Psychology, Health & Medicine

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/cphm20

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To cite this article: Ana Joaquim, Anabela Amarelo, Pedro Antunes, Catarina Garcia, Inês Leão, Eduardo Vilela, Madalena Teixeira, Bárbara Duarte, Micael Vieira, Vera Afreixo, Andreia Capela, Sofia Viamonte, Horácio Costa, Luisa A. Helguero & Alberto Alves (29 Aug 2023): Effects of a Physical Exercise Program on Quality of Life and Physical Fitness of Breast Cancer Survivors: the MAMA_MOVE Gaia After Treatment Trial, Psychology, Health & Medicine, DOI: 10.1080/13548506.2023.2240074

To link to this article: https://doi.org/10.1080/13548506.2023.2240074

PSYCHOLOGY, HEALTH & MEDICINE
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Effects of a Physical Exercise Program on Quality of Life and Physical Fitness of Breast Cancer Survivors: the MAMA_MOVE Gaia After Treatment Trial

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ABSTRACT

To assess the effects of a group class physical exercise program on health-related quality of life (HRQOL), physical fitness and activity, and safety in early breast cancer women after treatment, a double-phase trial [16-week control phase (CP) followed by a 16-week intervention phase (IP)] was designed. Outcomes were evaluated at baseline (T1), 8 (T2) and 16 (T3) weeks (CP), and 24 (T4) and 32 (T5) weeks (IP). The primary endpoint was global health status. Out of 82 enrolled patients, 37 completed the IP. Global health status decreased (−10,1; 95% CI −19.8 to −0.4; $p = 0.040$) during the CP and stabilized during the IP. Physical and sexual functioning increased during the IP ($p = 0.008$; $p = 0.017$), while cardiorespiratory fitness increased in the CP ($p = 0.004$). Upper limb strength and lower limb functionality increased during both phases [CP: $p < 0.0001$, $p = 0.001$ (surgical and nonsurgical arm), $p = 0.028$; IP: $p < 0.0001$, $p = 0.002$, $p = 0.009$]. Body mass index decreased in the IP ($p = 0.026$). Waist circumference increased in the CP ($p = 0.001$) and decreased in the IP ($p = 0.010$); sedentary behaviours and moderate

ARTICLE HISTORY
Received 15 February 2023
Accepted 18 July 2023

KEYWORDS
Breast cancer; health-related quality of life; physical fitness; physical exercise

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/13548506.2023.2240074

and vigorous physical activity did not change. Adherence to 70% of the sessions was reported in 54% of patients. No serious adverse events related to the intervention were reported. In conclusion, the physical exercise program was able to prevent the decline in global health status and to improve other domains of HRQOL and physical fitness. As physical exercise is not the standard of care in many countries, the implementation of group class programs might be an option.

Introduction

Breast cancer (BC) is the most frequently diagnosed cancer worldwide, with an incidence of over 2.2 million new cases in 2020, and it is also the leading cause of cancer-related death in women (Sung et al., 2021). Notably, due to organized screening procedures across several countries and advances in diagnostic, staging, and therapeutic management, the prevalence is high and increasing, with over 7.7 million survivors living five years after diagnosis (Cardoso et al., 2019).

Early BC diagnosis and treatment negatively impact BC survivors' health-related quality of life (HRQOL) (Binkley et al., 2012; Cantarero-Villanueva et al., 2011; McNeely et al., 2012). Different therapeutic approaches, namely, surgery, radiotherapy, and several modalities of systemic treatment (chemotherapy, hormone therapy, and other targeted therapies), can have specific adverse effects that may compromise HRQOL (Furmaniak et al., 2016).

More recent evidence has shown that some components of physical fitness, such as cardiorespiratory fitness (CRF), muscle strength, and body composition, are hampered in BC survivors (Caspersen et al., 1985). Reductions in CRF, expressed as maximal oxygen consumption (VO_2max), can be more pronounced after adjuvant treatments and may have long-term consequences; in particular, low VO_2max can be associated with higher mortality among more advanced stage BC patients (Peel et al., 2014). Muscle strength can be markedly impaired in BC patients after anticancer treatment, with the muscular fatigue index (which defines the ability of an individual to maintain a level of performance, where higher indexes indicate quicker muscle fatigue) being higher in chemotherapy-treated patients (Klassen et al., 2017). Another frequent chronic adverse event in BC survivors is body composition changes, namely, increases in body weight and waist circumference, which are correlated with an increased risk of recurrence and death by BC (Holmes & Kroenke, 2004; Schapira et al., 1991). Furthermore, some studies report that fatigue can be present in 90% of BC survivors over a period that can last several years, being an important cause of a decrease in physical activity, muscle mass, muscle strength, and body composition (J. M. Jones et al., 2016; Mock et al., 2005).

Evidence shows that physical exercise is an effective supportive therapeutic approach for improving the HRQOL and physical fitness of breast cancer survivors (Joaquim et al., 2022). Moreover, in a recent review, physical exercise was considered one of the most evidence-based treatments for the selected hormone-induced side effects, such as fatigue and increase in body weight (Franzoi et al., 2021), which is of particular interest, as approximately 70% of BC survivors have hormone-positive cancer that is treated with

hormone therapy over many years (Cardoso et al., 2019). Hence, the American College of Sports Medicine (ACSM) has recommended specific doses of aerobic, resistance and/or combined aerobic plus resistance training for fatigue, physical functioning and HRQOL, among other common cancer-related health outcomes (Campbell et al., 2019; Peck et al., 2022).

Despite these data, the overall benefits of physical exercise programs are still not fully elucidated (Fakhraei et al., 2022). In addition, multiple studies have documented a lack of recommendation from oncology clinicians around the world. On the other hand, supervised physical exercise programs are not generally part of the standard of care for the management of BC survivors in many countries (Schmitz et al., 2021). Furthermore, the studied programs can have limitations in terms of generalization because of the need for specialized exercise professionals and equipment (Mcneely et al., 2022; Schwartz et al., 2017). Taking these concepts into account, we designed the trial MAMA_MOVE Gaia After Treatment to pragmatically assess whether a supervised physical exercise program applied in group classes by certified exercise physiologists using exercise strategies with limited training equipment improves HRQOL and physical fitness and is safe in BC survivors after primary treatment with curative intent.

Material and methods

Design, setting, and protocol registration

MAMA_MOVE GAIA After Treatment is a one-center, prospective, double-phase, longitudinal trial comprising a 16-week control phase (CP) followed by a 16-week intervention phase (IP) consisting of a physical exercise program (Clinicaltrials.gov: NCT04024280).

