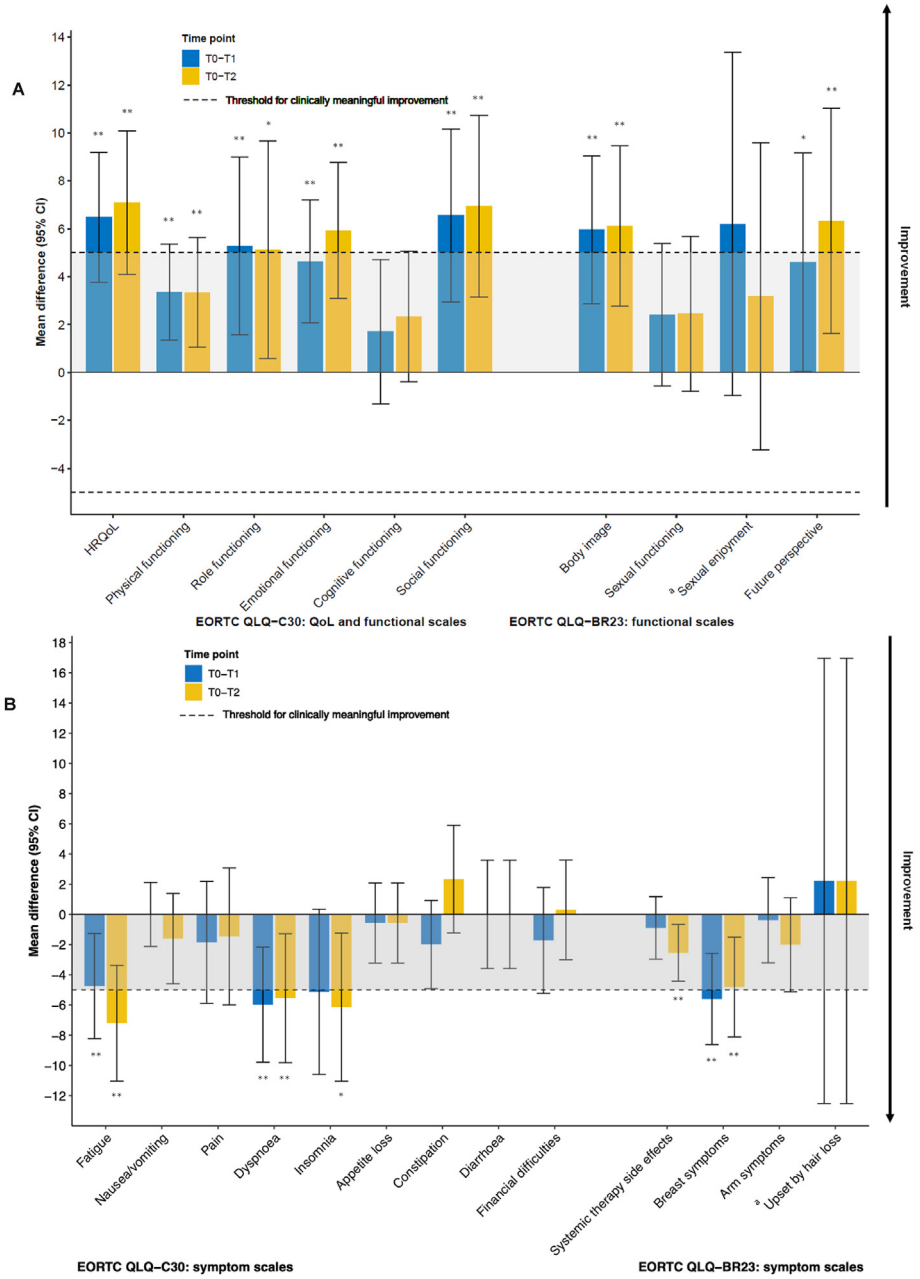

Fig. 3. Overall change from baseline. **(A)** EORTC QLQ-C30: QoL and functional scales; EORTC QLQ-BR23: functional scales. **(B)** EORTC QLQ-C30: QoL and symptom scales; EORTC QLQ-BR23: symptom scales. EORTC, European Organization for Research and Treatment of Cancer; QLQ-C30; Quality of Life Questionnaire Core 30; QLQ-BR23, Quality of Life Questionnaire breast cancer module; HRQoL, health-related quality of life; CI, confidence interval; T0-T1, change from baseline to post-intervention (week 12); T0-T2, change from baseline to follow-up (week 26). Asterisks denote that the change from baseline was statistically significant with two-sided p values (*, $p \leq .05$; **, $p \leq .01$). [a]The sample sizes for the 'sexual enjoyment' functional scale and 'Upset by hair loss' symptom scale were smaller than other scales.

