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Research article

Effects of aerobic combined with resistance exercise on cardiorespiratory fitness and cardiometabolic health in breast cancer survivors: A Systematic Review, meta-analysis and meta-regression

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A R T I C L E I N F O

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Breast cancer
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A B S T R A C T

Background: Cardiotoxicity from chemotherapy is a serious risk to the quality of survival of breast cancer survivors (BCS), and aerobic combined with resistance exercise (CE) has the potential to combat this cardiac damage. However, there is a lack of high-quality studies to assess the specific effects of CE. This study aimed to investigate the effects of CE on cardiopulmonary function (CRF) and cardiometabolic health in BCS.

Methods: A comprehensively searched of the 4 databases (PubMed, Embase, Web of Science, Cochrane Library) from the database construction until March 1, 2023. The included studies were randomized controlled trials (RCTs) reporting the effects of CE on CRF and cardiometabolic health in BCS. The quality of the literature was assessed by two independent reviewers using the Cochrane Collaboration Risk of Bias Tool. Weight means difference (WMD), or standardized mean difference (SMD), were combined using random or fixed effects models. Subgroup and meta-regression explored heterogeneity as well as covariate effects.

Results: 40 studies were included in the meta-analysis, with 2849 participants. Results showed that CE significantly increased maximal oxygen uptake (VO_2max) (WMD:4.55; 95% CI:2.84, 6.26; $I^2 = 91.90\%$, $P < 0.001$) and reduced body weight (BW) (WMD: 1.61; 95% CI: 2.44, −0.78; $I^2 = 38.60\%$, $P = 0.032$) and body mass index (BMI) (WMD: 0.86; 95% CI: 1.43, −0.29; $I^2 = 70.50\%$, $P < 0.001$) in BCS. Subgroup analysis showed that BMI (WMD: 1.15; 95% CI: 1.89, −0.41; $I^2 = 76.90\%$, $P < 0.001$) and VO_2max (WMD:4.21; 95% CI:2.40, 6.02; $I^2 = 96.4\%$, $P < 0.001$) were more effective with supervision. Meta-regression analysis showed that sample size had a significant moderating effect on BW (Coeff: 0.03, 95% CI: 0.00, 0.06).

Conclusions: CE significantly increases CRF in BCS and improves most cardiometabolic health-related outcomes. In addition, there will be a need for many larger RCTs to explore the effects of CE on inflammatory biomarkers in BCS.

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1. Introduction

Breast cancer (BC) is one of the most common malignancies in women worldwide and seriously threatens women's physical and mental health [1]. In the United States, BC accounts for 31% of newly diagnosed malignancies in women, with approximately 43,000 BC patients dying in 2022. Although chemotherapy, targeted therapy, surgery, endocrine therapy, immunotherapy, and radiotherapy remain conventional treatments for BC [2], these methods often come with side effects such as cardiac toxicity, metabolic syndrome, and physical fatigue, further reducing the quality of life of breast cancer survivors (BCS) [3,4]. In particular, cardiac toxicity and increased sedentary behavior after treatment lead to a decrease in cardiorespiratory function and increase body fat percentage [5]. Research has shown that cardiac toxicity and cardiovascular complications are the main threats to the life and health of BC patients in the early stages. BCS risk developing cardiovascular disease more than their peers without BC [6].

In current clinical practice, reducing the use of chemotherapy drugs or radiation dosage, improving the methods of drug administration, and using cardioprotective medications, are employed to alleviate the side effects of cancer treatment [2]. However, it should be noted that adjusting the dosage may reduce the effectiveness of tumor-killing, and the use of cardiovascular drugs may also produce new side effects [7]. Therefore, there is an urgent need to find a therapeutic approach to alleviate chemotherapy-induced cardiotoxicity. Exercise is a potential intervention that can stimulate various physiological and biochemical adaptations that can reduce chemotherapy-induced cardiac injury without compromising drug efficacy [8]. Currently, the American College of Sports Medicine and the American Cancer Society recommends that cancer survivors engage in appropriate aerobic combined with resistance exercise (CE) as an adjunct to cancer treatment weekly [9,10]. Cardiopulmonary function (CRF), a predictor of cardiovascular prognosis, decreases by 31% throughout cancer treatment, and VO_2max, the gold standard for assessing CRF, reduces by 6%–10% throughout chemotherapy [11]. A recent meta-analysis showed that CE effectively increased maximal and peak oxygen uptake in BCS, improved cardiopulmonary function, and reduced triglyceride (TG) levels. However, the included literature for this study was small and of low quality and did not elucidate the effect of CE on treatment outcomes [12]. Furthermore, in a study on metabolic syndrome, sarcopenia, and circulating biomarkers in overweight and obese BCS, it was shown that CE effectively relieves fatigue in BCS, boosts their substance metabolism, enhances immune function, and reduces inflammation, but this study lacked intervention reproducibility and may have experimental errors, and compliance of patients outside of a supervised environment could not be determined [13].

In summary, the efficacy of CE for CRF and cardiometabolic health in BCS has yet to be systematically evaluated, and the optimal combination of aerobic and resistance exercise forms has yet to be discovered. Therefore, this study used a meta-analysis to investigate the effect of CE on indicators related to CRF and cardiometabolic health in BCS, and meta-regression analysis and subgroup analysis were used to explore the variables that might influence the effect of the CE intervention.