The trial was presented to potentially eligible patients by their attending medical oncologists. Eligible patients who provided informed consent were assessed by a physiatrist and referred for musculoskeletal rehabilitation during CP if needed, as per standard of care in the Department for all cancer patients proposed to integrate a physical exercise program, either in the research setting or in the community. Afterwards, each participant was assessed at five time points: baseline (T1), 8 and 16 weeks (T2 and T3) (CP), and 24 and 32 weeks (T4 and T5) (IP) (Figure 1). The last evaluation was conducted

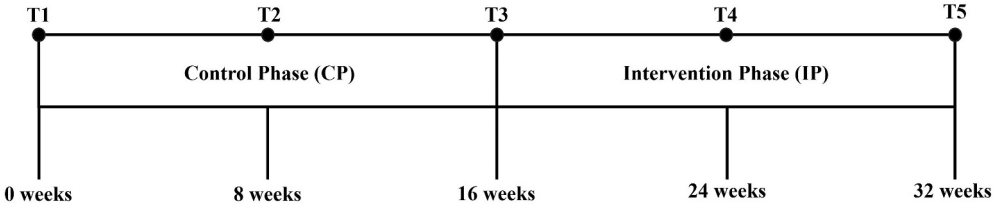

Figure 1. Timeline of assessments. Note: Legend: Assessments at T1, T2, T3, T4 and T5 - HRQOL, body composition, upper-limb strength, lower-limb functionality, physical activity, adherence, and safety. Assessments at T1, T3 and T5: cardiorespiratory fitness.

48 hours after the last exercise session. CRF was assessed at three time points: T1 and T3 (CP) and T5 (IP).

The trial was approved by the hospital Ethics Committee.

Participants

Participants were considered eligible if they met the following inclusion criteria: women over 18 years old with BC diagnosis staged 0-IIIC [American Joint Cancer Committee (AJCC) v.7("AJCC Cancer Staging Manual 7th Edition",, 2020] who had completed the primary treatment with curative intent (defined as surgery plus/minus neoadjuvant or adjuvant chemotherapy and/or radiotherapy) at least one month prior to enrolment and not meeting the ACSM physical activity guidelines (moderate activity ≥150 minutes/week or vigorous activity ≥75 minutes/week or an equivalent combination of moderate- and vigorous-intensity aerobic activity plus ≥ 2 resistance training/week) assessed at eligibility evaluation by direct questioning about a regular week (Campbell et al., 2019).

Exclusion criteria comprised: severe anaemia [haemoglobin (Hb) ≤ 8 g/dL]; symptomatic moderate anaemia (Hb > 8 and ≤10 g/dL; symptoms included sustained tachycardia, exertional dyspnoea, chest pain or syncope); uncontrolled hypertension (hypertensive patients without stable antihypertensive medication for at least one month or, for those on stable medication, confirmed grade 3 hypertension [Common Terminology Criteria for Adverse Events (CTCAE) v4.03 (NCI, NIH, 2009)]; uncontrolled diabetes (diabetic patients without stable antidiabetic medication for at least one month); heart failure grade > 1 (New York Heart Association classification) (McDonagh et al., 2021); history of osteoporosis with a T-score < −2.5 in the lumbar spine and/or femur in menopause; contraindication given by the assistant surgeon.

Population characteristics, such as socio-demographic and clinic-pathologic data, were collected through patient clinical records.

Intervention

The intervention comprised a 16-week supervised exercise training program encompassing 60-minute sessions, three times a week, of combined exercise training. Participants were distributed in group classes, with up to 20 participants, that took place in a local gymnasium. Supervisors were Canrehab® certified exercise physiologists and part of the research team (Schmitz et al., 2021). The prescribed physical exercise program was specifically developed for BC patients based on the ACSM guidelines (Liguori, 2021).

Each session involved an initial warm-up with light mobility exercises, followed by aerobic and resistance training, and ended with a cool-down phase of light stretching exercises. The aerobic training component encompassed two blocks of aerobic exercises: walking, running, and stepping. The duration of each block of aerobic exercise was ten minutes in the first two weeks, comprising a total of 20 minutes. The aerobic training was increased by one minute on each block (two minutes in total of the two blocks) every two weeks of the program, completing a total duration of 36 minutes in the last 2 weeks of the intervention. The aerobic exercise started at a moderate intensity [65–76% of maximal heart rate (HR), 12–13 on the Borg scale of perceived exercise] and increased progressively to vigorous exercise intensity (77–85% of HR, 14–17 on the Borg scale of perceived

exercise), according to individual tolerance. HR was measured during the exercise sessions by a chest-based heart rate monitoring device system (Firstbeat Technologies Ltd, Jyväskylä, Finland). The resistance exercise consisted of three sets of 15 submaximal repetitions of the upper body (upright row, chest press, bent over row, frontal arm raises, and seated row) and lower body (squat, leg extension, and leg curl) using free weights. The resistance training program began without load and increased to the minimal greater resistance possible when 15 repetitions were obtained without pain and below moderate intensity according to the recommended perceived exertion (12–14 on the Borg scale of perceived exertion).

Outcome measures

Primary outcome measure

The primary outcome was HRQOL, which was assessed by the global health status domain of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) version 3.0 (Aaronson et al., 1993). This score ranges from 0 to 100, with a high score representing a high HRQOL. We used ten points as the threshold for clinically meaningful changes, as previously described (Snyder et al., 2015).

Secondary outcome measures

Secondary outcomes included a) the scores of the EORTC QLQ-C30 version 3.0 functional scales (physical, role, cognitive, emotional, and social function) and symptom scales (fatigue, nausea pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties) (Aaronson et al., 1993) and the functional scales (body image, sexual functioning, sexual enjoyment, and future perspective) and symptom scales (systemic therapy side effects, breast symptoms, arm symptoms, and upset by hair loss) of the EORTC Breast Cancer Specific Quality of Life Questionnaire Module BR23 (Sprangers et al., 1996); b) measures of physical fitness, such as CRF, upper limb strength, lower limb functionality, and body composition; c) physical activity; d) adherence; and e) safety.

Scores on the functional scales of the EORTC QLQ range from 0 to 100, and a high score represents a high level of functioning. The symptomatic scales range from 0 to 100, and a high score represents a high level of symptomatology/problem.

CRF was assessed through a symptom-limited exercise stress test performed on a treadmill using a modified version of the Bruce protocol (Bruce & McDonough, 1969), and metabolic equivalents of task (METs) were calculated according to the stage of protocol and time reached at peak exercise. The maximal HR was also recorded for the determination of the intensity of exercise sessions (Mezzani, 2017; Mezzani et al., 2013; Ross et al., 2016).

For the upper limb strength assessment, maximal voluntary handgrip strength was measured using a digital hand dynamometer (Saehan model SH1001, DHD-1, Saehan Corp. South Korea). Each participant performed a total of six trials, three on each hand (both surgical and nonsurgical arm), with an alternating bilateral sequence. Before each trial, the position of the limb was adjusted so that the participant placed the elbow flexed

at a 90° angle with the wrist as close to 0° as possible. The average of the three tests on each member was used for analysis (Massy-Westropp et al., 2011).

The 30-second chair sit-to-stand test (STS) was used to evaluate the functionality of the lower limbs. Each participant was instructed to stand up and sit as many times as possible on a 40-cm-high chair for 30 seconds, keeping arms crossed close to the chest (C. J. Jones et al., 1999). The number of repetitions was used for analysis.

Body composition was assessed by body mass index (BMI) and waist circumference. BMI was calculated by dividing the weight in kilograms by the square of height in meters (kg/m^2). A BMI of 25 to 29.9 kg/m^2 corresponds to overweight and a BMI of 30 kg/m^2 or greater defines obesity (Renehan et al., 2008). In terms of waist circumference, participants were asked to stand straight with their arms resting along the torso, and waist circumference was measured at the midpoint between the lower rib and the upper border of the iliac crest with a Gulick anthropometric tape, measured to the nearest 0.5 cm, after expiration (Ross et al., 2020; WHO Expert Committee, 1995).

