UNIVERSITÀ DI GENOVA

PHD PROGRAM IN SCIENZE DELLA SALUTE

Promozione delle performance fisiche e della qualità della vita in donne operate per tumore alla mammella mediante attività fisica adattata e olio ozonizzato
Health through Ozonized oil and Physical Exercise for breast cancer - HOPE project

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TABLE OF CONTENTS

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ABSTRACT

Background: Breast cancer survivorship is frequently characterised by persistent impairments in cardiorespiratory fitness, muscle strength and health-related quality of life (QoL). The HOPE project evaluated a multicentre Exercise Therapy (ET) programme, with exploratory adjunctive use of high-ozonide ozonised oil, in women who had completed primary treatment for breast cancer.

Methods: HOPE was a retrospective, multicentre observational study conducted across Italian Breast Units. Fifty-six women were screened; one declined participation. Thirty-five were allocated by routine clinical practice to ET plus high-ozonide ozonised oil (HOO), and twenty to ET alone. During the 8-week programme, five participants per group discontinued, leaving 45 completers (IG n = 30; CG n = 15) for analysis. ET was delivered twice weekly in a hybrid format (one supervised in-person session and one remote session). Outcomes were assessed at baseline (T0) and after 2 months (T1) and included estimated VO_2max (2-km walk test), QoL (SF-36; PCS/MCS and domains), estimated 1RM strength, anthropometry/body composition (BIA), circumferences, and lower-limb function (SPPB). Within-group changes were tested with Wilcoxon signed-rank tests; between-group comparisons of change scores (Δ=T1–T0) used Mann–Whitney U tests (two-sided α=0.05).

Results: In the total cohort, VO_2max increased significantly (mean Δ +4.42 ml/kg/min; p = 0.001; n = 38). Improvements were significant in IG (mean Δ +5.82; p = 0.002) but not in CG (mean Δ +1.73; p = 0.196), with no significant between-group difference in ΔVO_2max (p = 0.115). QoL improved, with significant increases in PCS (mean Δ +3.65; p = 0.0001) and MCS (mean Δ +3.78; p = 0.0005); between-group differences in ΔPCS and ΔMCS were not significant (p = 0.87 and p = 0.914, respectively). Maximal strength increased across all assessed muscle groups (deltoid, latissimus dorsi, pectoralis, quadriceps;

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all p≤0.0002). Weight, BMI and fat mass decreased (p≤0.0029), whereas fat-free mass did not change significantly. Peripheral circumferences showed selective reductions (e.g. chest and thigh), while waist and hip circumferences were unchanged. SPPB change did not reach significance (mean Δ +0.11; p = 0.059), consistent with near-ceiling baseline performance.

Conclusions: A short, supervised hybrid ET programme implemented in routine Breast Unit care was associated with clinically meaningful improvements in cardiorespiratory fitness, QoL and strength, alongside favourable changes in body composition. No statistically significant between-group differences were detected for primary or secondary outcomes over 8 weeks, suggesting that the exercise component was the dominant driver of benefit, while any additive effect of high-ozonide ozonised oil remains unproven and warrants prospective controlled evaluation.

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INTRODUCTION

Breast cancer is the most frequently diagnosed malignancy among women and remains one of the leading causes of cancer-related mortality worldwide. According to the most recent epidemiological estimates, more than 2.3 million new cases of breast cancer were diagnosed globally in 2020, with approximately 685,000 deaths recorded in the same year [1]. Projections for 2050 indicate a further increase in incidence, with an estimated 3.2 million new cases and approximately 1.1 million deaths annually [2]. In Italy, breast cancer remains the most common malignancy among women, with approximately 55,700 new cases estimated in 2023, including a concerning rise among younger age groups [3].

In recent decades, advance in early diagnosis, systemic treatments, and conservative surgical approaches have contributed to improving survival rates. Nevertheless, despite these, breast cancer remains a public health priority due to the persistent burden of mortality and the complex psychological, functional, and social consequences associated with the disease and its treatment. Breast cancer survivors frequently experience a range of persistent challenges, including chronic fatigue, lymphoedema, muscle weakness, balance impairments, anxiety, depression, and an overall reduction in quality of life [4]. These concerns have led to a redefinition of the concept of "cancer survivorship," which now encompasses functional rehabilitation, prevention of recurrence, and promotion of overall health.

Among the modifiable risk factors for cancer recurrence, body composition—specifically excess visceral adiposity—has been extensively documented. In postmenopausal women, adipose tissue represents the primary source of estrogen production through the activity of the enzyme aromatase,

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thereby promoting the proliferation of estrogen-dependent tumour cells [5]. Furthermore, visceral adiposity is closely associated with a state of chronic low-grade inflammation. This condition is characterized by the persistent activation of pro-inflammatory mediators such as interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α), and C-reactive protein (CRP). These mediators have been shown to promote tumour growth and suppress anti-tumour immune responses [6].

In this context, regular physical activity emerges as a key strategy not only for improving patients' quality of life but also for modulating the molecular mechanisms underlying tumour progression. Several studies have demonstrated that physical exercise program can reduce systemic inflammation by modulating the secretion of pro- and anti-inflammatory cytokines [7]. Additionally, physical activity influences hormonal regulation by lowering insulin levels and improving insulin sensitivity, thereby exerting favourable effects on the tumour microenvironment. From an immunological perspective, exercise enhances anti-tumour immune function by stimulating the activity of natural killer cells and cytotoxic T lymphocytes [8]. Furthermore, epigenetic and metabolic effects have been described, including modulation of intracellular signaling pathways involved in cell proliferation and apoptosis, such as the PI3K/Akt/mTOR pathway [9].

The American College of Sports Medicine (ACSM) and several international scientific societies recommend the inclusion of adapted physical activity programs within oncological care pathways, emphasizing their benefits in terms of cardiorespiratory fitness, muscle strength, body composition, fatigue reduction, and psychological well-being [10, 11, 12]. In addition to the physical and functional benefits, physical activity is associated with a statistically significant reduction in the risk of breast

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cancer recurrence and mortality, with estimates ranging from 24% to 40% among women who maintain an active lifestyle after diagnosis [13].

Concurrently, there has been growing interest in nutritional and integrative interventions aimed at supporting cancer treatments. Among these, the use of highly ozonated oil (HOO), classified as a supplement for special medical purposes and recognized at the European level, has gained attention for its potential anti-tumour properties. Preliminary preclinical and clinical studies suggest that HOO may selectively target tumour cells by inducing mitochondrial oxidative stress, promoting apoptosis, and enhancing the effects of chemotherapy and radiotherapy [14, 15]. However, clinical evidence regarding the use of ozonated oil remains limited, and large-scale controlled clinical trials are needed to confirm its efficacy.

Within this framework, the HOPE project (Health through Ozonized oil and Physical Exercise for breast cancer) aims to retrospectively evaluate the effectiveness of combining Exercise Therapy with ozonated oil in improving aerobic capacity and quality of life in women who have survived breast cancer. The ultimate goal of the project is to contribute to the body of scientific evidence supporting integrated health promotion strategies in oncology, based on a multidimensional and personalized approach to cancer survivorship.

This thesis presents the HOPE project, a retrospective observational study designed to evaluate the effectiveness of a combined intervention consisting of Exercise Therapy and the prior intake of a supplement for special medical purposes - highly ozonized oil - in improving aerobic capacity and quality of life among breast cancer survivors.

A total of 56 women were recruited from several certified Breast Units across Italy, where they

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participated in a supervised program lasting two months. Functional and psychometric assessments were performed both at baseline and after completion of the intervention. The study began in November 2023 and was carried out in collaboration with multiple breast cancer centres (Breast Unit). Preliminary observations indicated marked improvements in quality-of-life outcomes among participants who engaged in the exercise programme.

The HOPE project has several relevant implications for clinical practice and survivorship strategies in breast cancer. The inclusion of Exercise Therapy led to meaningful improvements not only in physical performance, but also in patients' ability to manage daily living activities. Participants showed enhanced cardiorespiratory fitness, muscle strength, and functional autonomy. Additionally, the intervention had a positive impact on mood, reducing symptoms of anxiety and psychological distress, and contributing to a more favourable emotional balance.

These outcomes underscore the importance of a comprehensive approach to tertiary prevention. By addressing both physiological and psychosocial domains, the HOPE protocol aligns with current models of personalised medicine and survivorship care.

A notable strength of the project lies in its feasibility within clinical settings. The personalized and supervised exercise programme was safely implemented in certified Breast Units, without interfering with standard medical care. This real-world applicability enhances its potential for integration into routine oncology practice.

Looking forward, the HOPE project offers a foundation for future expansion. A larger-scale, multicentre version of the protocol - possibly involving a broader geographic network and a higher number of

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participants - could provide further validation of these preliminary findings. Such an initiative would strengthen the case for incorporating exercise-based strategies and nutritional support into structured, multidisciplinary care pathways for breast cancer survivors.

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STATE OF THE ART

Exercise Therapy in Breast Cancer

Exercise Therapy (ET) constitutes an evidence-based intervention, structured and tailored according to the patient's clinical-functional status and aimed at promoting health and preventing complications associated with chronic conditions. Unlike competitive or performance-based sport, ET serves as a complementary approach, which is particularly pertinent in oncology care.

In the context of breast cancer, incorporating ET into treatment pathways has proven effective in improving several clinical outcomes, including cardiorespiratory function, fatigue reduction, weight control, sleep quality, and mood enhancement [16]. A robust body of literature indicates that regular physical exercise supports hormonal balance, decreases insulin resistance, and lowers circulating levels of pro-tumoral factors such as IGF-1 and leptin [10, 11].

The American College of Sports Medicine (ACSM) recommends at least 150 minutes per week of moderate-intensity aerobic exercise for breast cancer survivors, along with two weekly sessions of resistance and flexibility training [12]. Exercise has additionally demonstrated benefits including enhancing therapeutic adherence, minimising postoperative complications, and supporting lymphatic function recovery in individuals affected by lymphedema [17, 18].

Adherence to exercise programmes is significantly higher when prescribed by the medical team, with completion rates approaching 100% in prospective observational studies [19]. Furthermore, structured exercise interventions have yielded significant improvements in emotional well-being, mood, and sleep quality [19]. Several studies involving cancer survivors have also documented consistent

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enhancements in quality of life, aerobic capacity, and functional performance [20]. In prospective cohorts, physical activity has been associated with up to a 40% reduction in recurrence risk and prolonged survival compared to sedentary patients [21, 22].

Moreover, Exercise Therapy's benefits are not confined to breast cancer with recent research demonstrating its effectiveness in improving strength, VO_2max, and overall quality of life among survivors of other solid tumours and haematological malignancies [23, 24]. However, a considerable gap persists in the systemic implementation of reproducible, structured exercise protocols within standardised care pathways for breast cancer survivors. The HOPE Project is designed to help bridge this gap by offering a large-scale, retrospective observational model to validate the effects of ET on quality of life and aerobic capacity within a real-world, multicentric setting [25, 26]. The HOPE experience may thereby serve as a scalable model for integrating ET into long-term follow-up care across different tumour types.

Chronic inflammation and recurrence risk

Chronic inflammation is a critical pathogenic mechanism in the onset and progression of breast cancer. Visceral adipose tissue functions as an active source of pro-inflammatory cytokines (e.g. IL-6, TNF-α) and chemokines, fostering malignant transformation, neo angiogenesis, and suppression of anti-tumour immunity [6, 27].

Sedentary behaviour, obesity, and insulin resistance together propel a chronic systemic inflammatory state, thereby sustaining a microenvironment conducive to tumour recurrence. In contrast, regular

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physical activity stimulates the secretion of anti-inflammatory cytokines (e.g. IL-10) and muscle-derived myokines such as IL-6, which exert protective effects on immune function and glucose metabolism [7].

At a molecular level, physical activity can modulate key intracellular pathways involved in inflammation and cell proliferation. Notably, it has been shown to diminish NF-κB activation, thereby tempering pro-inflammatory mediator production and creating a less tumour-promoting milieu [28]. Emerging evidence also suggests that exercise may favourably influence the epigenetic landscape of immune cells, altering the expression of inflammatory genes and enhancing anti-tumour immune responses.

Ozonised Oil in oncology

Highly Ozonated Oil (HOO), which is recognised in Europe as a medical food for special purposes, has gained scientific attention for its potential tumour-selective cytotoxicity observed in in vitro studies. Such findings have sparked interest in its possible role as an adjuvant in oncology.

The principal mechanisms proposed include the controlled generation of reactive oxygen species (ROS), induction of mitochondrial oxidative stress, disruption of bioenergetic processes, and apoptotic activation via caspases [14, 15]. In vitro, HOO has demonstrated synergistic effects with chemotherapeutic and radiotherapeutic agents and may help maintain redox balance in healthy cells, potentially reducing treatment-related toxicity [29].

Within the HOPE Project, HOO supplementation is incorporated as an adjunct alongside Exercise Therapy, with the hypothesis that it may enhance exercise-induced improvements in performance and recurrence prevention. Nonetheless, current clinical evidence is limited, and robust, large-scale

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randomized controlled trials are essential to ascertain HOO's efficacy and therapeutic positioning in oncology.

Quality of life in Breast Cancer

Quality of life (QoL) is a paramount endpoint in the management of breast cancer survivors. Fatigue, anxiety, depression, and altered body image are commonly experienced even years after treatment completion [16, 30].

Multiple systematic reviews and meta-analyses have underscored the efficacy of physical activity in enhancing QoL among breast cancer patients, with demonstrable improvements in psychological well-being, physical function, and social interaction [31, 32]. Complementary therapies—such as yoga, meditation, relaxation techniques, and psycho-oncological support—also positively influence subjective well-being [32].

Assessing QoL using validated instruments (e.g. EORTC QLQ-C30, FACT-B, SF-36) is now recommended across clinical settings as a crucial parameter for tailoring therapeutic interventions. In the HOPE Project, QoL enhancement is a core endpoint, with Exercise Therapy and nutritional supplementation evaluated through multidimensional indicators, aiming to restore active, autonomous, and fulfilling lives for survivors.