2. Methods

This meta-analysis follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [14]. No patient consent or ethical approval is required, as all data are based on previously published data.

2.1. Search strategies and study selection

We conducted a comprehensive search of the four databases (PubMed, Embase, Web of Science, Cochrane Library) from the database construction until March 1, 2023. We combined Boolean operators with medical subject terms for the search. The following concept-related subject terms and keywords are indirectly retrieved: 'breast cancer', 'aerobic exercise', 'resistance exercise', 'cardiorespiratory fitness', and 'cardiometabolic'. There are no language, ethnicity, or region of publication restrictions on publications (**Appendix 1 Search strategy**).

All titles, abstracts, and primary text of the literature were reviewed independently by two authors (Lj C and Wx T) to ensure that the included studies met the potential criteria. If two authors disagreed on the extraction of studies for inclusion, then a third author (HM) resolved these issues.

2.2. Inclusion and exclusion criteria

We included studies in the meta-analysis according to the PICOS principles.

(1) Participants: all participants were female BCS. By broad definition, when an individual is diagnosed with cancer, he becomes a cancer survivor and remains one for the rest of his life [15].
(2) Intervention: the intervention includes any form of aerobic exercise (AE) (exercises aimed at improving cardiovascular health, such as running, swimming, and cycling.) combined with resistance exercise (RE) (Exercises aimed at improving muscle strength, such as elastic bands, weightlifting, dumbbells).
(3) Comparison: the comparison group is all the control groups without exercise intervention, such as the daily care group, waiting list, and health education group.
(4) Outcomes: at least one of the following was assessed: Body weight (BW), body fat % (BF%), body mass index (BMI), waist circumference (WC), hip circumference (HC), waist-to-hip ratio (WHR), maximal oxygen uptake (VO_2max), fasting blood glucose (FBG), serum insulin (SI), Homeostasis model assessment-insulin resistance (HOMA-IR), systolic blood pressure (SBP),

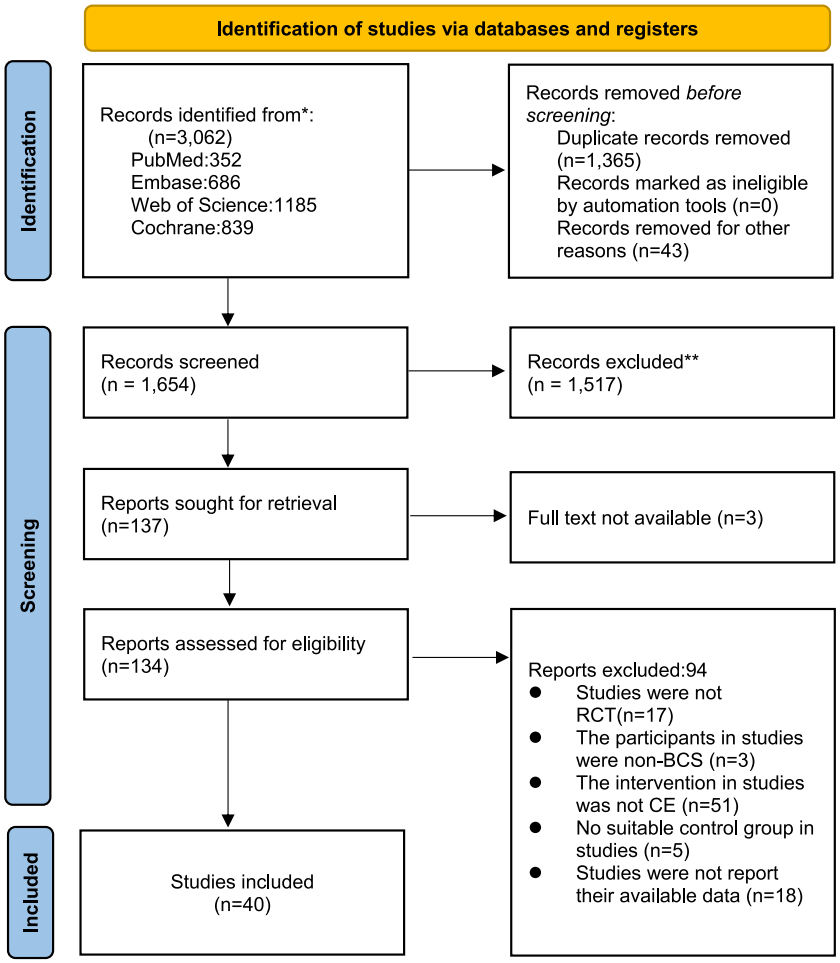

Fig. 1. Literature review flowchart. BCS, breast cancer survivor. CE, aerobic combined resistance exercise. RCT, randomized controlled trial.

diastolic blood pressure (DBP), triglycerides (TG), total-cholesterol (TC), high density lipoprotein (HDL), low density lipoprotein (LDL), interleukin-6 (IL-6), C-reactive protein (CRP), and tumor necrosis factor-α (TNF-α).

(5) Study: all randomized controlled trials.

Studies will be excluded if they meet the following criteria.

(1) Exercise in combination with other interventions, such as psychotherapy.
(2) Experimental protocols, review articles, and animal studies.
(3) No data or incomplete data in the study.