Physical activity was objectively assessed by an accelerometer (ActiGraph wGT3X, Pensacola, FL, U.S.A.), which was worn on the waist, during waking hours for seven consecutive days. Patients were asked to remove the accelerometer only during bathing or swimming activities. The accelerometers were programmed to record data in 60-second periods (counts/min). Patients had to wear the accelerometer for at least 600 minutes per day to be considered a valid recording day, and only patients who wore the accelerometer for a minimum of 3 days (2 weekdays and 1 weekend day) were included in the analysis. Dedicated software (ActiLife Software, ActiGraph, Florida, U.S.A.) was used to sum the accelerometer counts/min over the seven days and to compute the average min/day spent at different intensities of physical activity according to Freedson's cut-points: sedentary behavior (<100 count/min), light (100–1951 count/min) and moderate to vigorous (≥1952 count/min) (Freedson et al., 1998).

Adherence to the exercise sessions was calculated as the relative ratio between the number of exercise sessions attended and the total number of exercise sessions that were predicted for the full exercise intervention (K et al., 2014; Kampshoff et al., 2016).

The occurrence of serious adverse events related to the physical exercise program was recorded for the determination of exercise session safety (European Medical Agency, 2016). A serious adverse event was defined as any adverse event resulting in death, life-threatening situation, requiring or prolonging hospitalization, and/or resulting in persistent or significant disability or incapacity (European Medical Agency, 2016). The relationship of adverse events to the physical exercise program was determined by the principal investigator.

Data collection procedure

The assessments were conducted at the Medical Oncology Department of the center, except for the CRF assessment, which was done at the Cardiology Department. Each participant began filling out general sociodemographic and HRQOL paper questionnaires. Thereafter, anthropometric measures were taken in privacy, upper-limb strength and lower-limb functionality were assessed, and patients were equipped with the accelerometer.

Deviations from the original protocol

Due to the COVID-19 pandemic, the fourth group (22 patients) could not start the IP.

Although stage IV was not within the eligibility criteria, two patients with disease-free stage IV were included, as they had bone oligometastatic disease radically treated with stereotaxic radiotherapy and were disease-free.

Statistical analysis

Differences in the characteristics between the completer and non-completer groups were tested with t-tests (continuous variables) and chi-square test (qualitative variables). To compare the variation in the primary and secondary outcomes over time, in each study phase, we used a repeated analysis of covariance (ANOVA), which has been shown to be robust to violations of normality. Multiple comparisons analysis was performed with paired samples t-tests for within-group comparisons, with Bonferroni correction for the number of post hoc comparisons: in the CP, from baseline to 8 weeks (T1-T2) and 16 weeks (T1-T3); in the IP, from 16 weeks to 24 weeks (T3-T4) and 32 weeks (T3-T5). Patients with missing values at each timepoint were excluded from all the analyses in both phases. The continuous variables are expressed as the means and standard deviations, whereas the categorical variables are presented as counts and percentages. The level of significance was set as a p-value less than 0.05. All analyses were conducted with SPSS version 24.0 (SPSS Inc).

Sample size

Considering differences in HRQOL previously reported (Antunes et al., 2019), a clinically significant difference induced by physical exercise would be detected with 54 participants (setting as the effect of interest a moderate effect d = 0.5, alpha = 0.05 and power = 0.95).

For the prevision of the expected dropout rate, we referred to a meta-analysis on adherence to physical activity interventions among three chronic conditions – cancer, cardiovascular disease, and diabetes. Out of the 3721 participants, 1661 were cancer patients. The average adherence rate was 77%, regardless of condition. However, cancer patients had greater variability in adherence and dropout, with the maximum dropout reaching 40.1%. After adjusting for an expected dropout rate of 30–40%, we aimed to recruit 80 participants (Bullard et al., 2019).

The sample size estimation was performed based on a two-tailed t test with a parametric approach to evaluate the effect of the intervention between moments T3 and T5 using paired samples, assuming stabilization in the control phase.

Results

Participants

A total of 135 patients met the eligibility criteria, of whom 82 agreed to participate. Of these, 37 did not initiate the IP (22 of them due to the COVID-19 pandemic), and eight patients missed at least one assessment and/or had missing values on the global health

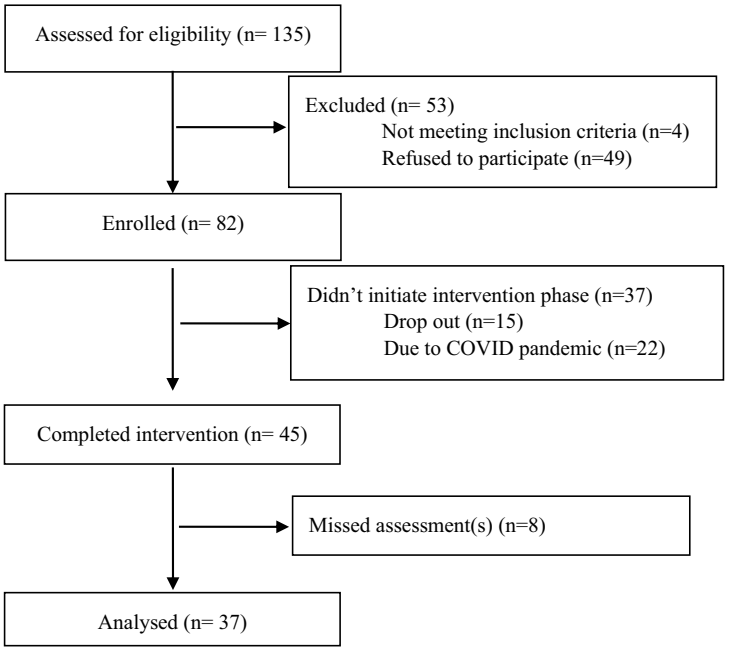

Figure 2. Flowchart.

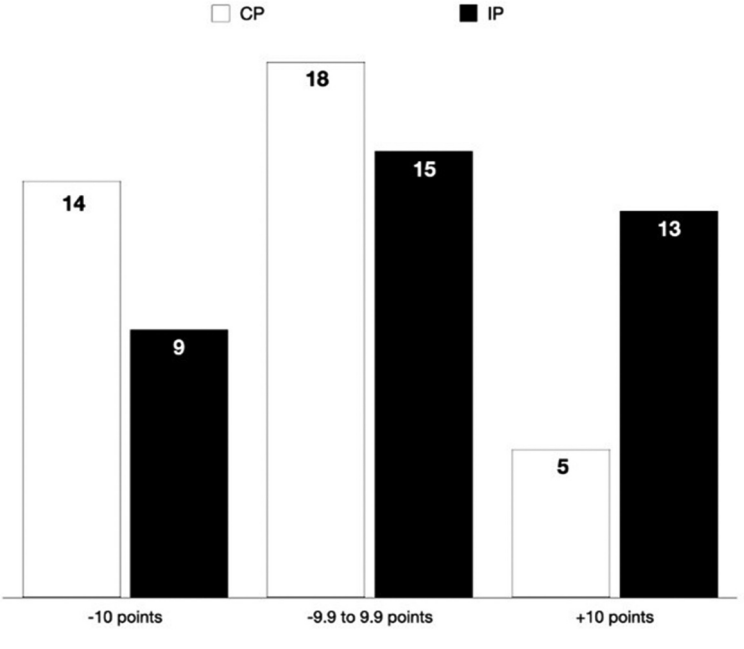

Figure 3. Clinically meaningful changes in global health quality of life during the control phase (CP) and intervention phase (IP). Note: Legend: Ten points was the considered threshold for clinically meaningful changes in the global health status score of quality of life(Snyder et al., 2015).