Strategies for tertiary prevention in Breast Cancer

Tertiary prevention targets relapse prevention, reduction of long-term sequelae, and improvement of functional outcomes. In breast cancer, this approach relies on a multidisciplinary integration of oncological follow-up, structured physical exercise, nutritional strategies, and psychological support.

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International agencies such as the World Cancer Research Fund/AICR [33] advocate for survivors to maintain a healthy weight, adopt predominantly plant-based diets, abstain from alcohol and engage in regular physical activity. Recent reviews [34] further confirm that health-conscious lifestyle choices post-diagnosis are correlated with lower overall mortality and enhanced relapse-free survival.

Within this framework, the HOPE Project represents an operational model to validate multidimensional strategies—encompassing Exercise Therapy and nutraceutical supplement use—for tertiary prevention. The synthesis of adapted physical activity and adjunctive nutraceutical interventions may establish a new, sustainable standard in long-term cancer care.

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MATERIALS AND METHODS

Study design

The HOPE Project is a retrospective, multicentre observational study involving women who are breast cancer survivors. The intervention consisted of participation in an Exercise Therapy (ET) programme and, for the intervention group, administration of high-ozonide ozonised oil (HOO) for two consecutive months. All participants undertook Exercise Therapy twice per week for two consecutive months in a hybrid format under the supervision of a Clinical Exercise Physiologist: one in-person session and one remote session via the Google Meet online platform. Reporting follows STROBE recommendations for observational studies [35].

Setting, centres and study period

Four Italian Breast Units, comprising five cohorts in total, participated:

- Policlinico Gemelli, Rome (n = 9) — periods: 28 April 2023–22 July 2023 and 15 March 2024–31 May 2024;
- Ospedale Castelli di Verbania (n = 4) — period: 15 September 2023–1 December 2023;
- ASL1 – Ospedale Civile di Sanremo (n = 3) — period: 24 January 2024–27 March 2024;
- Spedali Civili di Brescia (n = 29) — period: 2 April 2025–30 May 2025.

Enrolment periods differed across centres (2023 – 2025); in the analyses, centre/period will be considered for as a covariate. All participants followed the same Exercise Therapy programme, with

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individualised adjustments of volume and intensity based on baseline functional capacity, in line with principles for tailored exercise prescription in oncology [36].

Participants

Inclusion criteria

- Women with a history of breast cancer who were disease-free or in established post-treatment follow-up;
- Age 18 – 69 years;
- Ability to understand and complete the SF-36 questionnaire;
- Medical clearance for exercise issued by the Breast Unit;
- BMI ≥ 18.5 kg/m^2;
- Ability to perform the physical performance tests;
- Access to a smartphone/PC and an Internet connection.

Exclusion criteria

- Bone metastases;
- Prior chronic inflammatory bowel disease (e.g., enteritis, ulcerative colitis);
- G6PD deficiency (favism);
- Pregnancy;
- Previous intestinal surgery;

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- Clinical conditions incompatible with safe exercise.

Sample size and groups

Total sample n = 45:

- Intervention group (IG): n = 30, Exercise Therapy plus optional intake of the food for special medical purposes (HOO);
- Control group (CG): n = 15, Exercise Therapy only.

Participant flow diagram

To ensure transparency regarding participant flow and data completeness, a CONSORT flow diagram was prepared and adapted for a non-randomised observational design. Figure 1 depicts enrolment, allocation by clinical practice (no randomisation), follow-up and analysis [37].

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Numerical summary: assessed for eligibility n = 56; excluded n = 1 (declined to participate n = 1); allocated to ET+HOO n = 35 (completed follow-up n = 30; lost to follow-up n = 5); allocated to ET-only control n = 20 (completed follow-up n = 15; lost to follow-up n = 5); included in the analysis: 30 and 15, respectively (total 45). Figure 1 provides details.

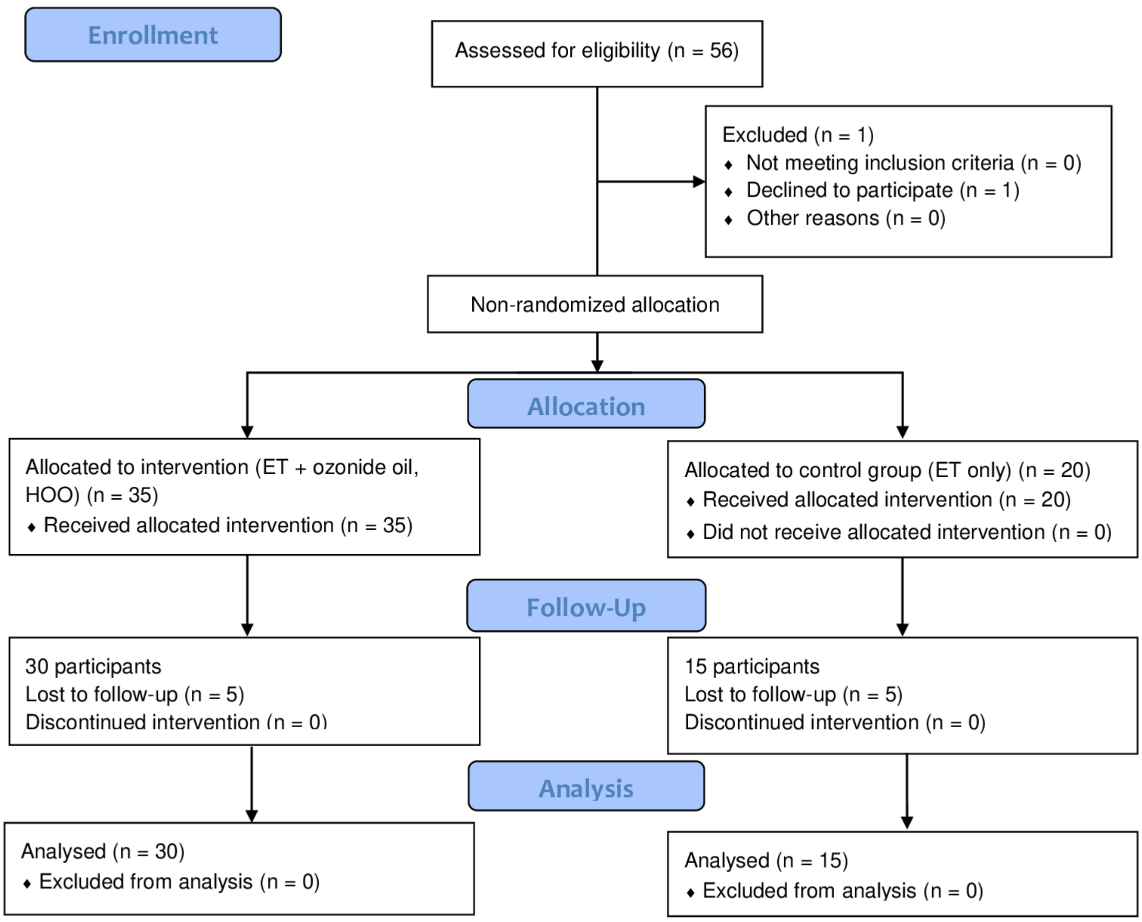

Figure 1. Participant flow diagram (CONSORT diagram, adapted for an observational study): enrolment, non-randomised allocation, follow-up, and analysis.

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Assessments and Instruments

At enrolment (T0) and at the end of the intervention after two months (T1), the following measurements were performed in both groups using identical procedures:

- Aerobic capacity/power (VO_2max) using the 2-km Walk Test (Oja & Laukkanen);
- Maximal strength (deltoid, pectoralis, latissimus dorsi (lats), quadriceps) using the 1RM test;
- Lower-limb strength and balance using the Short Physical Performance Battery (SPPB);
- Body mass, BMI, fat mass and fat-free mass by bioimpedance analysis;
- Circumferences (chest, waist, hips, arm, thigh);
- Health-related quality of life (QoL) using the 36-Item Short-Form Health Survey (SF-36).

Aerobic capacity (estimated VO_2max)

Aerobic capacity was estimated using the 2-km Walk Test performed on a treadmill (Excite+ Run 600 Unity Treadmill, Technogym) at 0% incline, with distance set to 2000 m and recording of completion time and final heart rate. VO_2max was calculated using the equation:

$$VO_2max \;\; (ml/kg/min) = 116 - (2.98 \times T) - (0.11 \times FC) - (0.14 \times age) - (0.39 \times BMI)$$

where T = time to completion (min), HR = heart rate at the end of the test (bpm), and BMI = body mass index (kg/m^2).

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The equation was validated outdoors on a level course but using a 0% treadmill may introduce bias in absolute values. However, T1–T0 differences obtained in the same setting are considered interpretable as the response to the intervention [38, 39].

Maximal strength

Maximal strength was assessed using isotonic machines, according to the muscle group: pectoralis (Technogym Selection 700 Chest Press), latissimus dorsi (Technogym Selection 700 Low Row or Venere 900 Tech–BAS, air machine), quadriceps (Technogym Selection 700 Leg Press or air-machine Leg Press), and deltoid using dumbbells (shoulder press). In clinical settings, machine-based exercises facilitate standardisation of movement, reduce stabilisation demands and may improve measurement repeatability compared with free weights [40].

The Brzycki equation was used to estimate 1RM from submaximal efforts, a widely adopted, methodologically recommended approach for load prescription [41, 42]. In general, the 1RM test demonstrates good-to-excellent test–retest reliability across multiple exercises and muscle groups, supporting its suitability as a strength outcome in clinical and non-clinical populations [43].

Brzycki formula:

$$1RM\ (kg) = \frac{P}{1.0278 - (0.0278 \times R)}$$

where P = lifted load (kg) and R = repetitions.

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Among breast cancer survivors, progressive resistance training is considered safe and does not exacerbate lymphoedema when appropriately supervised but leads to benefits in strength and symptoms [36, 44].

Lower-limb performance

Lower-limb strength and balance were assessed using the Short Physical Performance Battery (SPPB). The SPPB comprises three tests (standing balance, 4-metres walk, five chair rises), each scored 0–4, yielding a total score 0–12 (higher scores indicate better performance). Administration time was approximately 5–10 minutes, following the standardised protocol [45, 46].

Anthropometry and body composition

Body mass, BMI, fat mass and fat-free mass were assessed by bioimpedance analysis using TANITA BC-420 MA and BIA 101 BIVA® (AKERN) under standard conditions (bladder emptied, 2–4 h after the last meal, no vigorous exercise in the previous 24 h), with procedures aligned to methodological recommendations [47].

Bioelectrical impedance analysis (BIA) is a non-invasive technique that estimates body composition by passing a low-amplitude alternating current (typically 50 kHz) through the body and measuring whole-body resistance (R) and reactance (Xc); from these, impedance (Z) and phase angle (arctan Xc/R) are derived. Validated prediction equations that incorporate height, sex and age convert these electrical properties into estimates of total body water and fat-free mass, from which fat mass is obtained.

With TANITA BC-420 MA, participants stood barefoot on the scale with footplate electrodes integrated at the base, maintaining an upright posture during measurement. For AKERN BIA, participants were positioned supine and four disposable electrodes were applied on the right side in a tetrapolar

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configuration: two on the dorsum of the hand and two on the dorsum of the foot, ensuring direct skin–electrode contact.

Circumferences

The following circumferences were recorded: chest/thorax, waist, hips, right and left upper arm (biceps)—to detect asymmetries compatible with lymphoedema—and right and left thigh (quadriceps). Measurements were taken with a non-stretchable tape (precision 0.1 cm), in a standardised posture, with the tape parallel to the floor and without skin compression. Each site was measured twice (a third time if the difference was >0.5 cm), and the mean was used; where possible, the same assessor performed T0 and T1 to reduce variability. For the waist, the site was identified at the mid-point between the lower costal margin and the iliac crest, with reading at the end of a normal expiration; for the hips, at the point of maximum gluteal prominence [48]. For the upper arm (biceps), circumference was measured at the mid-point between the acromion and olecranon with the arm relaxed alongside the trunk; bilateral assessment enables quantification of asymmetries useful for lymphoedema monitoring [49, 50]. For the thigh (quadriceps), the measurement was taken at mid-thigh—half the distance between the inguinal fold and the superior border of the patella—while standing; the use of reproducible landmarks and duplicate measurements reduces anthropometric error [51].

Quality of life

Health-related quality of life was measured with the SF-36, a generic 36-item questionnaire. It yield eight domains: Physical Functioning (PF), Role-Physical (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Role-Emotional (RE), Mental Health (MH). There are two summary indices, the Physical Component Summary (PCS) and Mental Component Summary (MCS). Domain scores are

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transformed to a 0–100 scale (higher scores indicate better health status). Administration requires approximately 8–10 minutes and is self-administered; interpretation follows the official scoring manuals and, where available, clinically important differences for each domain [52].

Interventions

The intervention group (IG) completed follow-up by performing Exercise Therapy (ET), with intake of the food for special medical purposes according to protocol and received tertiary prevention recommendations for breast cancer (balanced diet, physical activity, stress management, avoidance of smoking and alcohol).

The control group (CG) completed follow-up by performing Exercise Therapy according to the training protocol and received the same tertiary prevention recommendations.

Group allocation reflected real-world clinical practice (no randomisation). Concomitant treatments and clinical covariates (age, BMI) were recorded to control for confounding in the analyses.

Exercise Therapy intervention

Exercise Therapy followed American College of Sports Medicine (ACSM) guidance and the FITT principle (Frequency, Intensity, Time, Type), enabling individualised programmes consistent with each participant's capacity.

Exercise Therapy was delivered in dedicated facilities equipped with isotonic machines, cardio-fitness equipment, mats, dumbbells and elastic bands, either within the hospital or at accredited centres, following participant registration and insurance coverage.