2.3. Data extraction, outcome measures

Two independent authors (Lj C and Wx T) extracted relevant information from eligible studies, including first authorship, year of publication, participant demographics (age, sample size), outcomes related to cardiorespiratory fitness and cardiometabolic health, variables used for subgroup analysis or regression analysis, and information on the control group. If the data is unavailable in the articles or additional files, we will contact the corresponding author to obtain it. When two authors disagreed on the information extracted, it was reassessed by a third author (H M).

A total of 19 outcomes were extracted, including five parts: cardiorespiratory health-related outcomes (including VO_2max; measured as a single-stage submaximal treadmill test, Bruce protocol estimation), body composition-related outcomes (including weight, waist, hips, waist-hip ratio, BMI; measured as routine measurements, bioresistance analysis, dual-energy X-ray absorptiometry), blood pressure-related outcomes (including SBP, DBP; measured as a sphygmomanometer), adipokine/inflammatory marker-related outcomes (including TC, TG, HDL, LDL, IL-6, CRP, TNF-α; measured as blood biochemical assays), and glucose/insulin metabolism marker-related outcomes (including FBG, serum insulin, HOMA-IR; measured as blood biochemical assays).

Table 1
Demographic characteristics of included 40 RCT studies.

Author, year	Intervention/N	Control/N	Baseline age (mean ± sd)		Intervention duration, frequency	Stage of cancer	Treatment	Region	Outcomes	Description
			Intervention	Control						
Lee et al., 2019	AE + RE = 50	Usual care = 50	53	52	16weeks, 3times, 80min	1–3	After	USA	SBP, HDL, LDL	A 16-week supervised aerobic and resistance exercise intervention appeared to reduce the Framingham Risk Score-predicted 10-year risk of cardiovascular disease in women with early-stage breast cancer with overweight condition or obesity.
Dieli-Conwright et al., 2021	AE + RE = 29	Usual care = 27	46.8 ± 10.2	46.8 ± 10.2	16weeks, 3times, 80min	NA	After	USA	VO2max	Clinical exercise interventions may attenuate existing health disparities among minority breast cancer survivors.
Chung et al., 2022	AE + RE = 16	Usual care = 16	50.3 ± 7.7	52.4 ± 8.9	12weeks, 2-3times. 55,min	1–3	During	Thailand	VO2max	Moderate-to-high–intensity exercise training in breast cancer patients undergoing chemotherapy may prevent impaired cardiac function.
Gómez et al., 2011	AE + RE = 8	Usual care = 8	50	48.8	8weeks, 3times, 90min	NA	After	Spain	IL-6, TNF-a,	A combined (aerobic + strength) 8-week exercise training intervention did not induce major changes in the basal cytokine levels of breast cancer survivors.
Jones et al., 2020	AE + CRE = 26	Delayed intervention = 25	55.8 ± 7.2	55.9 ± 7.1	12weeks, 2times, 60min	NA	After	New Zealand	BW, BMI, BF%, SBP, VO2max	Twelve weeks training improves muscle and cardiorespiratory fitness and is also an effective strategy for decreasing a proven cardiovascular risk factor in breast cancer survivors.
Mijwel et al., 2018	HIIT + RE = 43	Usual care = 30	54.4 ± 10.3	52.6 ± 10.2	16weeks, 2times, 60min	1-3a	During	Sweden	BW	Sixteen weeks of training significantly improved muscle strength and reduced pain sensitivity. Both exercise programs were well tolerated and were equally efficient in preventing increases in body mass and in preventing declines in cardiorespiratory fitness.
Bolam et al., 2019	HIIT + RE = 74	Usual care = 60	54.4 ± 10.3	52.6 ± 10.2	16weeks, 2times, 60min	1-3a	During	Sweden	BW, VO2max	The findings provide novel evidence that being involved in an exercise program during chemotherapy can have long-term benefits for women with breast cancer.
Dieli-Conwright et al., 2018	AE + RE = 50	Usual care = 50	<60.0	<60.0	16weeks, 3times, 80min	NA	After	USA	VO2max	A 16-week combined aerobic and resistance exercise program designed to address metabolic syndrome in ethnically-diverse overweight or obese breast cancer survivors also significantly improved quality of life and physical fitness.
Chang et al., 2020	AE + RE = 23	Keep daily = 23	51.4 ± 7.5	50.0 ± 6.1	12weeks, 2times, 60min	NA	After	Korea	BW, BMI, BF%, WC, TG, TC, HDL, LDL, FBG, FBI, IR	In conclusion, a 12-week community-based exercise intervention resulted in significant reductions in serum β-catenin and Wnt1-inducible signaling pathway protein-1 levels, accompanied by favorable improvements in body composition, physical fitness, and biochemical parameters in breast cancer survivors.
Mutrie et al., 2007	AE + CRE = 99	Usual care = 102	51.6 ± 9.5	51.3 ± 10.3	12weeks, 3times, 45min	0–3	During	Britain	BMI	Supervised group exercise provided functional and psychological benefit after a 12 week intervention and six months later.
Casla et al., 2015	AE + RE = 47	Usual care = 47	45.9 ± 8.2	51.9 ± 8.2	12weeks, 2times, NA	1–3	After	Spain	BW, BMI, BF%, WHR	A combined exercise intervention produced considerable improvement in cardiorespiratory fitness, physical function, and quality of life in breast cancer patients