Table 1. Baseline patient characteristics.

Age (years) (mean ± SD) (*N* = 37)	57.9 ± 9.5
Weight (Kg) (mean ± SD) (*N* = 36)	73.1 ± 12.6
Height (cm) (mean ± SD) (*N* = 36)	156.9 ± 6.7
BMI (Kg/m^2) (mean ± SD) (*N* = 36)	29.7 ± 5.0
Normal weight (18.5 to 24.9 kg/m^2) [N (%)]	5 (13.9%)
Overweight (25 to 29.9 kg/m^2) [N (%)]	15 (41.7%)
Obesity (≥30 kg/m^2) [N (%)]	16 (44.4%)
Stage [N (%)] (*N* = 37)	
0	3 (8%)
I	10 (27%)
II	14 (38%)
III	8 (22%)
IV	2 (5%)
Treatment [N (%)] (*N* = 37)	
Chemotherapy	27 (73%)
Radiotherapy	29 (78%)
Hormone therapy	32 (86%)
Trastuzumab	8 (22%)
Pertuzumab	4 (11%)
Breast Surgery [N (%)] (*N* = 37)	
Mastectomy	23 (62%)
Tumorectomy	14 (38%)
Axillary Surgery [N (%)] (*N* = 37)	
None	0 (0%)
Axillary lymph node dissection	18 (49%)
Sentinel lymph node biopsy	19 (51%)
Comorbidities [N (%)] (*N* = 37)	
Diabetes	4 (11%)
Hypertension	15 (41%)
Time from last primary treatment (*N* = 37)	
Mean ± SD (years)	1,4 ± 1.8
Median (min-max) (years)	0.7 (0.08–8.9)
>1 year [N (%)]	15 (40,5%)
MVPA ≥150 min [N (%)] (*N* = 22)	19 (54.3%)

Note: Legend: BMI – body mass index; cm – centimetres; Kg – kilograms; MVPA – moderate to vigorous physical activity; N – number; SD – standard deviation.

status of HRQOL questions of the EORTC QLQ-C30 (primary endpoint), resulting in 45 non-completers. Hence, the final analysis comprises 37 completers (Figure 2).

Baseline patient characteristics are shown in Table 1. There were no differences between completers and non-completers in any of the sociodemographic or clinical baseline variables (Supplementary Table). The mean age was 57.5 ± 9.1 years. Eighty-six percent of patients were overweight or obese. The majority underwent chemotherapy, radiotherapy, and/or hormone therapy. Most patients underwent mastectomy and sentinel lymph node biopsy. Approximately 52% had diabetes and/or hypertension.

Primary outcome

HRQOL

Global health status significantly changed during CP ($p = 0.022$) but not during IP ($p = 0.198$) (Table 2). It decreased from T1 to T3 (−10,1; 95% CI −19.8 to −0.4; $p = 0.040$).

Table 2. Health-related Quality of Life during control and exercise phases.

	Control phase								
	0-week T1	8-week T2	16-week T3	Mean difference (Adjusted CI) T1-T2	*p*-value T1-T2	Mean difference (Adjusted CI) T1-T3	*p*-value T1-T3	Effect Size (η^2)	*p*-value
2. A - EORTC-QLQ-C30									
Global Health Status									
Quality of Life (*N* = 37)	68.5 ± 23.0	59.7 ± 17.7	58.3 ± 24.7	−8,8 (−17.9; 0,3)	0.062	**-10,1 (−19.8; −0.4)**	**0.040**	0.100	**0.022**
Functional Scales									
Physical Function (*N* = 37)	76.9 ± 13.8	72.4 ± 13.2	75.9 ± 13.1	−4.5 (−10,7; 1.7)	0.192	−1.1 (−6.1; 4.0)	1.000	0.053	0.141
Role Function (*N* = 37)	72.1 ± 24.2	73.4 ± 22.0	73.9 ± 20.2	1.4 (−10.5; 13.2)	1.000	1.8 (−6.4; 10.0)	1.000	0.003	0.880
Emotional Function (*N* = 37)	64.9 ± 29.9	68.5 ± 22.4	66.7 ± 24.8	3.6 (−3.6; 10.8)	0.502	1.7 (−6.8; 10.2)	1.000	0.017	0.547
Cognitive Function (*N* = 37)	71.6 ± 26.0	68.0 ± 24.9	72.4 ± 22.7	−3.6 (−11.5; 4.3)	0.582	0.9 (−7.4; 9.2)	1.000	0.030	0.336
Social Function (*N* = 37)	83.3 ± 16.2	76.1 ± 28.7	83.8 ± 22.0	−7.2 (−18.9; 4.4)	0.314	0.5 (−7.2; 8.1)	1.000	0.056	0.137
Symptom Scales									
Fatigue (*N* = 37)	32.3 ± 21.0	31.5 ± 20.9	30.6 ± 18.0	−0.8 (−9.7; 8.2)	1.000	−1.7 (−9.2; 5.9)	1.000	0.003	0.888
Nausea (*N* = 37)	6.8 ± 10.7	3.2 ± 6.6	3.2 ± 7.7	−3.6 (−8.4; 1.2)	0.176	−3.6 (−8.6; 1.4)	0.206	0.064	0.106
Pain (*N* = 37)	36.9 ± 24.3	34.7 ± 28.2	31.9 ± 26.8	−2.3 (−13.2; 8.7)	1.000	−5.0 (−15.1; 5.2)	0.520	0.015	0.571
Dyspnea (*N* = 33)	14.1 ± 22.1	14.1 ± 23.6	13.1 ± 23.5	0.0 (−10.8; 10.8)	1.000	−1.0 (−10.9; 8.9)	1.000	0.001	0.965
Insomnia (*N* = 35)	34.3 ± 34.8	32.4 ± 28.6	29.5 ± 28.9	−1.9 (−15.9; 12)	1.000	−4.8 (−19.1; 9.6)	0.886	0.010	0.709
Appetite Loss (*N* = 37)	4.5 ± 11.6	7.2 ± 17.8	9.9 ± 22.0	2.7 (−4.9; 10.3)	0.826	5.4 (−3.9; 14.7)	0.366	0.028	0.359
Constipation (*N* = 37)	26.1 ± 35.3	23.4 ± 31.3	22.5 ± 28.4	−2.7 (−12.9; 7.5)	1.000	−3.6 (−14;6.8)	0.844	0.012	0.654

(*Continued*)

Table 2. (Continued).