In-person sessions (total duration 60 minutes):

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- Warm-up: low-intensity joint mobility with controlled range of motion (ROM) (5 minutes);
- Aerobic activity: moderate intensity (40–59% VO_2R; 64–76% HRmax; Borg 12–13) or vigorous (60–89% VO_2R; 77–95% HRmax; Borg 14–17) (20 minutes);
- Resistance training: 2 circuits × 3 exercises on isotonic machines; time-based work, 60 seconds per exercise at moderate intensity (~40–50% 1RM) with progression up to ~60% 1RM; 30 seconds recovery between exercises; 4 sets per circuit (30 minutes);
- Cool-down: low-intensity stretching, controlled ROM (5 minutes).

Remote (telematic) sessions (total duration 60 minutes):

- Warm-up: low-intensity mobility, controlled ROM (10 minutes);
- Resistance training: 2 circuits × 4 exercises using bodyweight/elastics/dumbbells; time-based work, 60 seconds per exercise at moderate intensity (~40–50% 1RM), with a progressive increase in task complexity over time; 30 seconds recovery; 3 sets per circuit (40 minutes);
- Cool-down: low-intensity stretching, controlled ROM (10 minutes).

Consistent with observed performance improvements, in-person training incorporated intensity progression, whereas remote programmes underwent an increase in volume (total amount of exercise) at the end of the first month. Tables A – C provide detailed exercise lists for each session type.

In-person training	
Joint mobility – head and neck	1 minutes

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Upper-limb circumduction	1 minutes
Circuit 1 (60 seconds work / 30 seconds recovery) × 4 sets	
Chest press	40% RM
Row	40% RM
Leg extension	40% RM
Rest	2 minutes
Circuit 2 (60 seconds work / 30 seconds recovery) × 4 sets	
Shoulder press (overhead press)	40% RM
Lat pulldown	50% RM
Leg press	50% RM
Rest	2 minutes
Cardio (choose one machine)	50 - 60 % HR Max
Treadmill / cycle ergometer / elliptical	20 minutes

Table A. In-person training—structure and parameters (timings, sets, %1RM, cardio).

Online session 1	
Joint mobility – head and neck	1 minutes
Upper-limb circumduction	1 minutes
Pelvic tilts in quadruped (anterior/posterior)	10 repetitions

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Circuit 1 (60 seconds work / 30 seconds recovery) × 3 sets	
Quadruped hip extension (alternate legs)	1 minutes
High plank (hands)	(10 seconds – 20 seconds rest) x 2 sets
Band front raises	1 minutes
Band shoulder press	1 minutes
Rest	2 minutes
Circuit 2 (60 seconds work / 30 seconds recovery) × 3 sets	
Floor chest press + floor fly (alternate or half-and-half)	1 minutes
Isometric palm press against bent knees (supine, hook-lying)	1 minutes
Band biceps curl	1 minutes
Forearm plank on fitball	10 seconds x 2 sets
Rest	2 minutes
Upper-limb stretching	2 minutes
Breathing practice (diaphragmatic, thoracic)	2 minutes

Table B. First online training—structure and parameters (timings, sets).

Online session 2 (after 1 month)	
Joint mobility – head and neck	1 min

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Upper-limb circumduction	1 min
Pelvic tilts in quadruped (anterior/posterior)	10 reps
Threat the neddle (thoracic rotation in quadruped)	1 min
Circuit 1 (60 seconds work / 30 seconds recovery) × 3 sets	
High-knee march / “skip” (low-impact)	(10 seconds on / 10 seconds off) × 4 sets (slightly exceeds 60 seconds; acceptable as month-2 progression)
Overhead press + upward arm raise	1 minutes
Alternating forward lunges	1 minutes
Biceps curl (band or dumbbells)	1 minutes
Rest	2 minutes
Circuit 2 (60 seconds work / 30 seconds recovery) × 3 sets	
Lateral lunges	1 minutes
Dumbbell chest press + chest fly, supine on fitball	1 minutes
Squat to chair with push press	1 minutes
Forearm plank on fitball	30 seconds x 2 sets
Rest	2 minutes
Upper-limb stretching	2 minutes
Breathing practice (diaphragmatic, thoracic)	2 minutes

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Table C. Second online training—structure and parameters (timings, sets).

Safety strategies were implemented for participants with or at rick of lymphoedema (conservative progressions, volumetric monitoring where available, and education on warning signs), consistent with the literature on the safety of resistance training [44]. Participants received home-based instructions for low-impact activity on non-structured days (light walking 20–30 minutes). Adherence to medical recommendations is known to improve compliance with Exercise Therapy programmes [36].

High-ozonide ozonised oil intervention

In the Exercise Therapy + high-ozonide ozonised oil group, ozonised oil was administered for 8 weeks in addition to exercise. The product used was O3ZONE 00® (manufacturer: O3 ZONE LIMITED, Acquaviva, Republic of San Marino). Dosage: 4 capsules/day (2 in the morning and 2 in the evening). Ozonide titration, batch number, detailed formulation, and manufacturing certifications will be reported according to the product label and the manufacturer's documentation (Table D). The rationale for use remains exploratory and is based on preclinical/in vitro evidence concerning mitochondrial oxidative stress, redox modulation, and potential synergies with anticancer therapies [14, 15, 29]. Participants received instructions on mode and timing of administration. At the time of writing, clinical evidence for high-ozonide ozonised oil in oncology remains limited; its use in the project is exploratory and integrated with Exercise Therapy, with a clear distinction between a priori hypotheses and observed outcomes.

Ingredients	Dosage for adults 3 capsules	% VNR for adults	Quantity for 100 g

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Piano Nazionale di Ripresa e Resilienza Missione 4, componente 1 "*Potenziamento dell'offerta dei servizi di istruzione: dagli asili nido all'Università*

Ozonated sunflower Oil	450 mg		50 g
Pantothenic acid	18 mg	300%	1 g
Vitamin B6	4,2 mg	300%	0,46 g
Thickner: Calcium phosphates; capsule (coating agent: hydroxypropyl-methylcellulose, gelling agents: pectin, gellan gum); ozonated vegetable oil**; anti-caking agent: magnesium salt of fatty acids; pyridoxine hydrochloride (Vitamin B6). **Origin of the ozonated sunflower oil: extra European Union. *%VNR (nutrient Reference Values) per day for vitamins and minerals(adults) - Reg. (EU) No. 1169/2011.			

Table D. Declared composition of O3ZONE 00®

Outcomes (endpoints)

- Primary: VO_2max (Δ T1–T0); health-related quality of life (SF-36 domain and summary scores (PCS, MCS); Δ T1–T0).
- Secondary: Strength (estimated 1RM); body composition (fat mass, fat-free mass, BMI).
- Exploratory: Adverse events related to exercise / high-ozonide ozonised oil.

Data collection procedures

Scope and timing

Assessments were conducted at two time-points: T0 (baseline at enrolment) and T1 (after 2 months of intervention), across all participating centres, following standardised procedures and STROBE-

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compliant reporting [35]. T0 and T1 measurements were performed in the same setting, preferably at the same time of day and by the same assessor where feasible, to reduce within-subject variability.

Standardised testing sequence

1. Brief medical history/eligibility check and review of concomitant therapies;
2. Anthropometry and BIA (body mass, BMI, fat mass/fat-free mass) under standard conditions (morning, bladder emptied, 2–4 h after last meal, no vigorous exercise in the previous 24 h) according to methodological recommendations [47];
3. Circumferences: chest; waist (mid-point between the inferior costal margin and iliac crest, during quiet expiration); hips (maximum gluteal prominence) (Ross et al., 2020 [48]); right/left upper arm (biceps) (mid-point acromion–olecranon); right/left thigh (quadriceps) (mid-thigh). Two measurements per site (a third if difference >0.5 cm), using the mean value; same assessor at T0/T1 where possible [49, 50, 51];
4. Maximal strength (estimated 1RM using the Brzycki equation from submaximal attempts) on isotonic machines (Chest Press, Low Row/air machine, Leg Press/air machine; deltoid with dumbbells—overhead press). Exercise-specific warm-up; 2–3 min rest between attempts; record P (kg) and R (repetitions) for 1RM calculation. Machine-guided exercise facilitates standardisation and repeatability [40];
5. Aerobic capacity: 2-km walk test on treadmill (Technogym Excite+ Run 600 Unity, 0% incline). Distance set to 2,000 m; record completion time and final heart rate. VO_2max calculated using the equation validated outdoors [38, 39]. As the original equation was developed for a level

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outdoor course, absolute treadmill values should be interpreted with caution, whereas within-setting pre–post changes are informative;

6. SPPB (balance, 4-metres walk, five chair rises; total 0–12) according to the original procedure [45];
7. Quality of life (SF-36), self-administered (8–10 min), 0–100 scoring for 8 domains; PCS/MCS computed per manuals [52].

Pre-test standardisations

Light clothing and usual footwear; removal of metallic objects for BIA; documentation of medications affecting HR/BP; abstention from alcohol and caffeine for 12 h; no vigorous exercise for 24 h [47]. Brief warm-up before strength tests and the 2-km walk; termination criteria: chest pain, worsening dyspnoea, dizziness, abnormal BP, or participant request [36].

Personnel and training

Exercise Therapy supervision was provided exclusively by Clinical Exercise Physiologists (LM-67 Master's degree). Assessors followed Standard Operating Procedures (SOPs) and centre-specific operational manuals. Where feasible, the same assessor performed T0 and T1 to maximise intra-rater reliability.

Safety

Adverse events related to exercise / high-ozonide ozonised oil were collected prospectively on a dedicated form (type, severity, relatedness), with predefined management procedures. In the presence (or risk) of lymphoedema, conservative progressions, volumetric/circumferential monitoring, and

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Piano Nazionale di Ripresa e Resilienza Missione 4, componente 1 "*Potenziamento dell'offerta dei servizi di istruzione: dagli asili nido all'Università*

education on warning signs were employed, consistent with evidence on the safety of resistance training in women with breast-cancer-related lymphoedema [36, 44].

Data management and quality control

Data were captured on paper Case Report Form's, with pseudonymisation using centre ID + participant ID. Consistency checks (range checks, double data entry on a random sample) and inter-centre audits were implemented prior to database lock. Final datasets are stored in a secure repository with role-based access and version traceability, in compliance with GDPR.

Statistical analysis

Analyses were performed using KNIME Analytics Platform (KNIME AG, Talacker 50, 8001 Zurich, Switzerland). Non-parametric tests were used: the Wilcoxon signed-rank test for within-group comparisons (T1 vs T0) and the Mann–Whitney U test for between-group comparisons of change (Δ = T1–T0). Continuous variables were summarised as mean ± SE for within-group analyses and as median [IQR] for between-group comparisons. Two-sided tests were performed with $\alpha = 0.05$. Ninety-five percent confidence intervals (95% CI) were reported. Graphs were generated using GraphPad Prism (GraphPad Software, Boston, Massachusetts USA)

Bias and mitigation strategies

- Selection: retrospective design; participant flow by centre and eligibility criteria described [35].
- Performance/adherence: measured systematically; sensitivity analysis excluding adherence <70%.

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- Measurement: test standardisation (same order at T0/T1; same time-window for BIA; same instruments where possible).

Ethical aspects

Approval was given by the University Research Ethics Committee (CERA) (protocol No. 2025/18). Data processed in accordance with GDPR. Given the retrospective nature, consent was managed according to local practice (informed consent).

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RESULTS

Sample characteristics

A total of forty-five participants were assessed at T0 (baseline) and T1 (after two months), with a mean (± Standard Error) age of 54.0 ± 5.67 years. As breast cancer survivors in the post-treatment phase, the cohort was overall deconditioned from a cardiorespiratory standpoint, as indicated by low baseline VO_2max values (19.40 ± 8.76 ml/kg/min).

Group allocation reflected routine clinical practice: the intervention group (IG) comprised thirty participants, while the control group (CG) comprised fifteen. The multicentre setting, standardised procedures and retrospective observational design are detailed in the preceding chapters, together with participant flow, measurement instruments and assessment timing, in accordance with STROBE recommendations [35].

This study is framed within exercise oncology and tertiary prevention assuming that a regular and appropriately dosed exercise programme improves cardiorespiratory and neuromuscular fitness, enhances quality of life, and promotes more favourable body-composition profiles, plausibly modulating low-grade inflammatory processes and relevant hormonal–metabolic pathways across the cancer continuum.

This rationale is consistent with recent literature that positions Exercise Therapy as a transversal health measure, from primary prevention to survivorship with operational recommendations on the minimum effective volume and on combining aerobic and resistance modalities [53].