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Table 1 (*continued*)

Author, year	Intervention/N	Control/N	Baseline age (mean ± sd)		Intervention duration, frequency	Stage of cancer	Treatment	Region	Outcomes	Description
			Intervention	Control						
										previously treated with chemotherapy and radiation therapy.
Luca et al., 2016	AE + RE = 10	Keep daily = 10	52.2 ± 9.7	46.0 ± 2.8	24weeks, 2times, 90min	1–3	After	Italy	VO2max, BF%	After 24 weeks the intervention group showed significant improvement in VO2max (38.8%), strength of upper and lower limbs (ranging from 13 to 60%) and decrease in fat mass percentage (6.3%)
Paulo et al., 2018	AE + RE = 18	Placebo = 18	63.2 ± 7.1	66.6 ± 8.6	36weeks, 3times, 70min	0-3a	After	Brazil	BW, BF%, TC, TG, HDL, LDL, FBG, CRP	Our aerobic + resistance exercise program prevented fat gain, but may not have been sufficient to improve metabolic or bone health markers in older breast cancer survivors undergoing aromatase inhibitor therapy
Dieli-Conwright et al., 2018	AE + RE = 50	Usual care = 50	52.8 ± 10.6	53.6 ± 10.1	16weeks, 150min AE+2-3times RE	0–3	After	USA	BW, BMI, BF%, SBP, DBP, HDL, TG, TC, FBG, FBI, IGF, HC, CRP, IL-6, TNF-α, WC, IR	Combined resistance and aerobic exercise effectively attenuated metabolic syndrome, sarcopenic obesity, and relevant biomarkers in an ethnically diverse sample of sedentary, overweight, or obese survivors of breast cancer.
Ergun et al., 2013	AE + RE = 20	Education = 20	49.7 ± 8.3	50.3 ± 10.4	12weeks. 3times,45min	NA	During	Turkey	IL-6, IL-8, TNF-α	Exercise programmes are safe and effective on quality of life and depression in breast cancer patients whose treatments are complete.
Herrero et al., 2006	AE + RE = 10	Keep daily = 10	50.0 ± 5.0	51 ± 10	8weeks, 3times, 90min	NA	After	Spain	BW, BF%, VO2max	Combined cardiorespiratory and resistance training, even of very brief duration, improves the quality of life and the overall physical fitness of women breast cancer survivors
Hojan et al., 2020	AE + RE = 26	Usual care = 21	54.4 ± 6.3	54.6 ± 5.3	9weeks, 5times, 50min	1-3a	During	Poland	SBP, DBP, CRP, IL-6	Moderate-intensity exercise training prevented a decrease in the LVEF and physical capacity during trastuzumab therapy in HER2+ BC. Further research is needed to validate our results.
Monazzami et al., 2021	AE + RE = 21	Keep daily = 21	46.2 ± 8.7	46.1 ± 8.9	8weeks, 3times, 80min	1–2	During	Iran	BW, BMI, BF%, TNF-a, WC, WHR	The results indicate that resistance and endurance training could be used as a useful method to improve salivary pro-inflammatory factors and hormonal levels in patients with breast cancer.
Ligibel et al., 2008	AE + RE = 51	Usual care = 49	52.0 ± 9.0	53.0 ± 9.0	16weeks, 2times,140min	1–3	After	USA	BW, BMI, BF%, FBI, FBG, WC, HC, WHR, IR	Participation in an exercise intervention was associated with a significant decrease in insulin levels and hip circumference in breast cancer survivors. The relationship between physical activity and breast cancer prognosis may be mediated, in part, through changes in insulin levels and/or changes in body fat or fat deposition.
Kim et al., 2017	AE + RE = 15	Keep daily = 15	56.0 ± 6.5	52.4 ± 6.5	12weeks, 3times, 50min	NA	After	Korea	BW, BF%, FBI, CRP, WC	Long-term exercise improves physical fitness and biomarker levels related to metabolic conditions in breast cancer survivors.
Hiensch et al., 2021	HIIT + RE = 30	Usual care = 29	52.2 ± 10.1	52.9 ± 10.1	16weeks, 2times, 60min	1-3a	During	Sweden	IL-6, IL-10	Supervised training partially counteracted the increase in inflammation during chemotherapy, i.e., IL-6 and soluble CD8a, which resulted in lower fatigue levels postintervention.
Rogers et al., 2013	AE + RE = 15	Keep daily = 13	58.0 ± 6.1	53.7 ± 13.9	12weeks, 2times RE, 150min AE	1-3a	After	USA	VO2max, BF%, BMI, IL-6, IL-8.IL-10, TNF-α, WHR	Physical activity behavior change interventions in BCS can achieve large effect size changes for several health outcomes. Although effect sizes for inflammatory markers were often small and not significant, changes were in the hypothesized direction for all except IL-6 and IL-10.