Diarrhea ($N = 35$)	2.9 ± 9.5	3.8 ± 10.8	3.8 ± 13.5	1.0 (−3.0; 4.9)	1.000	1.0 (−5.8; 7.7)	1.000	0.003	0.858
Financial Difficulties ($N = 36$)	36.1 ± 33.2	36.1 ± 31.2	36.1 ± 31.2	$-7{,}1^{-15}$ (−13.6; 13.6)	1.000	$-7{,}1^{-15}$ (−12.8; 12.8)	1.000	0.000	1.000
	Control phase								
	0-week T1	8-week T2	16-week T3	Mean difference (Adjusted CI) T1-T2	*p*-value T1-T2	Mean difference (Adjusted CI) T1-T3	*p*-value T1-T3	Effect Size (η^2)	*p*-value
EORTC-QLQ-BR23									
Functional Scales									
Body Image ($N = 36$)	69.4 ± 30.7	73.8 ± 27.3	77.3 ± 25.6	4.5 (−5.7; 14.7)	0.624	7.9 (−2.4; 18.3)	0.160	0.048	0.178
Sexual functioning ($N = 36$)	17.1 ± 20.9	18.1 ± 20.5	15.7 ± 20.7	0.9 (−4.9; 6.7)	1.000	−1.4 (−8.1; 5.3)	1.000	0.013	0.602
Sexual enjoyment ($N = 7$)	57.1 ± 31.7	57.1 ± 31.7	57.1 ± 31.7	0		0		0.125	0.351
Future perspective ($N = 35$)	35.2 ± 32.3	38.1 ± 30.4	46.7 ± 33.5	2.9 (−10.9; 16.6)	1.000	11.4 (1.3; 21.5)	0.024	0.061	0.129
Systemic therapy side effects ($N = 36$)	21.9 ± 15.9	24.1 ± 19.9	22.8 ± 18.0	2.1 (−4.1; 8.4)	0.860	0.9 (−4.1; 5.8)	1.000	0.010	0.695
Breast symptoms ($N = 36$)	25.5 ± 20.7	24.2 ± 19.5	20.4 ± 16.0	−1.4 (−7.5; 4.8)	1.000	−5.2 (−10.2; −0.1)	0.042	0.067	0.088
Arm symptoms ($N = 36$)	31.6 ± 22.3	29.8 ± 18.8	29.9 ± 22.0	−1.9 (−8.5; 4.8)	1.000	−1.7 (−8.3; 4.9)	1.000	0.008	0.743
	Intervention phase								
	16-week T3	24-week T4	32-week T5	Mean difference (Adjusted CI) T3-T4	*p*-value T3-T4	Mean difference (Adjusted CI) T3-T5	*p*-value T3-T5	Effect Size (η^2)	*p*-value
2. B – EORTC-QLQ-C30									
Global Health Status									
Quality of Life ($N = 37$)	58.3 ± 24.7	65.1 ± 18.4	60.6 ± 22.9	6.8 (−2.7; 16.2)	0.208	2.3 (−6.1; 10.7)	1.000	0.044	0.198
Functional Scales									

(*Continued*)

Table 2. (Continued).

Physical Function ($N = 37$)	75.9 ± 13.1	82.3 ± 14.0	79.3 ± 12.8	**6.5 (1.1; 11.8)**	**0.014**	3.4 (−0.7; 7.5)	0.116	0.143	**0.008**
Role Function ($N = 37$)	73.9 ± 20.2	77.9 ± 22.9	74.8 ± 23.8	4.1 (−3.7; 11.8)	0.460	0.9 (−7.4; 9.2)	1.000	0.020	0.489
Emotional Function ($N = 37$)	66.7 ± 24.8	70.3 ± 24.3	71.8 ± 21.8	3.6 (−3.2; 10.4)	0.444	5.2 (−1.8; 12.2)	0.186	0.047	0.180
	Intervention phase								
	16-week T3	24-week T4	32-week T5	Mean difference (Adjusted CI) T3-T4	*p*-value T3-T4	Mean difference (Adjusted CI) T3-T5	*p*-value T3-T5	Effect Size (η^2)	*p*-value
Cognitive Function ($N = 37$)	72.4 ± 22.7	73.4 ± 22.7	68.5 ± 23.8	0.9 (−5.1; 6.9)	1.000	−4.1 (−11.8; 3.7)	0.460	0.041	0.222
Social Function ($N = 37$)	83.8 ± 22.0	88.3 ± 17.1	85.1 ± 19.6	4.5 (−1.2; 10.1)	0.134	1.4 (−6.3; 9.0)	1.000	0.037	0.259
Symptom Scales									
Fatigue ($N = 37$)	30.6 ± 18.0	29.4 ± 19.5	33.3 ± 23.0	−1.2 (−7.8; 5.4)	1.000	2.7 (−4.9; 10.3)	0.818	0.020	0.486
Nausea ($N = 37$)	3.2 ± 7.7	4.1 ± 9.9	6.8 ± 13.9	0.9 (−3.4; 5.2)	1.000	3.6 (−1.2; 8.4)	0.176	0.044	0.199
Pain ($N = 37$)	32.0 ± 26.8	31.1 ± 23.9	32.9 ± 25.9	−0.9 (−9.6; 7.8)	1.000	0.9 (−8.5; 10.3)	1.000	0.003	0.905
Dyspnea ($N = 33$)	13.1 ± 23.5	12.1 ± 20.1	13.1 ± 20.3	−1.0 (−12.1; 10.0)	1.000	$1,8^{-15}$(−10.2; 10.2)	1.000	0.001	0.496
Insomnia ($N = 35$)	29.5 ± 28.9	27.6 ± 31.8	32.4 ± 31.8	−1.9 (−16.2; 12.4)	1.000	2.9 (−9.7; 15.4)	1.000	0.010	0.705
Appetite Loss ($N = 37$)	9.9 ± 22.0	9.9 ± 23.4	7.2 ± 16.0	$-1,8^{-15}$ (−11.7; 11.7)	1.000	−2.7 (−8.3; 2.9)	0.524	0.008	0.667
Constipation ($N = 37$)	22.5 ± 28.4	23.4 ± 28.2	26.1 ± 32.5	0.9 (−7.4; 9.2)	1.000	3.6 (−3.0; 10.2)	0.420	0.015	0.551
Diarrhea ($N = 35$)	3.8 ± 13.5	0.0 ± 0.0	3.8 ± 13.5	−3.8 (−9.1; 1.5)	0.206	0.0 (−7.9; 7.9)	1.000	0.038	0.265
Financial Difficulties ($N = 36$)	36.1 ± 31.2	29.6 ± 29.6	25.9 ± 21.2	−6.5 (−15.7; 2.8)	0.218	−10.2 (−21.3; 1.0)	0.078	0.074	0.068
EORTC-QLQ-BR23									
Functional Scales									
Body Image ($N = 36$)	77.3 ± 25.6	83.1 ± 19.8	80.1 ± 22.4	5.8 (−0.3; 11.9)	0.064	2.8 (−5.1; 10.7)	0.830	0.050	0.167
Sexual functioning ($N = 36$)	15.7 ± 20.7	16.2 ± 19.7	20.8 ± 20.8	0.5 (−3.5; 4.4)	1.000	**5.1 (0.2; 10.0)**	**0.040**	**0.110**	**0.017**
Sexual enjoyment ($N = 7$)	57.1 ± 31.7	52.4 ± 37.8	52.4 ± 37.8	−4.8 (−18.9; 9.4)	1.000	−4.8 (−18.9; 9.4)	1.000	0.143	0.397

(*Continued*)

Table 3. Changes in physical fitness during the control and intervention phases.