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Primary outcomes

Aerobic capacity (VO_2max)

In the cohort (n = 38), VO_2max increased significantly over two months (Δ mean ± SE = +4.42 ± 1.11 ml/kg/min; p = 0.001). (Figure 2) (Summary Table 1)

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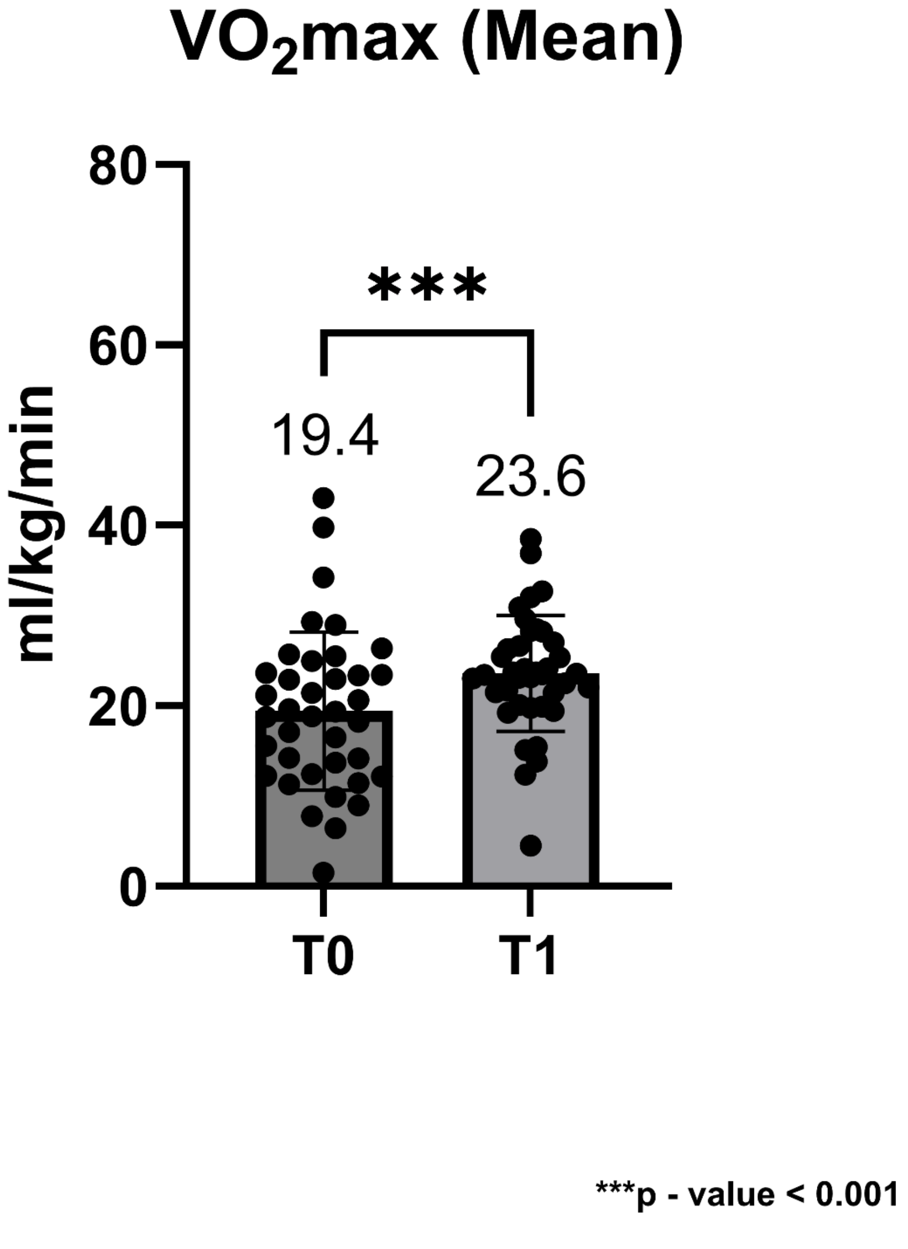

Figure 2. Change in estimated VO_2max from baseline (T0) to 2 months (T1) in the whole cohort (n = 38). Bars represent mean ± SE.

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Within-group analyses showed a significant improvement in the intervention group (IG; n = 25) (Δ mean ± SE = +5.82 ± 1.45 ml/kg/min; p = 0.002), whereas the control group (CG; n = 13) exhibited a more modest, non-significant change (Δ mean ± SE = +1.73 ± 1.51 ml/kg/min; p = 0.196). (Summary Table 2) These findings align with evidence that cardiorespiratory fitness gains can be achieved by women with breast cancer engaging in supervised, structured programmes over relatively short timeframes.

The Mann–Whitney U test comparing CG and IG on the median Δ did not reach statistical significance (CG: +0.63 [IQR −0.03; +6.67] ml/kg/min; IG: +4.83 [IQR −0.52; +11.66] ml/kg/min; p = 0.115). (Figure 3)

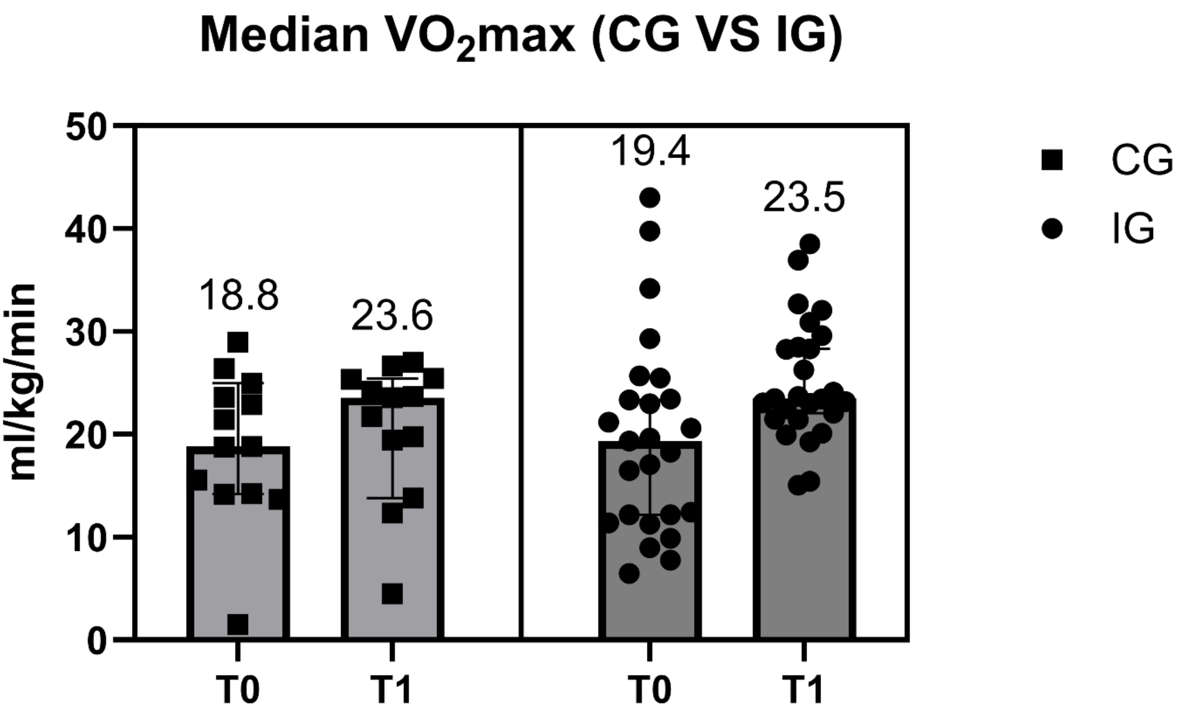

Figure 3. Median estimated VO_2max at baseline (T0) and after 2 months (T1) in the control group (CG, squares; n = 13) and intervention group (IG, circles; n = 25). Bars represent group medians in ml/kg/min.

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Given that Mann–Whitney U is a rank-based test reflecting the median of the distributions, Δ values are presented as median [IQR] rather than mean ± SE for inter-group comparisons. (Summary Table 2)

Supporting evidence comes from a feasibility study offering participants a choice of delivery modes (one-to-one, home-based or group sessions), which reported increased cardiorespiratory fitness after 12 weeks, alongside very high adherence and no serious adverse events [54]. Over longer time horizons, a 6-month rowing programme demonstrated significant improvements in aerobic endurance together with other functional indices during survivorship [55]. Despite heterogeneity in setting and duration, these data support the plausibility that the increase observed in the present cohort reflects a specific effect of cardiorespiratory training [54, 55].

To explore whether the cardiorespiratory response varied according to baseline characteristics, the cohort was stratified by the median age (≤54 vs >54 years) and by baseline body fat percentage (median cut-off: 37.04%). Analyses were performed on median Δ VO_2max using two-tailed Mann–Whitney U with exact estimation.

For age groups, VO_2max data were available for n = 38 participants (18 aged ≤54 years; 20 aged >54 years). Distributions of Δ were comparable and the test showed no significant difference ($p = 0.767$). In other words, within an eight-week horizon there was no evidence that age modified the change in VO_2max—acknowledging that the study was not powered to test formal interactions and that the available sample size may limit detection of small effects.

Similarly, stratification by baseline fat percentage yielded n = 38 usable cases, with near-balanced groups (19 with FM% ≤37.04; 19 with FM% >37.04). Again, Mann–Whitney U showed no significant

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difference between distributions of median Δ VO_2max (p = 0.204), suggesting that, in the short term, initial adiposity was not associated with a different magnitude of cardiorespiratory response. It should be noted that a median split is a descriptive device and does not replace modelling of continuous interactions; hence, the absence of differences between halves of the distribution does not exclude subtler gradients that might emerge with larger samples, longer follow-up or multivariable analyses.

Overall, these subgroup analyses are consistent with the primary picture: the improvement in VO_2max observed at cohort level—and confirmed within the intervention arm, does not differ between experimental groups and shows no systematic heterogeneity by age or baseline fat percentage. This reading accords with evidence from supervised oncology settings whereby early gains in cardiorespiratory fitness are driven chiefly by exposure to training and progressive overload, whereas differences attributable to baseline characteristics are more likely to emerge over longer timeframes or within multicomponent programmes.

Quality of life (SF-36)

Overall, the SF-36 summary indices and domain scores show a pattern of improvement that is internally consistent and clinically plausible given the intervention. The Physical Component Summary (PCS), reflecting perceived global physical functioning and the ability to undertake daily activities without substantial limitations due to pain, fatigue or reduced strength [52, 56], increased in the total cohort with a mean change (±SE) of +3.65 ± 0.94 points (p = 0.0001). This improvement is not only statistically significant but also suggests a perceived gain in functional capacity over a relatively short, eight-week timeframe. (Figure 4) (Summary Table 1)

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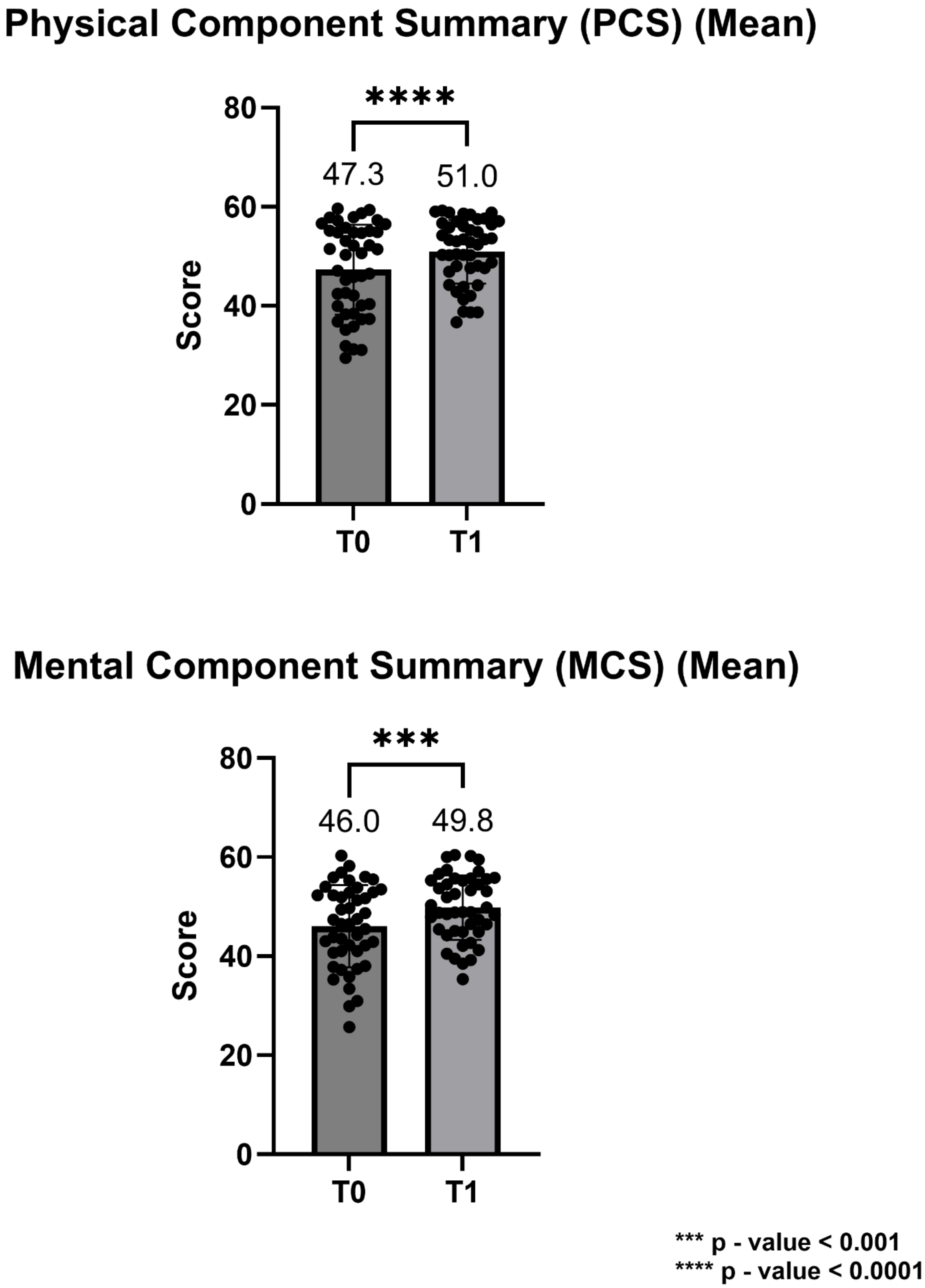

Figure 4. Change in SF-36 Physical Component Summary (PCS) and Mental Component Summary (MCS) scores from baseline (T0) to 2 months (T1) in the whole cohort (n = 45). Bars represent mean ± SE.