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Table 1 (*continued*)

Author, year	Intervention/ N	Control/N	Baseline age (mean ± sd)		Intervention duration, frequency	Stage of cancer	Treatment	Region	Outcomes	Description
			Intervention	Control						
Thomas et al., 2017	AE + RE = 60	Usual care = 61	62.0 ± 7.0	60.5 ± 7.0	52weeks, 2times RE, 150min AE	NA	After	USA	BW, BMI, BF%	A combined resistance and aerobic exercise intervention improved body composition in breast cancer survivors taking aromatase inhibitors.
Dieli-Conwright et al., 2018	AE + RE = 10	Keep daily = 10	53.0 ± 10.0	55.0 ± 4.5	16weeks, 2-3times, 80min	1–3	During	USA	BW, BF%, FBG, FBI, TC, LDL, HDL, TG, WC, IR	A 16-week aerobic and resistance exercise intervention attenuates adipose tissue inflammation in obese postmenopausal breast cancer survivors.
Nuri et al., 2012	AE + RE = 14	Keep daily = 15	58.3 ± 6.3	58.3 ± 6.3	15weeks, 2times 45min AE, 2times RE	1–3b	After	Iran	BW, BMI, SBP, VO2max, TG, HDL, FBG, FBI, WC, HC, WHR, IR	Combination exercise training can improve metabolic syndrome parameters in postmenopausal women with breast cancer.
Cornette et al., 2016	AE + RE = 20	Keep daily = 22	49	52	27weeks, 2times 40 min AE, 1time RE	1–3b	During	France	VO2max, BMI	In breast cancer patients, a home-based supervised program during chemotherapy and radiotherapy treatment may be safe, feasible and increase VO2peak.
Dethlefsen et al., 2016	HIIT + RE = 37	Education = 37	46.0 ± 9.6	48.2 ± 7.8	24weeks, 180min	1–3	During	Denmark	BW, BMI, BF%, VO2max, WC	Systemic changes to a 2 h exercise session reduced breast cancer viability, while adaptations to 6 months of training had no impact.
Alberto et al., 2022	AE + RE = 32	Keep daily = 28	52.6 ± 8.8	52.0 ± 9.4	12weeks, 2times, 60min	NA	After	Spain	VO2max	In female breast cancer survivors who had completed their core treatments within the past 10 years, adding two weekly sessions of supervised resistance training to a prescription of home-based physical activity for 12 weeks produced a large increase in upper-, lower-, and full-body muscular strength, while other fitness components and patient-reported outcomes did not improve
Travier et al., 2015	AE + RE = 102	Usual care = 102	NA	NA	18weeks, 2times, 60min	M0	During	Netherlands	BW, VO2max	A supervised 18-week exercise programme offered early in routine care during adjuvant breast cancer treatment showed positive effects on physical fatigue, submaximal cardiorespiratory fitness, and muscle strength.
Vincent et al., 2020	AE + RE = 32	Keep daily = 31	56.5	50.5	24weeks, 2times AE, 1time RE, 60min	1–3	During	France	VO2max, BMI	Home-based physical activity in breast cancer patients has a positive effect on cardiopulmonary function and physical functions, with no differences based on the timing of this program based on specific cancer treatment.
Reis et al., 2018	AE + RE = 14	Keep daily = 14	47.6 ± 7.6	45.8 ± 8.1	12weeks, 3times, 60min	1–4	During	Brazil	BMI, VO2max,	Combined training was effective in decreasing pain and increasing VO2 max, flexibility and static strength in patients with breast cancer
Parma et al., 2015	AE + RE = 31	Keep daily = 32	57.6 ± 6.6	54.4 ± 7.0	24weeks, 3times, 60min	NA	After	USA	BW, BF%, BMI, IL-6, IL-8, TNF-A, CRP	The results support the effectiveness of yoga-based exercise modified for breast cancer survivors for improving body composition. Larger studies are needed to determine if there are significant changes in inflammatory serum markers as a result of specific exercise modalities.
Lee et al., 2020	AE + RE = 50	Usual care = 50	52.8 ± 10.6	53.6 ± 10.1	16weeks, 150min AE, 2-3times RE	1–3	After	USA	SBP, CRP, TC, HDL	A 16-week aerobic and resistance exercise intervention is an effective approach to reduce the risk of cardiovascular disease in breast cancer survivors.
Dieli-Conwright	AE + RE = 29	Keep daily = 27	46.9 ± 10.2	46.7 ± 10.0	16weeks, 3times, 80min	0–3	During	USA	BW, BF%, SBP, DBP, HDL, TG, FBG, WC	Hispanic breast cancer survivors appear to have poorer metabolic profiles and therefore may derive relatively larger metabolic changes from exercise compared with

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Table 1 (*continued*)