	Control phase								
	0-week T1	8-week T2	16-week T3	Mean difference (Adjusted CI) T1-T2	*p*-value T1-T2	Mean difference (Adjusted CI) T1-T3	*p*-value T1-T3	Effect Size (η^2)	*p*-value
3. A –									
BODY COMPOSITION									
Weight (kg)	73.2±12.8	73.2±12.8	73.5±12.9	0.0 (-0.6; 0.6)	1.000	0.3 (-0.5; 1.2)	0.766	0.019	0.517
BMI (kg/m^2) (N=35)	29.9±4.9	29.9±4.9	30.0±4.9	0.0 (-0.3; 0.3)	1.000	0.1 (-0.2; 0.5)	0.760	0.019	0.518
Waist Circumference (cm) (N=27)	96.6±13.7	101.8±11.9	101.1±12.0	**4.2 (1.3; 7.1)**	**0.002**	**4.3 (1.0; 7.6)**	**0.026**	0.221	**0.001**
PHYSICAL FITNESS									
Exercise treadmill test duration (min) (N=30)	6.4±1.6		7.0±1.6			**0.6 (0.2; 1.0)**	**0.006**		
Exercise treadmill test duration (METs) (N=30)	7.7±1.4		8.2±1.5			**0.5 (0.2; 0.9)**	**0.004**		
Handgrip strength (surgical arm, kg) (N=32)	20.2±5.6	21.6±5.3	23.5±6.4	1.3 (-0.1; 2.6)	0.070	**3.5 (2.1; 4.8)**	**0.000**	0.297	**<0.0001**
Handgrip strength (non-surgical arm, kg) (N=31)	21.3±5.7	22.8±6.0	23.9±6.6	**1.6 (0.7; 2.4)**	**0.000**	**3.0 (1.4; 4.6)**	<0.000	0.242	**0.001**
Sit-and-stand (repetitions) (N=32)	12.5±3.0	13.9±3.2	13.6±3.7	**1.4 (0.3; 2.5)**	**0.014**	1.1 (-0.2; 2.5)	0.134	0.109	**0.028**
PHYSICAL ACTIVITY									
Sedentary (min) (N=22)	2997.5 ±703.2	2825.9 ±849.8	2770.3 ±731.6	-171.5 (-475.9; 132.9)	0.376	-227.2 (-524.1; 69.7)	0.158	0.072	0.209
Light PA (min) (N=22)	2052.5 ±542.5	1987.5 ±602.7	2005.5 ±593.6	-65.1 (-276.2; 146.0)	0.930	-47.0 (-244.9; 150.8)	1.000	0.015	0.735
MVPA (min) (N=22)	207.6±139.3	184.1±128.9	191.5±159.6	-23.5 (-91.1; 44.2)	0.824	-16.1 (-105.8; 73.6)	1.000	0.014	0.740
Total PA (min) (N=22)	2260.1 ±637.5	2171.6 ±671.0	2196.9 ±649.7	-88.5 (-339.1; 162.0)	0.806	-63.2 (-293.2; 166.8)	1.000	0.020	0.656
	Intervention phase								
	16-week T3	24-week T4	32-week T5	Mean difference (Adjusted CI) T3-T4	*p*-value T3-T4	Mean difference (Adjusted CI) T3-T5	*p*-value T3-T5	Effect Size (η^2)	*p*-value
3. B –									
BODY COMPOSITION									
Weight (kg)	73.5±12.9	72.5±12.8	73.2±12.7	**-1.0 (-1.9; -0.1)**	**0.026**	-0.4 (-1.3; 0.5)	0.684	0.099	**0.029**
BMI (kg/m^2) (N=35)	30.0±4.9	29.6±4.7	29.8±4.7	**-0.4 (-0.8; -0.1)**	**0.020**	-0.2 (-0.6; 0.2)	0.604	**0.102**	**0.026**
Waist Circumference (cm) (N=27)	101.1±12.0	100.2±13.1	97.3±10.5	-0.9 (-3.7; 1.8)	0.844	**-3.8 (-6.9; -0.7)**	**0.014**	0.163	**0.010**

(*Continued*)

Table 3. (Continued).

PHYSICAL FITNESS	Intervention phase								
	16-week T3	24-week T4	32-week T5	Mean difference (Adjusted CI) T3-T4	*p*-value T3-T4	Mean difference (Adjusted CI) T3-T5	*p*-value T3-T5	Effect Size (η^2)	*p*-value
Exercise treadmill test duration (min) (N=30)	7.0±1.6		7.4±1.8			0.4 (0.4; 0.9)	0.076		
Exercise treadmill test duration (METs) (N=30)	8.2±1.5		8.5±1.6			0.3 (-0.1; 0.7)	0.093		
Handgrip strength (surgical arm, kg) (N=32)	23.5±6.4	25.4±5.9	26.9±6.5	**1.8 (0.3; 3.3)**	**0.014**	**3.3 (1.5; 5.2)**	**<0.0001**	0.266	**<0.0001**
Handgrip strength (non-surgical arm, kg) (N=31)	23.9±6.6	26.1±6.1	26.5±4.7	**2.1 (0.5; 3.7)**	**0.008**	**2.5 (0.5; 4.5)**	**0.010**	0.181	**0.002**
Sit-and-stand (repetitions) (N=32)	13.6±3.7	14.7±3.5	15.7±4.0	1.1 (-0.6; 2.8)	0.266	**2.1 (0.6; 3.5)**	**0.004**	0.154	**0.009**
PHYSICAL ACTIVITY									
Sedentary (min) (N=22)	2770.3 ±731.6	2769.2 ±719.8	2648.5 ±766.0	-1.2 (-248.8; 246.6)	1.000	-121.8 (-486.1; 242.6)	0.858	0.041	0.657
Light PA (min) (N=22)	2005.5 ±593.6	2209.4 ±824.6	2030.7 ±729.8	**203.9 (0.2; 407.7)**	**0.050**	25.2 (-200.6; 252.0)	1.000	0.141	**0.041**
MVPA (min) (N=22)	191.5±159.6	241.5±158.4	184.3±125.1	50.0 (-28.7; 128.7)	0.280	-7.2 (-81.7; 67.3)	1.000	0.096	0.121
Total PA (min) (N=22)	2197.0 ±649.7	2450.9 ±931.9	2215.0 ±807.3	**253.9 (16.1; 491.8)**	**0.036**	18 (-241.1; 277.2)	1.000	0.161	**0.025**

Legend: BMI – body mass index. MET – metabolic equivalent of task. PA – physical activity. MVPA – Moderate or vigorous physical activity.
Note: Continuous variables are expressed as the means and standard deviations, whereas categorical variables are presented as counts and percentages.