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When analysed separately by group, PCS increased significantly in both the intervention group (IG; n = 30; Δ mean ± SE = +3.84 ± 1.21 points; p = 0.003) and the control group (CG; n = 15; Δ mean ± SE = +3.27 ± 1.53 points; p = 0.020). (Summary Table 1)

Notably, despite improvements in both arms, the direct comparison of median Δ between CG and IG did not show statistically significant differences (CG: +4 [IQR +0,5; +7,2] points; IG: +2,86 [IQR -0,3; +9,1] points; p = 0,872). (Figure 5) (Summary Table 2)

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Università di Genova

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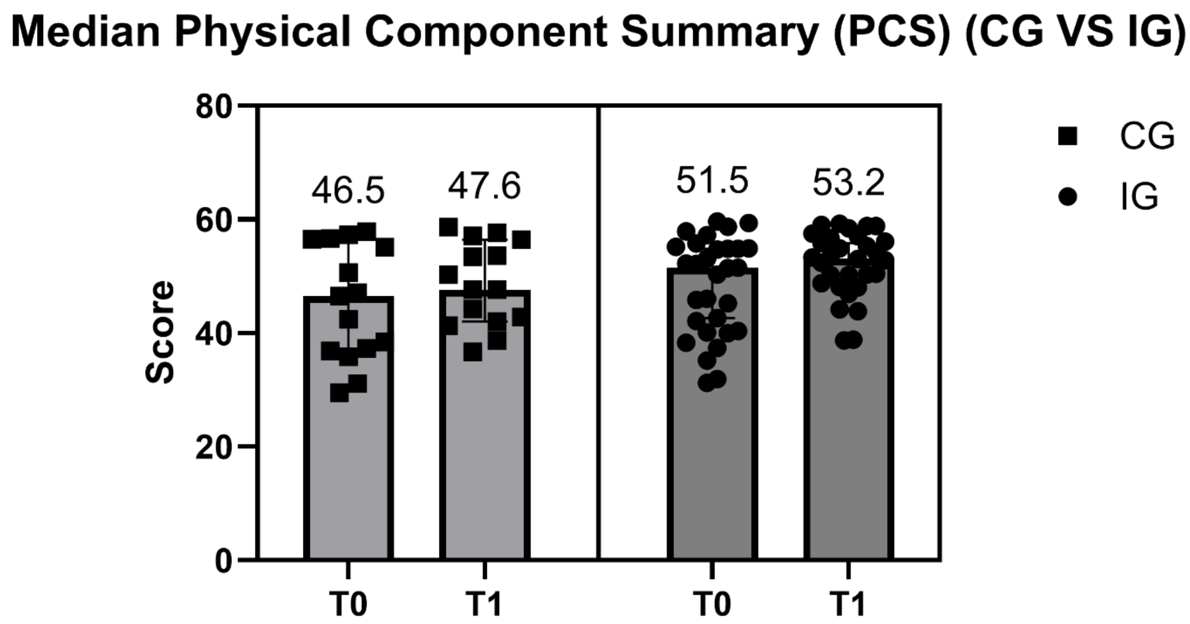

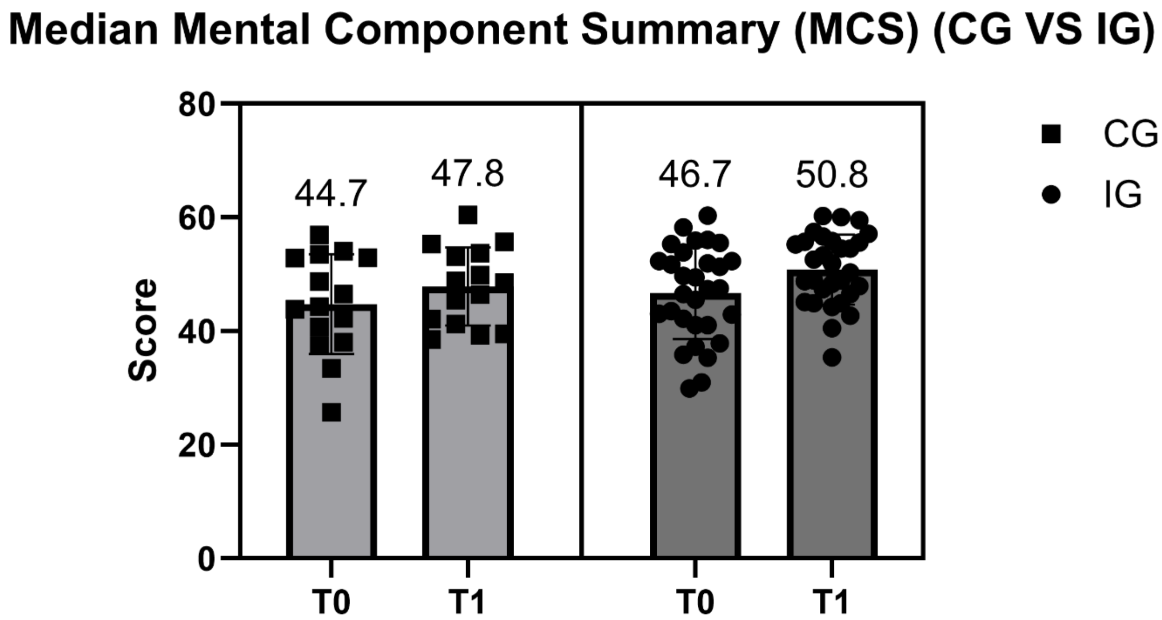

Figure 5. Median SF-36 Physical Component Summary (PCS) and Mental Component Summary (MCS) scores at baseline (T0) and 2 months (T1) in the control group (CG, squares; n = 15) and intervention group (IG, circles; n = 30). Bars represent group medians.

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This is consistent with the premise that adapted Exercise Therapy per se is capable of yielding short-term perceived physical benefits, irrespective of the additional component planned for the experimental arm.

In parallel, the Mental Component Summary (MCS)—capturing psychological well-being, mood, subjective vitality and perceived emotional balance [52, 56]—also improved. In the total cohort the mean change (±SE) was +3.78 ± 1.06 points (p = 0.0005), indicating a statistically significant enhancement in perceived mental and emotional quality of life. (Figure 4) (Summary Table 1)
The within-group analysis confirmed an increase in the IG (n = 30; Δ mean ± SE = +4.11 ± 1.34 points; p = 0.004), while the CG showed a non-significant mean change (n = 15; Δ mean ± SE = +3.12 ± 1.80 points; p = 0.10). (Summary Table 1) As with PCS, the inter-group comparison of median Δ MCS did not reveal significant differences (CG: +4,1 [IQR -0,4; +9] points; IG: +3,87 [IQR +0,42; +6,11] points; p = 0,914), suggesting that enrolment in a structured, supervised adapted-exercise programme is, in its own right, capable of reducing perceived psychological symptom burden (anxiety, depressive symptoms, sense of loss of bodily control) and of supporting subjective feelings of energy and vitality. (Figure 5) (Summary Table 2)

Clinically, the concurrent improvement in PCS and MCS is particularly relevant. Among women with a history of breast cancer, impairments in physical and mental domains frequently co-exist: residual post-surgical pain, stiffness, fear of movement, persistent fatigue and a sense of physical vulnerability tend to interact with fear of recurrence, altered body image and reduced confidence in the body's ability to "function well" in every day and social contexts [10, 57]. The present finding, parallel gains in physical and mental components within only two months, is consistent with reports from adapted-exercise

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programmes in oncology, where intervention structuring (progression, clinical oversight, personalisation), the relational dimension and the implicit psychological support inherent in "returning to safe movement" act jointly, rather than purely biomechanically, on perceived health status [54, 58].

Analysis of individual SF-36 domains further clarifies which aspects of quality of life appear most responsive to structured exercise. In the present sample, significant increases were observed in Role-Physical (RP), Bodily Pain (BP), Mental Health (MH) and Physical Functioning (PF). These domains correspond to the ability to perform daily activities without being limited by prominent physical symptoms, the perception and interference of pain in everyday tasks; emotional stability and mood and the extent to which physical limitations restrict habitual motor activity.

The observed increases suggest that after eight weeks, participants not only report feeling "physically better" overall, but also perceive pain as less limiting, feel more capable of sustaining daily activities without interruption or delegation, and experience a greater sense of bodily control. (Summary Table 1)

In contrast, Social Functioning (SF) and General Health (GH) showed positive trends that did not reach statistical significance under conservative estimates. (Summary Table 1)

This pattern is consistent with two methodological/clinical considerations. First, these domains often change more slowly than physical-functional indices, as they reflect dimensions that require time to consolidate (social reintegration, reduced self-limitation in public contexts, global health perception). Second, they are influenced by factors outside the exercise intervention (family dynamics, return to work, psychosocial fatigue, fear of recurrence) that rarely shift substantially over two months and frequently call for multimodal, psychological and behavioural support [10, 11]. Thus, favourable but non-significant trends in social/perceptual domains are expected and do not contradict the

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improvement in PCS and MCS; rather, they suggest that trajectories of social quality-of-life and global health perception may continue beyond the two-month timepoint, as shown in interventions lasting ≥12 weeks and employing flexible, preference-based delivery models [54].

At the inter-group level, Mann–Whitney U comparisons of median Δ across all eight SF-36 subscales revealed no statistically significant differences between CG and IG at two months. Subscale distributions were broadly similar across groups, and the absence of relevant divergence is consistent with the findings for the summary indices PCS and MCS.

Secondary outcomes

Maximal strength (one-repetition maximum test)

In the total cohort (n = 45), increases in maximal strength were evident across all muscle groups assessed: deltoid (mean Δ ± SE = +3.02 ± 0.51 kg; p = 0.0000051), latissimus dorsi (mean Δ ± SE = +5.38 ± 1.29 kg; p = 0.000074), pectoralis (mean Δ ± SE = +3.73 ± 0.88 kg; p = 0.0002) and quadriceps (mean Δ ± SE = +13.23 ± 3.80 kg; p = 0.0002). (Figure 6) (Summary Table 1)

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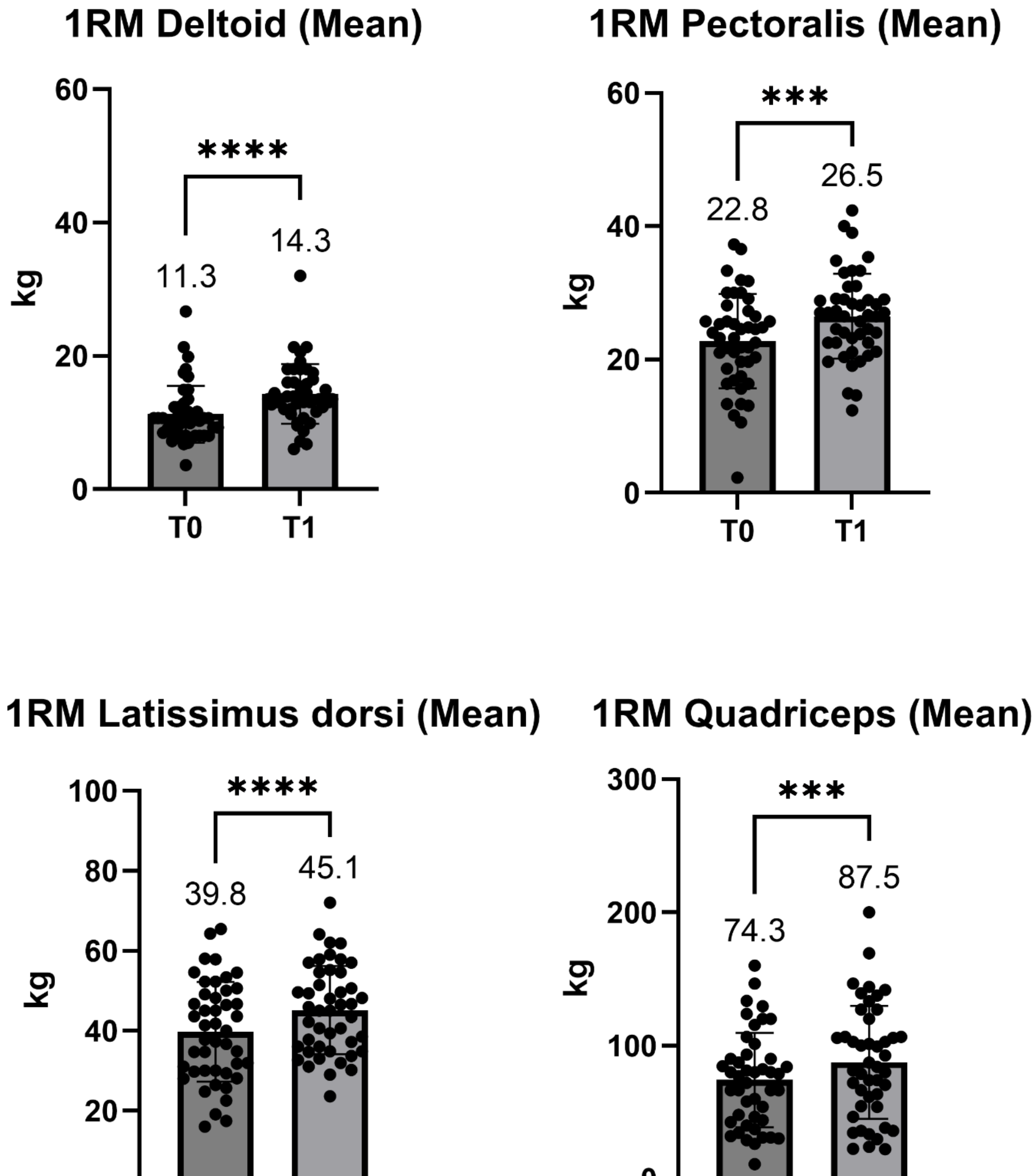

Figure 6. Change in estimated one-repetition maximum (1RM) strength from baseline (T0) to 2 months (T1) in the whole cohort (n = 45) for deltoid, pectoralis, latissimus dorsi, and quadriceps. Bars represent mean ± SE.