Author, year	Intervention/ N	Control/N	Baseline age (mean ± sd)		Intervention duration, frequency	Stage of cancer	Treatment	Region	Outcomes	Description
			Intervention	Control						
et al., 2019										non-Hispanic breast cancer survivors. Clinical exercise interventions may attenuate existing health disparities across diverse groups of breast cancer survivors.
D'Alonzo et al., 2021	AE + RE = 50	Consult = 51	59.3 ± 8.8	60.5 ± 8.5	48weeks, 180min AE, 2times RE	NA	After	USA	FBG, FBI, IR	The weight loss and combined intervention groups showed significant reductions in levels of: insulin, C-peptide, homeostatic model assessment 2 (HOMA2) insulin resistance (IR), and HOMA2 beta-cell function (β) compared to the control group. Independent of intervention group, weight loss of ≥10% was associated with decreased levels of insulin, C-peptide, and HOMA2-IR compared to 0–5% weight loss. F
Irwin et al., 2015	AE + RE = 61	Usual care = 60	62.0 ± 7.0	60.5 ± 7.0	48weeks, 150min AE, 2times RE	0–3	During	USA	BW, VO2max	Exercise significantly reduced body composition and aerobic capacity in breast cancer patients taking aromatase inhibitors.
Rahnama et al., 2010	AE + RE = 14	Keep daily = 15	NA	NA	15weeks, 2times 35min AE, 2times 60min RE	1–3b	After	Iran	BW, VO2max, SBP, BMI, WC, HC, WHR	It can be concluded that exercise training may improve maximum aerobic capacity, RHR and anthropometric variables in postmenopausal women with breast cancer.
Mijwel et al., 2019	HIIT + RE = 74	Usual care = 60	52.7 ± 10.3	52.6 ± 10.6	16weeks, 2times, 60min	1-3a	During	Sweden	BW, BMI, VO2max	RT-HIIT displayed beneficial effects on cancer-related fatigue, symptoms, and muscle strength, 12 months following the commencement of chemotherapy.
Mostarda et al., 2017	AE + RE = 9	Keep daily = 9	30–59	30–59	4weeks, 3times, 70min	1–3	During	Brazil	BW, BMI, SBP, DBP, BMI, VO2max	A month of exercise trianing is able to reverse impaired cardiorespiratory fitness and autonomic modulation in women with breast cancer receiving adjuvant therapy.
Sturgeon et al., 2022	AE + RE = 80	Keep daily = 81	59.2 ± 8.2	58.7 ± 8.4	12weeks, 180min AE, 2times RE	NA	After	USA	CRP	In breast cancer survivors with overweight or obesity, weight loss or exercise plus weight loss reduced measures of inflammation that are associated with breast cancer recurrence and cardiovascular death.

Note: AE, aerobic exercise. RE, resistance exercise. BC, breast cancer. NA, not applicable. RCT, randomized controlled trial. BW, body weight. BMI, body mass index. SBP, systolic blood pressure. DBP, diastolic blood pressure. CRP, C-reactive protein. TNF-α, tumor necrosis factor-α. VO2max, maximal oxygen uptake. USA, United States of America. HIIT, high-intensity interval training. IL-6, interleukin-6. HC, hip circumference. WC, waist circumference. WHR, waist-to-hip ratio. BF%, body fat %. FBG, fasting blood glucose. FBI, fasting blood insulin. HOMA-IR, homeostasis model assessment-insulin resistance. TC, total-cholesterol. TG, triglyceride. HDL, high density lipoprotein. LDL, low density lipoprotein.

2.4. Quality assessment

Two authors (Lj C and Wx T) independently reviewed included studies based on the Cochrane Collaboration's risk-of-bias tool [16]. When disagreements arose, a third experienced author (H M) adjudicated. We assessed the 7 risk biases, including random sequence generation, allocation concealment, participant and personnel blinding, blinding of the outcome assessor, incomplete data, selective reporting, and other sources of bias. These entries are classified as high risk, low risk, and unclear risk.

2.5. Statistical analyses

We performed a traditionally paired meta-analysis. First, means and standard deviations (SD) were extracted for baseline and endpoints in the study. If data were missing from the study, an attempt was made to convert the data to a standard format using relevant methods [17,18]. If the studies were three-armed or more than three-armed, we split them into multiple studies for analysis. Quantitative pooled analyses were performed using random or fixed effects models to obtain weighted mean differences (WMDs) and 95% confidence intervals (CIs), and standardized mean differences (SMDs) and 95% confidence intervals (CIs) were calculated if some outcome measures differed in units, with $P < 0.05$ indicating significance [16]. Forest plots were generated, and the Cochran Q test was used to analyze the presence of heterogeneity in the studies, with I^2>50% or $P < 0.1$ considered high heterogeneity [19]. Egger test was used to detect publication bias when studies were larger than 10, with $P < 0.05$ indicating the presence of bias; in addition, contour-enhanced funnel plots were also generated to assess potential publication bias qualitatively, and when the heterogeneity of results was high, publication bias was mainly referred to the Egger test [20,21]. A literature-by-deletion approach was used to analyze the sensitivity of the studies.

To better detect sources of heterogeneity and variability in outcomes across variables, subgroup analyses were conducted for the primary outcomes, with variables of interest including region (Americas, other areas), supervision (supervised, unsupervised), and active treatment or not. In addition, multivariate meta-regression analyses were performed on VO_2max, BW, and BMI to understand the sources of heterogeneity better, as they had a significant heterogeneity, were significantly different, and had a sufficient number of studies (≥10). Size effects for effect estimates were calculated using a restricted maximum likelihood method using a randomized meta-regression model [22]. 95% confidence intervals in the regression coefficients, p-values, I^2, and corrected R^2 values will be reported. The corrected R^2 was used to assess the extent to which our included variables explain the variance in the experimental results. The variables for which meta-regression analyses were conducted were continuous, including year of publication, sample size, length of intervention, and age. All analyses were conducted in Stata software 14.2 (Stata, Corp, College Station, Texas, USA).