During the CP, 14 patients (37.8%) reported a clinically meaningful reduction (more than 10 points) in global health status, and five patients (13.5%) reported a clinically meaningful increase, whereas nine (24.3%) and 13 patients (35.1%) reported a clinically meaningful increase during the IP, respectively (Figure 3).

Secondary outcomes

HRQOL functional and symptom domains

Physical function was stable during the CP ($p = 0.141$) but changed significantly during the IP ($p = 0.008$) (Table 2). It increased from T3 to T4 (6.5; 95% CI 1.1 to 11.8; $p = 0.014$).

Sexual functioning also improved during IP ($p = 0.017$), whereas no changes were seen during CP ($p = 0.602$) (Table 2). It increased from T3 to T5 (5,1; 95% CI 0.2 to 10.0; $p = 0.040$).

The other functional and symptom scales remained stable.

CRF

CRF (assessed by METs) increased during the CP, from T1 to T3 (0.6 METs; 95% CI 0.2 to 1.0; $p = 0.004$) and remained unchanged during the IP ($p = 0.093$) (Table 3).

Maximal exercise duration achieved by patients during the exercise test also improved during the CP (0.5 minutes; 95% CI 0.2 to 0.9; $p = 0.006$) and tended to increase from T3 to T5 (0.3 minutes; 95% CI 0.4 to 0.9; $p = 0.076$) (Table 3).

Upper limb strength

Significant changes were found during the CP and IP in the handgrip isometric strength of both surgical and nonsurgical arms (Table 3).

The handgrip isometric strength of the surgical arm increased from T1 to T3 (3.5 kg; 95% CI 2.1 to 4.8; $p = 0.000$), T3 to T4 (1.8 kg; 95% CI 0.3 to 3.3; $p = 0.014$) and T3 to T5 (3.3 kg; 95% CI 1.5 to 5.2; $p = 0.000$).

Concerning the nonsurgical arm, it increased in all the studied periods: from T1 to T2 (1.6 kg; 95% CI 0.7 to 2.4; $p = 0.000$), T1 to T3 (3.0 kg; 95% CI 1.4 to 4.6; $p = 0.000$), T3 to T4 (mean difference 2.1 kg; 95% CI 0.5 to 3.7; $p = 0.008$) and T3 to T5 (2.5 kg; 95% CI 0.5 to 4.5; $p = 0.010$).

Lower limb functionality

Lower limb functionality measured by the STS (Table 3) increased during the CP ($p = 0.028$) and IP ($p = 0.009$) (Table 3).

Patients were able to complete more repetitions from T1 to T2 (1.4; 95% CI 0.3 to 2.5; $p = 0.014$) and from T3 to T5 (2.1; 95% CI 0.6 to 3.5; $p = 0.004$).

Body composition

The body weight and BMI were stable during the CP ($p = 0.517$ and $p = 0.518$) but changed significantly during the IP ($p = 0.029$ and $p = 0.026$). Both weight and BMI decreased from T3 to T4 (weight: −1.0 kg, 95% CI −1.9 to −0.1, $p = 0.026$; BMI: −0.4 kg/m^2, 95% CI −0.8 to −0.1; $p = 0.020$).

Waist circumference changed during both the CP ($p = 0.001$) and the IP ($p = 0.010$) (Table 3). It increased during the CP, from T1 to T2 (4.2 cm; 95% CI 1.3 to 7.1; $p = 0.002$) and from T1 to T3 (4.3 cm; 95% CI 1.0 to 7.6; $p = 0.026$), and decreased from T3 to T5 (−3.8 cm; 95% CI −6.9 to −0.7; $p = 0.014$).

Physical activity

Light physical activity (PA) and total PA were stable during the CP ($p = 0.735$; $p = 0.656$) and changed during the intervention phase ($p = 0.041$; $p = 0.025$), whereas no changes were found in the sedentary behaviors and in moderate and vigorous physical activity (MVPA) during the CP ($p = 0.209$; $p = 0.740$) and the IP ($p = 0.657$; $p = 0.121$) (Table 3).

Light PA increased from T3 to T4 (203.9 minutes; 95% CI 0.2 to 4407.7; $p = 0.050$), and total PA increased from T3 to T4 (253.9 minutes; 95% CI 16.1 to 491.8; $p = 0.036$).

Fifty-nine percent of the 55 patients who were assessed by accelerometery at baseline complied with the recommendations for aerobic MVPA (Campbell et al., 2019), with no differences between completers and non-completers (Supplementary Table).

Adherence

Among the patients who completed the program, the mean adherence to the exercise sessions was 61.7 ± 27.6% (minimum 1.72%; maximum 96%), with 54% and 35% of patients having participated in at least 70% and 80% of the exercise sessions, respectively.

Safety

No serious adverse events related to the physical exercise program were reported.

Discussion

MAMA_MOVE GAIA After Treatment shows that a supervised physical exercise program administered in group classes with limited training equipment can prevent the decline in the global health status of HRQOL in women after BC primary treatment with curative intent. Moreover, this study also shows that the physical exercise program is safe and can improve physical function, sexual function, body composition and physical fitness.

We opted for a prospective, double-phase, longitudinal trial design to control for within-subject individual differences and, at the same time, to include patients from a real clinical practice setting, in contrast to the necessary homogeneity of the arms of a randomized control trial. Furthermore, the inclusion of multiple evaluation moments enabled us to capture changes in outcome behaviour over time and detect whether the effects of the intervention were sustained over time.

It has been widely demonstrated that physical exercise, particularly combined exercise programs and supervised sessions, after BC treatment improves the global health status of HRQOL, independent of individual training or in group classes (Abdin et al., 2019; Joaquim et al., 2022). We assumed in our trial that the HRQOL was stable during the CP and increased during the IP. However, our observation was contrary: the global health status of HRQOL decreased during the CP and stabilized during the IP. These findings

suggest a buffering effect of physical exercise, preventing the steady decrease in global health status during the survivorship phase of BC patients. These findings are consistent with the scores and evolution of HRQOL in the BC survivors' population after primary treatments. Firstly, the global status score of the population of our study in the CP and IP was similar to those measured in a recent meta-analysis [64.72 points (95% CI 59.24 to 70.20)] (Javan Biparva et al., 2022). Additionally, HRQOL during BC survivorship, after primary treatments, is characterized by an improvement during the first year of follow-up after the end of primary treatments (Ganz et al., 2004; Härtl et al., 2010; Moro-Valdezate et al., 2013), followed by a decline associated with long-term side effects (Dow et al., 1996). In fact, in our trial, with a mean time from the last primary treatment of 1.4 years ±1.8, this decline was observed in the CP.

Among the other domains of HRQOL, physical function and sexual functioning were stable during the CP and increased during the IP, which also favoured the exercise programme to improve HRQOL.

Overall, our HRQOL findings are aligned with the pan-habilitation concept: the sooner physical exercise interventions are implemented during the cancer survivorship continuum, the better the benefit for cancer patients and survivors (Squires et al., 2018; Toohey, 2020).