***** p - value < 0.001**
****** p - value < 0.0001**

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In within-group analyses, the intervention arm (IG; n = 30) showed significant and consistent gains across all exercises (deltoid: mean Δ ± SE = +2.45 ± 0.67 kg; p = 0.001; latissimus dorsi: mean Δ ± SE = +5.67 ± 1.67 kg; p = 0.001; pectoralis: mean Δ ± SE = +3.97 ± 1.18 kg; p = 0.003; quadriceps: mean Δ ± SE = +17.51 ± 4.45 kg; p = 0.0001). In the control arm (CG; n = 15), the increase was particularly marked for the deltoid (mean Δ ± SE = +4.15 ± 0.71 kg; p = 0.001) and pectoralis (mean Δ ± SE = +3.23 ± 1.46 kg; p = 0.023). (Summary Table 2)

The comparison of median Δ between groups did not reach statistical significance for any muscle group (deltoid CG: +5,09 [IQR +2,06; +6] kg; deltoid IG: +2,71 [IQR +0,25; +4,23] kg; p = 0,057; latissimus dorsi CG: +3 [IQR -1,24; +8,57] kg; latissimus dorsi IG: +4,57 [IQR +1,02; +11,25] kg; p = 0,546; pectoralis CG: +1,49 [IQR -0,54; +5,11] kg; pectoralis IG: +2,23 [IQR -0,70; +8,01] kg; p = 0,694; quadriceps CG: +7,43 [IQR -5,9; +18,74] kg; quadriceps IG: +9,89 [IQR +2,66; +33,87] kg; p = 0,217), a pattern consistent with the nature of the intervention. The relatively short follow-up (8 weeks) and the asymmetric sample size

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(IG = 30; CG = 15) are both elements that may have limited statistical power to detect between-group differences of small-to-moderate magnitude. (Figure 7) (Summary Table 2)

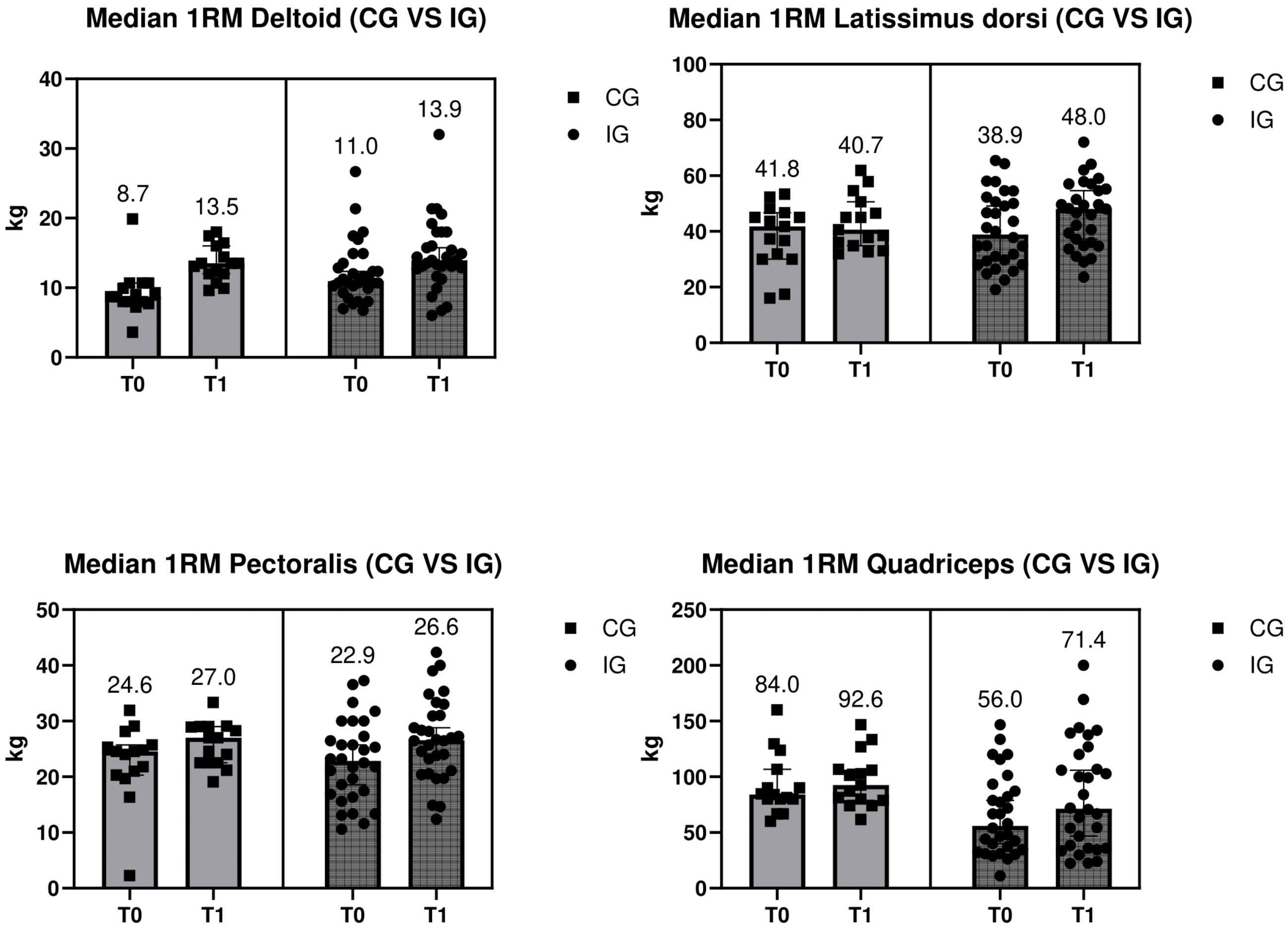

Figure 7. Median one-repetition maximum (1RM) strength for deltoid, latissimus dorsi, pectoralis and quadriceps at baseline (T0) and after 2 months (T1) in the control group (CG, squares; n = 15) and intervention group (IG, circles; n = 30). Bars represent group median.

The direction of these findings is, however, fully consistent with expected adaptations in the early phase of a strength-training programme: over an 8-week period, increases in one-repetition maximum are

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largely attributable to neural adaptations (improved recruitment and synchronisation of motor units, reduced antagonist co-activation, task-specific learning), which precede slower structural changes.

Because one-repetition maximum was estimated using the Brzycki formula from submaximal trials, participants may also have benefited from greater familiarity with the testing procedure at T1. This likely contributed to a proportion of the measured improvement, without undermining the substantive interpretation of a true gain in maximal strength.

Anthropometry and body composition

In the total cohort (n = 45), statistically significant reductions were observed in body weight (mean Δ ± SE = −0.68 ± 0.21 kg; p = 0.0029), body mass index (BMI) (Δ = −0.29 ± 0.08 kg/m^2; p = 0.0013) and fat mass (Δ = −1.30 ± 0.34 kg; p = 0.007), alongside a non-significant change in fat-free mass (FFM) (Δ = +0.51 ± 0.31 kg; p = 0.146). (Figure 8) (Summary Table 1)

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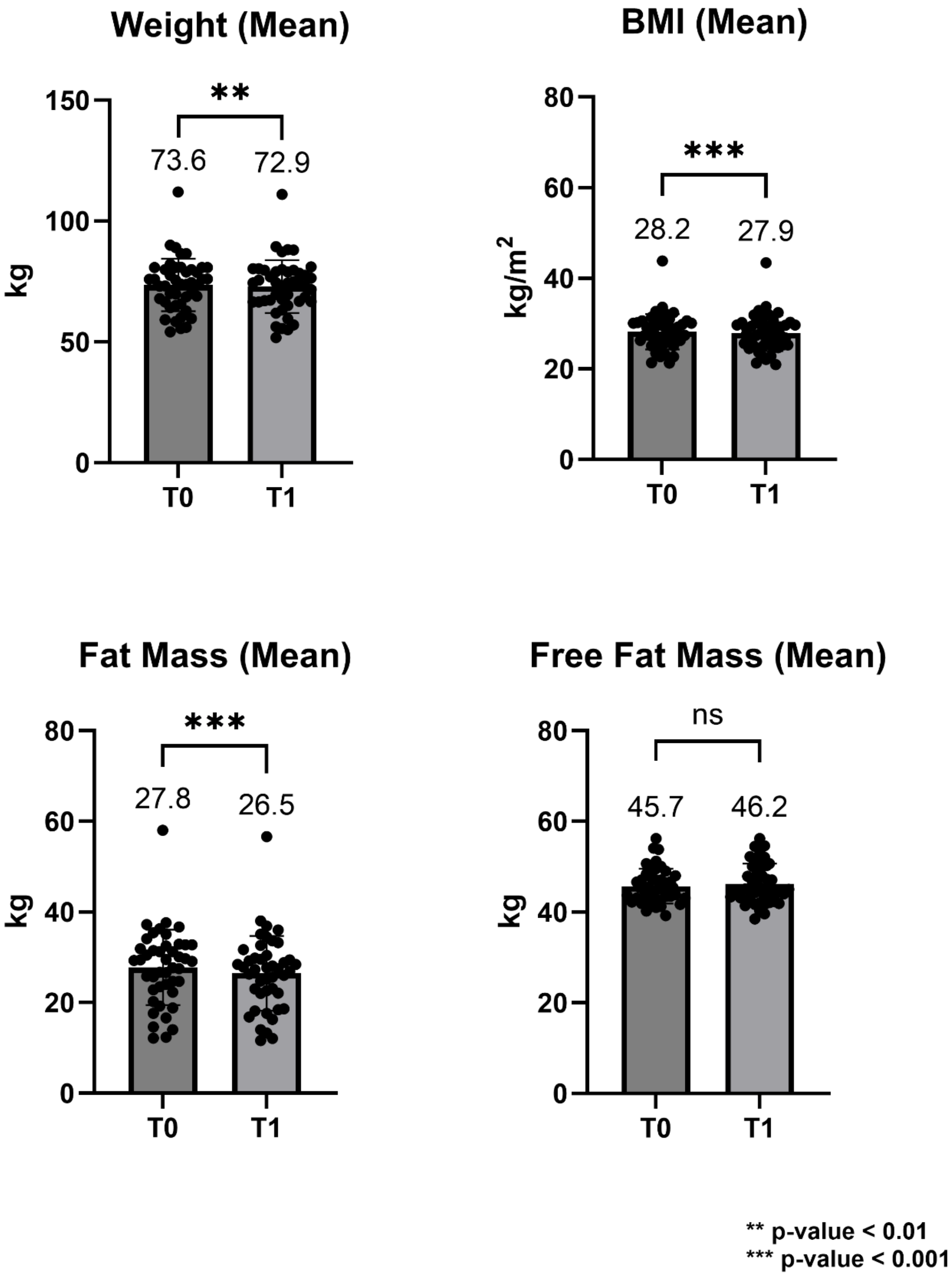

Figure 8. Change in anthropometric and body-composition parameters from baseline (T0) to 2 months (T1) in the whole cohort (n = 45). Panels show mean weight, BMI, fat mass and fat-free mass (FFM); bars represent mean ± SE.

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This profile is consistent with a short-duration (eight-week) therapeutic exercise intervention in which weight loss is mainly driven by the adipose component, while FFM is preserved. Clinically, maintaining lean mass in the presence of weight loss is a desirable outcome, as it is associated with preserved functional capacity, resting metabolic rate and the ability to tolerate training loads and activities of daily living. These findings are in line with physiological expectations that, over short timeframes, exercise induces modest but coherent reductions in weight/BMI/fat mass while preserving FFM [10, 11].

When groups are considered separately, the intervention group (IG; $n = 30$) shows significant reductions in weight ($\Delta = -0.580 \pm 0.248$ kg; $p = 0.035$) and fat mass ($\Delta = -1.120 \pm 0.416$ kg; $p = 0.011$), whereas in the control group (CG; $n = 15$) significant reductions emerge for BMI ($\Delta = -0.460 \pm 0.141$ kg/m^2; $p = 0.006$) and fat mass ($\Delta = -1.70 \pm 0.652$ kg; $p = 0.030$), supporting the notion that adapted, supervised exercise is, in itself, capable of improving body composition even in the short term. (Summary Table 2)

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At the inter-group level, two-tailed Mann–Whitney U comparisons of median Δ did not reveal statistically significant differences between CG and IG for weight, BMI, Fat Mass or FFM. (Figure 9)

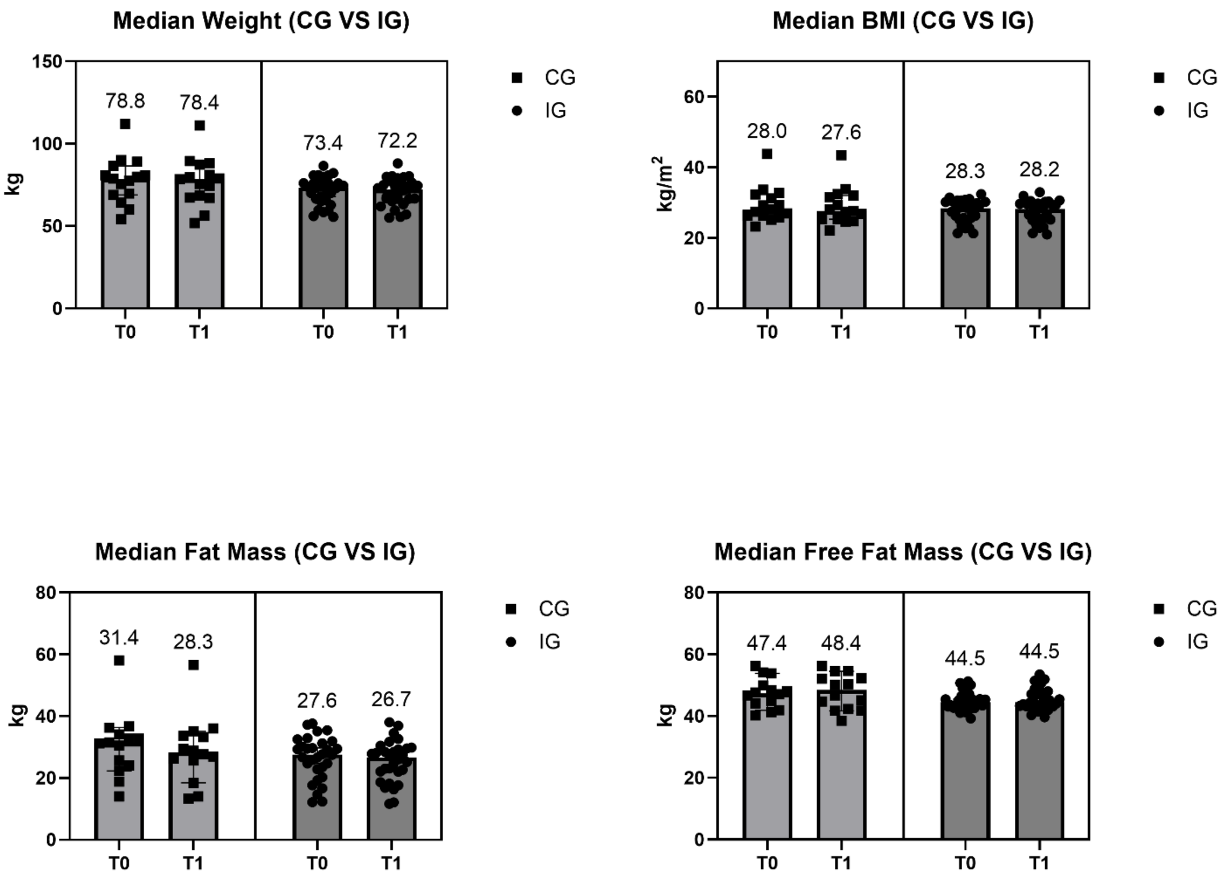

Figure 9. Median weight, BMI, fat mass and fat-free mass at baseline (T0) and 2 months (T1) in the control group (CG, squares; n = 15) and intervention group (IG, circles; n = 30). Bars represent group medians (kg or kg/m).