patients could substantially benefit from supervised exercise, as demonstrated by the current study [9]. Over half of our study population was obese at baseline, which does not reflect the general female population in the Netherlands where estimations from the WHO show rates of approximately 20% presence of obesity among Dutch adult women [34]. The low proportion of patients that were adhering to the national PA guideline at baseline in our sample (38.3%) is similar to findings from a large cohort study that compared PA of patients with breast cancer to the general Dutch female population [10]. A possible explanation for the statistically non-significant increase at T1 could be temporary discontinuation in physical exercise immediately after completion of the intervention. This phenomenon can be accredited to the transition from supervised to home-based, regular physical exercise [35,36]. Patients were frequently uncertain about incorporating physical exercise in a home-based setting. A possible solution could be a tapering period after completion of the intervention consisting of physiotherapy counselling sessions (lifestyle monitoring) by telephone to coach them in incorporating structural physical exercise as a routine lifestyle [37–40]. A study comparable to the current one investigated a 12-week exercise intervention that consisted of 12 supervised exercise sessions that were tapered over six weeks to a home-based exercise setting in patients with breast cancer [39]. This resulted in a statistically significant effect immediately post-

intervention on adherence to the PA guideline in that study. However, the impact of their intervention was not sustained at 26 weeks follow-up. Possibly, a more extended period of supervised exercise, 12 instead of six weeks, is more optimal to induce sustained PA behaviour. Another study described self-reported PA behaviour patterns during 24 months follow-up after an exercise intervention during adjuvant chemotherapy in patients with breast cancer and found that patients were less physically active at follow-up compared to post-intervention [35]. The difference with our results might be explained by the timing of the intervention (during adjuvant chemotherapy in their study compared to during adjuvant endocrine therapy in our study). Adjuvant chemotherapy treatment often interrupts patients' everyday daily life. In contrast, during the period of adjuvant endocrine therapy, patients already restored their routines of daily life. A clinically relevant finding is the exercise-induced effect on HRQoL as well as in several cancer-specific functional and symptom scales [41]. These findings are comparable with the beneficial small-to-moderate effect described by a recently published Cochrane review which pooled HRQoL data of 22 studies that investigated exercise-induced effects on HRQoL in patients with breast cancer [42].

Furthermore, our intervention statistically significantly attenuated the presence of MetS by improving cardiovascular risk factors including body composition. Comparable results were found in a recent study, where MetS was effectively attenuated by a supervised 16-week combined aerobic and resistance exercise intervention [43]. The effect was more pronounced in that study, probably caused by a higher adherence rate of 96% compared to our 72%. Adherence could be improved by identifying patients at risk for non-adherence to provide extra guidance [44]. Currently, there are promising studies in progress that will provide more information about lifestyle interventions in breast cancer patients, for example the German SUCCES-C trial [45] and BWEL trial [46]. In an interim-analysis of the SUCCES-C trial, no difference in disease-free survival of the intervention, a telephone-delivered two-year lifestyle intervention, was found.

Strengths of this study include the multicentre design, real-world setting of supervised exercise, objectively measured MVPA and relatively high adherence to the intervention. An important limitation, however, is the single-arm design. This design makes it difficult to differentiate between the effect of the intervention, a placebo effect, and the effect of natural history, hence caution is warranted in interpretation of results. Future lifestyle intervention studies preferably should use a randomised controlled trial study design [47]. The high dropout in our intervention was a limitation as well. Also, there is a need for consensus about cut-points, data collection and processing criteria for accelerometer use in studies as well [48]. Additionally, measurement of MVPA by accelerometer could be prone to measurement error caused by electric-assisted cycling, which is impossible to distinguish from regular cycling/cycle sport without a PA log or heart rate monitoring. Health-monitoring wearable devices, such as activity trackers and smartphone apps provide a promising alternative to measure or stimulate PA when incorporated in an intervention [49]. The additional measurement of daily food intake could have been interesting. The effect of the supervised exercise intervention on MetS and body composition could be confounded by alterations in daily food intake. However, our study focused primarily on the effect of supervised exercise on PA. Measurement of daily food intake could have diluted the effect of the intervention on PA. Also, this is a burdensome measurement which could have negatively impacted adherence to the intervention.

In conclusion, supervised exercise statistically significantly increased adherence to the PA guideline at 26 weeks follow-up during adjuvant endocrine therapy in overweight or obese breast cancer patients. Health care providers should use our findings to explain, convince and motivate this patient population. Referral to supervised exercise can be a powerful strategy to endorse a physically active lifestyle and reduce or manage adverse effects of adjuvant endocrine therapy [50]. Research is warranted to investigate further tapering to self-initiated exercise, cost-effectiveness, benefits and implement pathways.

Authors' information

Annemiek M.E. Walenkamp and Anna K.L. Reyners shared last authorship.

List of where and when the study has been presented in part elsewhere

Part of the data was presented at the ESMO virtual congress 2020.

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Declaration of competing interest

All authors have nothing to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2021.05.004.

Ethical approval

All procedures performed in this study were in accordance with the ethical standards of the local medical ethical committee of the University Medical Centre Groningen (ethical approval) and with the 1964 Declaration of Helsinki and its later amendments. Written consent was obtained from all participating patients. The study was registered in ClinicalTrial.gov (NCT02424292).

Eq. (A.1) metabolic z-score

Formula used in the current study:
HDL-C, high-density

$$((50 - \text{HDL} - \text{C}) / 15.3) + ((\text{TGs} - 150) / 60.7)$$

$+((\text{FBG}-100)/11.2)+((\text{WC}-88)/11.9)+((\text{SBP}-130)/19)+((\text{DBP}-85)/9.8)$

lipid cholesterol; TGs, triglycerides; FBG, fasting blood glucose; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure.

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