CRF increased during the CP and stabilized during the IP. Patients underwent three assessments of CRF. One could postulate that there was a learning effect from the first to the second assessment, as was recently demonstrated in a trial in which VO_2peak increased on average by ≈0.9 mL O2·kg^{-1}.min^{-1} (≈4%) from the first to the second assessments in a similar population (Scott et al., 2020). Considering the second measurement as a baseline assessment, a possible conclusion would be that there was no difference in CRF after the IP. The increase during the CP in our study was almost twice as high, and the final values were almost two times greater than the aforementioned trial, which could be due to a higher baseline fitness level of our study participants. The fact that more than half of the participants complied with the recommendations for aerobic MVPA is in line with these findings (Campbell et al., 2019). In fact, in a population with a high baseline CRF, there is a small margin for improvement.

Upper limb strength and lower limb functionality improved during the trial in both the control and exercise phases. As with CRF, one could postulate that there was a learning effect during the CP and positive effects of physical exercise during the IP. A previous study also showed that men with prostate cancer undergoing androgen depletion improved muscle strength after 32 weeks, both in the control and exercise groups, although to a lesser extent in the control group (Uth et al., 2016). This study also showed a nonsignificant mean difference between control and exercise of 1.86 repetitions in the STS (Uth et al., 2016). Likewise, in our study, participants increased their performance in the STS by 2.1 repetitions at the end of the exercise training program compared to exercise baseline.

Regarding body composition, we were able to demonstrate a beneficial effect in all variables. While body weight and BMI were stable during the CP and decreased during the first eight weeks of the IP, waist circumference increased during the CP and decreased during the entire IP. These findings are in line with the literature showing the positive role of physical exercise in weight control in a similar overweight and obese BC population (Brown et al., 2021). This is of particular importance, as weight control confers better

prognosis in terms of recurrence and death by BC (Holmes & Kroenke, 2004; Schapira et al., 1991; Wisse et al., 2018).

In this trial, we observed 18% dropouts in addition to those due to the COVID-19 pandemic and an adherence of 61.7 ± 27.6%, with only 35% of patients participating in at least 80% of the training sessions. In the previously published REACT trial, BC survivors were less likely to report high compliance with resistance and endurance exercises than survivors of other types of cancer (Kampshoff et al., 2016). Thus, education on behavior changes and active involvement of BC patients in survivorship programs is crucial to support long-term survival (Schmitz et al., 2021).

The beneficial effect of physical exercises seen in the IP of this study highlights the importance of establishing physical exercise programmes in daily clinical practice.

Limitations and strengths

This trial has some limitations that should be considered when analysing the current findings. Firstly, this trial was affected by the COVID-19 pandemic, which, in addition to the expected dropout rate, may have led to a diminished power to detect differences in the main outcome, in particular improvements in HRQOL during the exercise intervention. Secondly, the assessment of CRF was also substantially affected by the COVID-19 pandemic, not being performed at all prespecified timepoints. To ensure the consistency and integrity of the data during the comparative analysis of the control and exercise periods, only those patients who have completed all the pre-planned assessments over the designated periods were considered in the analysis. Although this approach might have introduced an element of bias, no differences in the demographic and clinical characteristics were observed between completers and non-completers at baseline. This suggests that no systematic confounding factors existed between these two groups that might significantly influence the results. Thirdly, the non-inclusion of pre-familiarization physical and functional tests could have allowed for some learning effects during the CP of the trial, which may have increased the CP values before the exercise intervention, limiting the interpretation of the results. Fourthly, the assessment of the eligibility criteria of not meeting the physical activity recommendations by non-validated questions might have led to the inclusion of physically active patients. Fifthly, our study was not designed to determine an optimal dose for clinically meaningful changes. Future research could focus on understanding the individual factors that might influence the relationship between adherence and health outcomes. This could help in determining an optimal dose of exercise for different patients. Lastly, the inclusion of a control period instead of an independent parallel control group has a few disadvantages, such as temporal changes in internal (e.g. disease progression and learning effects) or external factors (e.g. seasonality, lifestyle changes and medical treatments) over the study period that can impact the results. On the other hand, since each subject served as their own control, the individual variability was potentially reduced with this double-phase, longitudinal trial design. Thus, this design could enhance the sensitivity to detect the effects of the exercise intervention and might decrease the number of subjects required to achieve the same statistical power. Finally, this design ensures that all patients have access to the prospective benefits of the intervention.

Despite these limitations, we believe that the presented results of a pragmatic and structured intervention in a contemporary setting could be of relevance to the

field. We were able to show that the physical exercise program led to a buffering effect on the decline in global health status, suggesting that exercise training could have an overall positive effect in limiting the decrease in the global health of women after BC treatment. Interestingly, the self-reported perception of improvements in physical function and sexual function improved only during exercise training. We were also able to show significant improvements in muscle strength and physical function. Moreover, in outcomes where the learning effect was limited, such as BMI and waist circumference, patients improved only after the exercise training phase.

Conclusion

Physical exercise is not yet part of daily clinical practice in many countries. This study aimed to investigate the efficacy and safety of a supervised in-group combined exercise training program with limited equipment (Schmitz et al., 2021). Our results confirmed that physical exercise is a safe intervention and positively influences the HRQOL, physical function, sexual function, physical fitness, and body composition of BC survivors. The MAMA_MOVE GAIA After Treatment trial allowed us to open a community program named MAMA_MOVE GAIA Comunidade, under a partnership with the same local gymnasium, in which we have included more than 100 patients. Both the trial and the community programs support the implementation of group class programs supervised by certified exercise professionals as an option for physical exercise in the breast cancer survivor population.

Acknowledgments

- All the participants, for believing in the trial and agreeing to make part of it;
- Cristiana Marques and Joana Marinho for recruiting patients and giving support during the assessments;
- Sónia Gonçalves for support during the assessments;
- Enrique Dias for recruiting patients; Helena Guedes for the efforts to obtain last-minute missing data, essential to complete the final analysis;
- Ricardo Lopes, Patrícia Mendanha and Maria Inês Martins for their active role during the assessments, collecting data and supporting the supervision of the trainings;
- Ana João Tavares for support in scheduling and supervising the treadmill tests;
- Maike Collienne for the in-depth review of the manuscript;
- AICSO for supporting the trial under the ONCOMOVE® program and creating the conditions for its development;
- Solinca for believing in the trial since the first minute, for the partnership and for providing the conditions for the in-group classes.
- Direção Geral de Saúde (DGS) for accepting the trial as one of the pilot projects 'Recomendação da Atividade física no Serviço Nacional de Saúde para utentes com doenças crónicas', under the Programa Nacional para a Promoção da Atividade Física.
- Vera Afreixo is supported by the Fundação para a Ciência e a Tecnologia (FCT), through CIDMA - Center for Research and Development in Mathematics and Applications, within project UIDB/04106/2020 and UIDP/ 04106/2020.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

Liga Portuguesa Contra o Cancro - Núcleo Regional do Norte: grant up to 2000 € euros for training material and digital hand manometerCâmara Municipal de Gaia: travel grant for the participants up to 2500 €Instituto Português do Desporto e Juventude: grant of 5000 € under the Programa Nacional de Desporto para todos 2019, used for promotion of the trial and medical material (compression arm sleeves for participants with lymphoedema)Solinca Classic, SA, SC Fitness, SA, Lisbon: provision of a training studio and a certified exercise physiologist for the in-group classesUniversity of Maia: provision of the chest-based heart rate monitoring device system and the accelerometers.

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