This result is consistent with three methodological and clinical elements: the limited follow-up duration, which constrains the magnitude of changes that can realistically be observed; the delivery of exercise to both arms, which naturally attenuates between-group contrasts; and the asymmetric sample size (IG = 30; CG = 15), which reduces power to detect small between-group differences. Overall, the pattern of

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change points towards a diffuse exercise-related benefit, rather than a selective advantage of the experimental arm at two months.

It is also important to qualify the added value of the resistance-training component embedded in the programme, which contributes to preserving FFM during weight loss and to producing a small, non-significant increase over the short term. Progressive mechanical tension, combined with appropriate training volumes and recovery, supports myofibrillar protein synthesis and counteracts the loss of lean tissue typically observed with hypocaloric diets not accompanied by exercise, with favourable repercussions for strength, resting metabolic rate and exercise tolerance [57, 58].

From a tertiary prevention perspective, the reduction in fat mass—particularly abdominal fat—is clinically relevant because it is associated with lower systemic inflammation and a more favourable metabolic–hormonal profile, both of which are linked to long-term outcomes in survivors [25, 53]. While refraining here from causal inferences, the direction of the observed changes is consistent with these mechanisms and supports the hypothesis that structured exercise helps to favourably modulate metabolic–inflammatory determinants related to excess adiposity.

Circumferences

In the full cohort (n = 45), circumference measures showed a differentiated pattern, consistent with the observed changes in body composition. Chest circumference decreased significantly (mean Δ ± SE = −2.02 ± 0.41 cm; p = 0.00005), and the right biceps showed a small but statistically significant reduction (mean Δ ± SE = −0.84 ± 0.34 cm; p = 0.019), whereas the change in left biceps circumference did not reach statistical significance.

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Quadriceps circumferences showed a significant bilateral reduction (left quadriceps: mean Δ ± SE = −1.20 ± 0.39 cm; p = 0.006; right quadriceps: mean Δ ± SE = −1.00 ± 0.44 cm; p = 0.025), consistent with a decrease in fat mass. By contrast, waist and hip circumferences did not exhibit significant changes over the eight-week period.

From a physiological perspective, the reduction in limb circumferences in the context of preserved FFM suggests a predominant loss of regional subcutaneous adipose tissue, with maintenance of muscle mass. This is expected over short timeframes, in which exercise can induce remodelling of subcutaneous and visceral fat without large changes in total body weight. Classical evidence from randomised controlled trials has shown that exercise without weight loss can significantly reduce abdominal fat and subcutaneous thigh fat and improve metabolic profiles even in the absence of marked weight change [59, 60].

Subsequent meta-analyses have confirmed that exercise exerts robust effects on visceral adipose tissue (VAT), whereas abdominal circumference may require longer time horizons to fully reflect these changes [61]. In this context, the absence of a significant mean Δ at waist and hips at 8 weeks does not contradict the favourable trend in weight, BMI, fat mass and peripheral circumferences, but rather represents an early snapshot of the adaptation process.

Clinically, changes at arm level warrant a specific clarification: the data do not suggest pathological increases in upper-limb circumferences; on the contrary, only minimal variations or reductions are observed. This is consistent with the substantial body of evidence indicating that progressive upper-limb resistance training does not increase the risk of lymphoedema nor exacerbate pre-existing lymphoedema in breast cancer survivors, provided that training is gradual, supervised and

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individualised [44]. This element not only supports the safety of the protocol but also helps to interpret micro-variations in biceps circumference in the absence of adverse clinical signs.

The inter-group comparison of median Δ for all circumferences using the Mann–Whitney U test did not reveal statistically significant differences ($p > 0.05$) between IG (n = 30) and CG (n = 15), in line with the delivery of exercise in both arms and the limited duration of follow-up. (Summary Table 2)

Lower-limb function and balance (SPPB)

In the cohort (n = 45), change in the Short Physical Performance Battery (SPPB) did not reach statistical significance (mean Δ ± SE = +0.11 ± 0.05 points; p = 0.059), considering the high baseline score for most participants (mean baseline score: 11.82/12). (Summary Table 1)

The inter-group comparison of Δ SPPB using the Mann–Whitney U test showed no statistically significant differences ($p > 0.05$) between the intervention group (IG; n = 30) and the control group (CG; n = 15), which is consistent with the delivery of exercise in both arms and the limited duration of follow-up. (Summary Table 2)

Summary tables

Summary Table 1

Parameter	Mean Δ (cohort)	p-value (cohort)
	Cardiorespiratory fitness (n = 38)	
VO_2max (ml/kg/min)	+4.42	0.001
	SF – 36 questionnaire (n = 45)	
Physical Component Summary (PCS)	+3.657	0.0001
Mental Component Summary (MCS)	+3.783	0.0005

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Physical Functioning (PF)	+5.88	0.027
Role-Physical (RP)	+18.88	0.001
Bodily Pain (BP)	+8.00	0.004
General Health (GH)	+4.11	0.090
Vitality (VT)	+5.88	0.002
Social Functioning (SF)	+6.11	0.041
Role-Emotional (RE)	+17.03	0.006
Mental Health (MH)	+6.31	0.003
One-repetition maximus (1RM) (n = 45)		
1RM deltoid (kg)	+3.021	0.000005
1RM latissimus dorsa (kg)	+5.380	0.00007
1RM pectoralis (kg)	+3.73	0.0002
1RM quadriceps (kg)	+13.23	0.0002
Anthropometry and body composition (n = 45)		
Weight (kg)	-0.68	0.0029
BMI (kg/m^2)	-0.293	0.0013
Fat mass (FM) (kg)	-1.30	0.0007
Fat-free mass (FFM) (kg)	+0.51	0.1466
Left biceps circumference (cm)	-0.366	0.0780
Right biceps circumference (cm)	-0.844	0.0195
Chest circumference (cm)	-2.022	0.00005
Abdominal circumference (cm)	+0.244	0.9443
Hip circumference (cm)	-0.851	0.4309
Left quadriceps circumference (cm)	-1.208	0.0067
Right quadriceps circumference (cm)	-1.00	0.0259
Lower-limb function and balance (n = 45)		
SPPB (score)	+0.11	0,059

Summary Table 1. Mean change (Δ) from baseline to 2 months in the total cohort and corresponding p-values for all outcomes

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Summary Table 2

Parameter	Mean Δ (IG)	p-value (IG)	Mean Δ (CG)	p-value (CG)	p-value (Mann-Whitney U test)
Cardiorespiratory fitness (n = 38)					
VO_2max (ml/kg/min)	+5.82	0.002	+1.73	0.196	0.115
SF – 36 questionnaire (n = 45)					
Physical Component Summary (PCS)	+3.84	0.003	+3.27	0.020	0.872
Mental Component Summary (MCS)	+4.11	0.004	+3.12	0.100	0.914
Physical Functioning (PF)	+6.50	0.026	+4.66	0.375	0.712
Role-Physical (RP)	+17.50	0.003	+21.66	0.086	0.754
Bodily Pain (BP)	+7.33	0.019	+9.33	0.089	0.821
General Health (GH)	+5.33	0.064	+1.66	0.797	0.377
Vitality (VT)	+5.00	0.052	+7.66	0.014	0.319
Social Functioning (SF)	+6.66	0.098	+5.00	0.228	0.849
Role-Emotional (RE)	+21.11	0.004	+8.89	0.428	0.384
Mental Health (MH)	+6.13	0.024	+6.67	0.052	0.626
One-repetition maximus (1RM) (n = 45)					
1RM deltoid (kg)	+2.453	0.001	+4.159	0.001	0.057
1RM latissimus dorsa (kg)	+5.679	0.001	+4.785	0.05	0.546
1RM pectoralis (kg)	+3.979	0.003	+3.232	0.023	0.694
1RM quadriceps (kg)	+17.515	0.0002	+4.675	0.211	0.217
Anthropometry and body composition (n = 45)					
Weight (kg)	-0.58	0.035	-0.88	0.044	0.4342
BMI (kg/m^2)	-0.21	0.061	- 0.46	0.006	0.1973
Fat mass (FM) (kg)	-1.12	0.011	-1.7	0.030	0.3856
Fat-free mass (FFM) (kg)	+0.54	0.0150	+0.471	0.396	0.9752
Left biceps circumference (cm)	-0.283	0.446	-0.533	0.081	0.1513
Right biceps circumference (cm)	-0.733	0.305	-1.067	0.049	0.1856
Chest circumference (cm)	-1.950	0.001	-2.167	0.017	0.9381

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Abdominal circumference (cm)	-0.767	0.343	+2.267	0.244	0.2951
Hip circumference (cm)	-2.427	0.067	+2.300	0.293	0.0552
Left quadriceps circumference (cm)	-0.897	0.138	-1.833	0.017	0.2414
Right quadriceps circumference (cm)	-0.967	0.044	-1.067	0.244	0.6877
Lower-limb function and balance (n = 45)					
SPPB (score)	+0.1	0.083	+0.13	0.317	1.00

Summary Table 2. Mean change (Δ) from baseline to 2 months by group (intervention vs control), with within-group p-values and between-group p-values (Mann–Whitney U test)

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DISCUSSION

Summary of the main findings and consistency with the rationale

The HOPE study was situated within the fields of exercise oncology and tertiary prevention in breast cancer, with the aim of evaluating the effectiveness of a programme of Exercise Therapy (ET). The exercise study was combined in an exploratory manner with the administration of high-ozonide ozonised oil to evaluate, improving aerobic capacity and quality of life in women who are breast cancer survivors.

The cohort included 45 participants, with a mean age of 54 ± 5.67 years, who were globally deconditioned from a cardiorespiratory standpoint. This was indicated by low baseline VO_2max values (approximately 19.4 ml/kg/min), compatible with the post-treatment phase and with a functional frailty profile typical of breast cancer survivors.

Overall, the findings show that, at two months, the ET intervention, delivered in a hybrid format (in-person and remotely, with controlled progression), is associated with:

- a significant increase in VO_2max in the whole cohort, with a clear improvement in the intervention group (IG) and a more modest change in the control group (CG);
- a consistent improvement in health-related quality of life, documented by the SF-36 summary indices (PCS and MCS) and several specific domains, with significant gains in both IG and CG;
- a substantial increase in maximal strength in the main muscle groups assessed (deltoid, latissimus dorsi, pectoralis, quadriceps);

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- reductions in body weight, BMI and fat mass (FM), with overall preservation (and a small, non-significant increase) of fat-free mass (FFM);
- a selective reduction in peripheral circumferences (chest, thigh), alongside no significant changes in waist and hip circumference;
- no significant change in SPPB performance, in the context of very high baseline scores.

At inter-group level, comparison between IG (Exercise Therapy + high-ozonide ozonised oil) and CG (Exercise Therapy only) using the Mann–Whitney test showed no statistically significant differences in the median changes for either primary outcomes (VO_2max, PCS, MCS) or secondary outcomes.

Some non-significant trends were observed (e.g. in favour of IG for VO_2max, and in favour of CG for deltoid 1RM), but no additional benefit could be clearly attributed to the addition of ozonised oil within the eight-week time frame.

Taken together, these results are consistent with the rationale outlined in the introductory chapters. This is that structured, supervised Exercise Therapy to the clinical–functional status, represents a transversal health measure capable of improving cardiorespiratory fitness, strength, body composition and quality of life along the oncological continuum, from primary prevention to survivorship [10, 11, 53].

The present study confirms this framework in a real multicentre setting, albeit with the limitations of a retrospective observational design and a moderate sample size.

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Primary outcomes

Aerobic capacity and cardiorespiratory adaptations

The significant increase in VO_2max in the cohort and in the intervention group represents one of the central findings of the study. Starting from baseline values typical of deconditioned individuals, the ET intervention led, in just two months, to an increase compatible with a shift towards more favourable levels of cardiorespiratory fitness. This finding has clinical relevance, as VO_2max is a synthetic indicator of the capacity of the cardiorespiratory system to sustain prolonged physical activity and is associated in the literature with favourable prognostic outcomes both in the general population and in patients with cancer.

The pattern observed is consistent with implementation studies of supervised exercise programmes in breast cancer survivors, in which significant improvements in aerobic capacity have been documented even over relatively short time frames (10–12 weeks), provided that principles of progression, individualisation and clinical monitoring are respected [10, 54].

Similarly, interventions over longer periods, such as the six-month rowing programme described by Real-Pérez et al. [55], show marked increases in aerobic endurance and other functional indices, suggesting that the changes observed in HOPE represent the initial phase of an adaptive process that could continue beyond the eight-week period.

The absence of statistically significant differences between IG and CG in VO_2max changes (Δ) should be interpreted in light of several methodological aspects: the relatively small sample size, the limited follow-up duration, the exposure to exercise in both arms and the non-randomised nature of group allocation. In this context, the favourable trend towards a larger increase in the ET + HOO group is not

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sufficient to support a definite additive effect of ozonised oil, but rather underscores the central role of cardiorespiratory training, which appears to be the main determinant of the increase in VO_2max.