3. Results

3.1. Characteristics of the included studies

We obtained 3062 studies from the database and, after initial screening, excluded 1365 duplicate studies, 43 conference abstracts, 1517 studies with irrelevant content, and 3 studies for which full text was not available. The abstracts of the remaining 134 studies were further evaluated in full text, of which 17 were non-RCT studies, 3 studies did not match the study population, 51 studies did not match the intervention type, 5 studies did not have a control group, and 18 studies did not report their data. The final 40 studies were included in our meta-analysis, and the screening process is shown in Fig. 1.

All 40 studies [5,13,23–60] were randomized controlled studies, three of which were randomized parallel controlled trials. A total of 2849 participants were included in the studies, 1450 in the intervention group and 1399 in the control group, with a mean age of 46.0–66.6 years, all female. The participants' stage of disease was 0–4, and the mean length of the intervention was 17.9 weeks. Most of the studies were from the Americas (17, 42.5%) and Europe (15, 37.5%). Basic study information, as well as demographic characteristics, are presented in Table 1. In addition, 19 categories of outcomes related to CRF and cardiometabolic health were reported, and the main results, as well as subgroup and regression analyses, are presented in Tables 1 and 2 and **3**.

3.2. Quality of the included studies

Of the 40 studies included, 17 studies [5,13,23–25,27–29,34,37,39,40,47,48,52,56,59] were considered to be at low risk of bias in random sequence generation, 14 studies [5,13,23–25,28,29,33,34,37,47,52,56,59] were considered to be at low risk of bias in allocation concealment, all studies [5,13,23–60] were at high risk of performance bias, and similarly, 4 studies [25,36,59,60] were at high risk of detection bias. In selection bias, 8 studies [13,28,31,42,49,52,56,60] had low risk bias. Finally, 10 studies [23,25–27,30,36,38,41,47,50] were considered at high risk of other bias. For detailed information, see Table S1.

3.3. Primary results

3.3.1. BW

Twenty-two studies [13,27,28,30,33,35–37,40–45,47,50,52,54–57,60] described outcomes in BW with 1554 participants, 796 in the experimental group and 758 in the control group. Results from the random effects model showed that CE significantly reduced BW by 1.61 kg (WMD: 1.61; 95% CI: 2.44, −0.78) (Fig. S1), with high heterogeneity (I^2 = 38.60%, P = 0.032). The Egger test's non-significance suggests there may be no publication bias (P_{Egger} = 0.066) **(Table 2).**

Table 2
The meta-analysis results of the effect of aerobic combined resistance exercise on cardiopulmonary function and cardiometabolic health of breast cancer survivors.

Outcomes	Number of studies	Number of participants		Pooled effect sizes			Heterogeneity		$P_{Egger\ test}$
		Intervention	CON	WMD or SMD		P	I^2	P	
WMD									
BW	22	796	758	−1.61	(-2.44, −0.78)	<0.0001	38.60%	0.032	0.066
BF%	16	432	430	−2.41	(-3.45, −1.37)	<0.0001	71.10%	<0.0001	0.005
BMI	19	560	551	−0.86	(-1.43, −0.29)	0.003	70.50%	<0.0001	0.655
WC	10	283	284	−4.48	(-7.10, −1.87)	<0.0001	80.70%	<0.0001	0.819
HC	4	129	129	−2.37	(-3.77, 0.97)	0.128	24.20%	0.266	–
WHR	6	122	120	0.00	(-0.01, 0.00)	0.754	0.00%	0.578	–
VO_2max	19	647	617	4.55	(2.84, 6.26)	<0.0001	91.90%	<0.0001	0.584
SBP	8	211	213	−9.14	(-13.97, −4.31)	<0.0001	85.80%	<0.0001	–
DBP	5	133	133	−7.80	(-14.09, −1.51)	0.015	86.30%	<0.0001	–
TG	6	163	165	−75.07	(-96.94, −53.20)	<0.0001	88.70%	<0.0001	–
TC	3	101	101	−33.21	(-59.07, −7.34)	0.009	82.90%	0.001	–
HDL	7	213	215	14.75	(8.93, 20.56)	<0.0001	94.20%	<0.0001	–
LDL	3	101	101	−32.34	(-58.69, −5.99)	<0.0001	90.60%	<0.0001	–
SMD									
FBG	8	246	247	−0.74	(-1.30, −0.19)	0.006	87.80%	<0.0001	–
HOMA-IR	6	198	198	−0.65	(-0.99, −0.30)	<0.0001	46.70%	0.111	–
FBI	9	261	262	−0.80	(-1.24, −0.36)	<0.0001	81.30%	<0.0001	–
IL-6	8	187	183	−0.32	(-1.44, 0.81)	0.583	95.30%	<0.0001	–
CRP	6	212	209	−0.79	(-1.92, 0.35)	0.173	96.00%	<0.0001	–
TNF-α	6	145	144	−0.83	(-1.94, 0.29)	0.147	94.20%	<0.0001	–

Note: BW, body weight. BMI, body mass index. CON, control group. SBP, systolic blood pressure. DBP, diastolic blood pressure. CRP, C-reactive protein. TNF-α, tumor necrosis factor-α. VO_2max, maximal oxygen uptake. IL-6, interleukin-6. HC, hip circumference. WC, waist circumference. WHR, waist-to-hip ratio. BF%, body fat %. FBG, fasting blood glucose. FBI, fasting blood insulin. HOMA-IR, homeostasis model assessment-insulin resistance. TC, total-cholesterol. TG, triglyceride. HDL, high density lipoprotein. LDL, low density lipoprotein. WMD, weighted Mean Difference. SMD, standard mean difference. "-" indicates that there are less than 10 studies and Egger testing cannot be conducted.