Subgroup analyses by age (≤54 vs >54 years) and baseline fat mass percentage (≤ vs > median) did not reveal systematic heterogeneity in VO_2max response. In other words, within the two-month time frame, the cardiorespiratory benefit appeared independent of age and baseline adiposity, albeit with all the caution required given the limited statistical power for interaction analyses. This is consistent with the literature showing that, in supervised programmes, early adaptations in cardiorespiratory fitness are primarily driven by exposure to training and load progression, whereas gradients associated with age, BMI or body composition tend to emerge more clearly over longer time horizons or in larger studies [23, 25].

Health-related quality of life: physical and mental components

The other primary outcome, health-related quality of life (QoL), shows a robust and internally coherent pattern of improvement. The SF-36 composite indices PCS and MCS increase significantly in the whole cohort and in the intervention group, with changes that are clinically plausible over an eight-week period. In the control group, which performed the same ET programme without supplementation, PCS also improves significantly, whereas MCS shows a non-significant increase in the same direction.

Arguably the most noteworthy finding is that PCS and MCS improve in parallel, suggesting an integration between physical–functional gains (reduced pain and fatigue, lower perception of motor limitations) and psycho-emotional aspects (anxiety, mood, perceived energy and sense of bodily control). This profile closely matches descriptions in numerous reviews and meta-analyses that attribute to exercise

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a key role in improving QoL, depressive symptoms, fatigue and social functioning in women with breast cancer [10, 11, 31].

The absence of significant differences between IG and CG in PCS and MCS changes is consistent with the hypothesis – also supported by the literature – that exercise per se represents the dominant component in determining perceived benefit on both physical and mental dimensions. In this sense, enrolment in a structured, supervised and individualised exercise programme, with clear clinical legitimisation and a group context, appears sufficient to reduce perceived symptom burden and to improve psychosocial well-being, irrespective of ozonised oil supplementation.

Analysis of the individual SF-36 domains allows a more detailed understanding of which dimensions are most responsive to the stimulus provided by exercise: Role-Physical (RP), Bodily Pain (BP), Physical Functioning (PF), Vitality (VT), Mental Health (MH) and Role-Emotional (RE) show significant increases. This indicates that, beyond feeling "better overall", participants report less interference of pain with daily activities, a greater capacity to sustain physical tasks without interruption, more stable mood and a higher subjective sense of energy.

Domains such as Social Functioning (SF) and General Health (GH) show a positive but not always significant trend, which is plausible given that these aspects are more strongly influenced by contextual factors beyond the protocol (family and work environment, fear of recurrence, socio-economic conditions) and require longer time frames and multimodal interventions (psychological, educational, behavioural) to fully express change [11, 32].

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Overall, the pattern observed confirms the multidimensional nature of exercise effects: the HOPE protocol does not merely produce “mechanical” adaptations in strength and VO_2max but also contributes to rebuilding a sense of personal efficacy and confidence in the body’s fitness for purpose, in line with bio-psycho-social models of survivorship.

Secondary outcomes

Maximal strength and neuromuscular adaptations

The increases in 1RM observed in all muscle groups assessed are a clear signal of neuromuscular adaptation. Over eight weeks, with two Exercise Therapy sessions per week (one in person and one online), the programme produced significant increases in maximal strength both in the overall cohort and in the intervention arm. The control arm, which followed the same Exercise Therapy protocol, also shows significant gains in key muscle groups such as the deltoid and pectoralis.

From a physiological standpoint, this trajectory is fully consistent with the initial phases of a resistance-training programme, in which the largest proportion of improvement is attributable to neural adaptations (recruitment and synchronisation of motor units, reduced antagonist co-activation, motor learning), whereas hypertrophic adaptations require longer periods [57].

The use of predicted 1RM values based on the Brzycki equation, derived from submaximal tests, also implies a contribution of test familiarity: it is plausible that participants at T1 were able to express a more efficient performance partly through learning, without invalidating the interpretation of a genuine gain in strength.

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The absence of statistically significant differences between IG and CG in 1RM changes once again confirms, in this domain, the central role of exercise as the primary determinant of the adaptations observed, with any additional contribution of ozonised oil remaining, on the basis of available data, neither demonstrated nor conclusively excluded. Clinically, improvements in maximal strength in upper- and lower-limb muscle groups are relevant for the management of activities of daily living, for fall prevention and for the capacity to sustain subsequent progressive overload in training.

Anthropometry and body composition

The anthropometric and body-composition profile observed is consistent with what would be expected from a short-duration exercise-focused intervention: significant reductions in body weight, BMI and fat mass, with stable fat-free mass. This pattern is particularly desirable in the oncological setting, as it allows improvement of metabolic and inflammatory status without inducing sarcopenia or a decline in functional capacity [10, 11].

The fact that fat-mass reductions are accompanied by stable, or slightly (non-significantly) increased FFM supports the role of the strength component embedded in the HOPE programme. As shown in trials and meta-analyses in overweight/obese women with breast cancer, the most effective interventions for body composition are multicomponent programmes that combine structured diet and exercise, whereas exercise alone generally produces more modest weight loss but is crucial in preserving lean mass and improving functional capacity [42]. The HOPE findings are aligned with this evidence: even in the absence of a formalised dietary component, exercise ensures widespread improvement in anthropometric parameters, with a favourable redistribution between fat and lean compartments.

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From a tertiary-prevention perspective, reduction in fat mass, particularly in the abdominal compartment, is important because of the documented link between visceral adiposity, chronic low-grade inflammation, insulin resistance and recurrence risk [25, 53]. Without drawing causal inferences, the direction of the changes observed is fully consistent with these mechanisms and suggests that a structured exercise programme, even without intensive dietary interventions, may contribute to a favourable remodelling of metabolic–inflammatory determinants associated with excess adiposity.

Peripheral and abdominal circumferences and safety with respect to lymphoedema

Changes in circumferences further refine the body-composition picture. The significant reduction in chest circumference and thigh girths, alongside minimal (or absent) changes in waist and hip circumference, suggests a pattern of selective remodelling of peripheral subcutaneous adipose tissue, consistent with the short duration of the intervention. Classic evidence from randomised trials indicates that exercise, even in the absence of marked weight loss, can reduce abdominal and limb subcutaneous fat while simultaneously improving metabolic profiles [59, 60]. More recent meta-analyses confirm that exercise has a particularly robust effect on visceral adipose tissue (VAT), whereas abdominal circumferences require longer periods to fully manifest change [61].

From a clinical perspective, changes in upper-limb circumferences warrant specific consideration: the data do not indicate pathological increases but rather small reductions or stability, with no clinical signs of lymphoedema. This is consistent with the extensive literature showing that progressive resistance training of the upper limb, when well supervised and introduced gradually, does not increase lymphoedema risk nor worsen pre-existing lymphoedema in breast cancer survivors [44].

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The HOPE protocol, which includes upper-limb exercises both in person and online, therefore appears to confirm, in a real multicentre context, the safety of a structured strength approach for the upper limb.

Lower-limb function and balance (SPPB)

The Short Physical Performance Battery (SPPB) did not show a statistically significant change over the observation period, despite a positive mean Δ. This result should be interpreted in light of the very high baseline scores (mean ≈ 11.8/12), indicating near-maximal performance in most participants. Under these conditions, the margin for measurable improvement is reduced and the sensitivity of the instrument to detect small functional changes is limited.

It is plausible that, had the cohort included individuals with more pronounced baseline functional impairment, the SPPB might have captured larger changes. However, in a sample of women who are relatively autonomous in activities of daily living (ADL), SPPB retains primarily descriptive value at baseline, whereas other outcomes (VO_2max, strength, QoL) are more sensitive to the intervention effect.

Role of exercise and potential contribution of ozonised oil

One distinctive feature of the HOPE project is the inclusion, in the intervention arm, of a food for special medical purposes based on high-ozonide ozonised oil (HOO), the rationale for which draws on preclinical evidence of selective cytotoxicity towards tumour cells, modulation of intracellular redox balance and potential synergy with chemo- and radiotherapy [14, 15, 29].

In the present study, however, comparison between IG (Exercise Therapy + HOO) and CG (Exercise Therapy) did not show statistically significant differences in changes in primary or secondary outcomes.

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This does not allow a demonstrable additive benefit of ozonised oil to be claimed, at least within the eight-week time frame and given the sample size available.

Considering the observational design and the absence of randomisation, these findings must be interpreted cautiously: a specific effect of HOO cannot be completely excluded, but the data clearly indicate that exercise is the dominant driver of change, whereas the potential contribution of supplementation remains, at this stage, exploratory and inconclusive.

This consideration is important from both ethical and communication standpoints: in line with current literature, ozonised oil should be regarded as an experimental adjunctive option, to be assessed in future prospective controlled studies with specific endpoints and extended follow-up, rather than as an intervention already validated in oncology.

Strengths of the study

The HOPE study has several strengths that enhance its practical relevance:

1. **Multicentre context and real-world implementation**

   Recruitment within certified Breast Units across the national territory confers contextual heterogeneity and brings the protocol closer to everyday clinical practice conditions, thereby increasing the transferability of the findings.

2. **Structured and standardised intervention**

   The Exercise Therapy programme was designed and supervised according to ACSM recommendations and international guidelines, with systematic attention to progression, safety and individualisation [10, 36].

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3. **Multidimensional assessment**

   Inclusion of cardiorespiratory, neuromuscular, anthropometric, body-composition and QoL outcomes allows an integrated reading of the intervention effect, in line with bio-psycho-social survivorship models.

4. **Adherence to STROBE and procedural robustness**

   Data collection was conducted using standardised procedures, two time points, validated instruments (2-km walk test, SF-36, SPPB, BIA, strength testing) and reporting compliant with STROBE recommendations.

5. **Safety and acceptability**

   The absence of signals of worsening upper-limb circumferences and the functional improvements observed support the safety of the Exercise Therapy protocol, including in individuals at risk of lymphoedema, in keeping with the literature [44].

Methodological limitations

Alongside these strengths, the study presents several important limitations that should be explicitly acknowledged:

1. **Retrospective observational design and lack of randomisation**

   Group allocation reflects clinical practice rather than a randomised process, exposing the study to potential selection bias and confounding (e.g. patient preferences, clinical status, motivation to exercise) that cannot be fully ruled out.

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2. **Limited sample size and imbalance between groups**

   The total sample (n = 45), with 30 subjects in IG and 15 in CG, limits statistical power, particularly for inter-group comparisons and interaction analyses (age, body composition, setting). Some non-significant trends may reflect power issues rather than a true absence of effect.

3. **Short follow-up**

   Two months represent an adequate time frame to capture early adaptations, but not to fully assess effects on visceral body composition, social QoL domains, long-term adherence or hard outcomes (recurrence, cardiovascular events, survival).

4. **Indirect measurement of VO_2max and instrumental limitations**

   VO_2max was estimated via a 2-km walk test on a treadmill using an equation validated on flat outdoor surfaces; this may introduce bias in absolute values, although T1–T0 changes remain interpretable within the same setting [38, 39].

5. **Strength estimation via predictive equations**

   1RM was estimated using the Brzycki equation which, although widely used, adds predictive error compared with direct measurement. Test repetition and familiarity gained by T1 may have magnified part of the measured gain.

6. **Absence of inflammatory or hormonal biomarkers**

   No direct markers of systemic inflammation (e.g. CRP, IL-6, TNF-α) or hormonal–metabolic parameters (insulin, leptin, adiponectin) were included, which would have allowed a closer link to the pathophysiological rationale discussed [6, 25].

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7. **Non-structured measurement of adherence to supplementation**

   Although use of ozonised oil according to protocol was documented, the absence of a rigorous quantitative adherence measure (systematic capsule counts, daily logs) limits the ability to precisely correlate intake with outcomes.

Clinical implications and future directions

Despite its limitations, the HOPE study provides several operational indications for clinical practice:

- it confirms the feasibility and safety of a structured Exercise Therapy programme, delivered in a hybrid format, within Italian Breast Units;
- it shows that, even over a relatively short period, it is possible to obtain clinically meaningful improvements in cardiorespiratory fitness, strength, body composition and QoL;
- it suggests that exercise should be regarded as a cornerstone of tertiary prevention in breast cancer, on a par with structured oncological follow-up and appropriate nutritional counselling [25, 34];
- it offers a scalable operational model, potentially extendable to other oncological conditions and integrable with telemedicine and tele-exercise pathways.

With regard to future research, the HOPE findings point towards several priority directions:

1. **Prospective, randomised, multicentre controlled studies**, with larger samples and extended follow-up (≥6–12 months), to more robustly assess the effect of exercise and, where appropriate, ozonised oil on VO_2max, QoL, body composition and inflammatory/metabolic biomarkers.

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2. **Multicomponent analyses** integrating Exercise Therapy with structured dietary interventions and psychological support, with the aim of maximising impact on body weight, visceral fat mass, social QoL domains and long-term clinical outcomes, in line with WCRF/AICR recommendations and models of oncological "lifestyle medicine" [33, 53].

3. **Further exploration of the role of ozonised oil in oncology**, beginning with pilot prospective studies focused on biological endpoints (redox markers, inflammatory profile, immune response), to clarify whether the preclinical mechanisms described can translate into clinically measurable benefits and in which patient subgroups.

4. **Development of flexible delivery models** (in-person, online, hybrid) based on patient preferences, combined with adherence strategies (formal medical prescription, motivational counselling, digital tools), as proposed by recent implementation studies [54].

Concluding considerations

The HOPE project confirms that a structured, supervised Exercise Therapy programme, embedded in the follow-up pathways of Breast Units, is capable of producing significant and clinically relevant benefits in aerobic capacity, muscle strength, body composition and quality of life in women who are breast cancer survivors, within a relatively short time frame.

Ozonised oil, introduced on an exploratory basis, does not at this stage show a clearly demonstrable additive effect beyond exercise, but this study opens the way for further prospective work focused on biological mechanisms and potential synergy with lifestyle interventions.

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Taken together, the findings reinforce the notion – already highlighted in major international guidelines – that physical activity should be considered a structural component of oncological care, rather than an optional adjunct. It also indicates that tertiary prevention in breast cancer requires a multidimensional approach integrating therapy, rehabilitation, lifestyle and psychosocial support throughout the entire survivorship trajectory.

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