Table 3
Subgroup analysis of primary results.

Subgroup variables		Number of studies	Number of participants		Pooled effect sizes			Heterogeneity	
			Intervention	CON	WMD		P	I^2	P
BW									
Supervision	Supervised	20	722	682	−1.62	(-2.54. −0.78)	<0.0001	44.1%	0.016
	Unsupervised	2	74	76	−1.54	(-3.57, 0.50)	0.138	0.0%	0.83
Region	America	8	290	289	−2.27	(-3.51, −1.03)	<0.0001	50.3%	0.05
	Other regions	14	506	469	−0.63	(-1.32, −0.06)	0.048	0.0%	0.659
Active cancer treatment	During	11	477	438	−1.76	(-3.08, −0.45)	0.007	68.0%	0.001
	After	11	319	320	−1.19	(-2.17, −0.21)	0.021	0.0%	0.961
BMI									
Supervision	Supervised	14	419	409	−1.15	(-1.89, −0.41)	0.003	76.9%	<0.0001
	Unsupervised	5	141	142	−0.38	(-0.89, 0.13)	0.145	0.0%	0.421
Region	America	7	230	228	−1.07	(-2.06, −0.08)	0.034	84.1%	0
	Other regions	12	330	323	−0.77	(-1.52, 0.00)	0.048	54.5%	0.01
Active cancer treatment	During	10	269	261	−0.77	(-1.66, 0.12)	0.152	66.0%	0.002
	After	19	291	290	−1.03	(-1.88, −0.18)	0.037	76.2%	<0.0001
VO2max									
Supervision	Supervise	14	131	131	4.21	(2.40, 6.02)	<0.0001	91.1%	<0.0001
	Unsupervise	5	516	486	5.42	(-0.01, 10.84)	0.050	94.3%	<0.0001
Region	America	5	197	195	7.52	(3.19, 11.86)	<0.0001	96.4%	<0.0001
	Other regions	14	450	422	2.44	(1.25, 3.63)	0.001	67.1%	<0.0001
Active cancer treatment	During	9	421	395	2.02	(1.19, 2.84)	0.003	46.3%	0.061
	After	10	226	222	6.88	(2.81, 10.96)	<0.0001	95.0%	<0.0001

Note: Patients who received chemotherapy or radiotherapy as initial cancer treatment or as treatment for metastases or cancer recurrence were classified as "during", and those trials that included patients who were not currently receiving chemotherapy or radiotherapy were classified as "after". Trials that included both types of patients were classified as "both"; trials that included patients receiving androgen suppression therapy without chemotherapy or radiotherapy were defined as "after".BW, body weight. BMI, body mass index. CON, control group. VO_2max, maximal oxygen uptake. WMD, weighted Mean Difference. Intervention methods*, the first method is aerobic exercise and resistance exercise were performed in a single intervention, the second method is aerobic exercise and resistance exercise were not performed in a single intervention.

Table 4
Meta-regression analysis ofprimary outcomes.

Variables		Age				Intervention duration (weeks)				Sample size				Publication Date (year)				I^2	Adjusted R^2(%)
	n	Coeff	LCI	UCI	P	Coeff	LCI	UCI	P	Coeff	LCI	UCI	P	Coeff	LCI	UCI	P		
BW	22	−0.06	−0.40	0.29	0.734	−0.01	−0.12	0.09	0.805	0.03	0.00	0.06	0.045	−0.12	−0.47	0.23	0.486	0.00%	49.87%
BMI	19	0.12	−0.20	0.44	0.444	0.03	−0.10	0.15	0.642	−0.03	−0.10	0.04	0.373	−0.09	−0.36	0.19	0.502	73.58%	−26.63%
VO_2max	19	−0.40	−1.10	0.29	0.234	0.03	−0.24	0.29	0.840	−0.02	−0.13	0.08	0.640	0.13	−0.51	0.77	0.667	92.56%	−9.68%

Note: BW, body weight. BMI, body mass index. CON, control group. VO_2max, maximal oxygen uptake. WMD, weighted Mean Difference. Intervention methods*, the first method is aerobic exercise and resistance exercise were performed in a single intervention, the second method is aerobic exercise and resistance exercise were not performed in a single intervention. Coeff, coefficient; LCI, 95%lower CI; n, number of studies; UCI, 95%upper CI.

Subgroup analyses revealed that heterogeneity may have arisen from supervised studies ($I^2 = 44.10\%$, $P = 0.016$), studies in the Americas ($I^2 = 50.30\%$, $P = 0.05$), and studies that during active treatment ($I^2 = 68.00\%$, $P = 0.001$). Moreover, CE significantly affected BW only in supervised situations (SMD = −1.62, 95%CI, −2.54, −0.78) **(Table 3)**. In the regression analysis, all variables explained 49.87% of the heterogeneity in the study (corrected $R^2 = 49.87\%$). In addition, sample size had a significant moderating effect on BW (Coeff: 0.03, 95% CI: 0.00, 0.06) **(Table 4)**.

3.3.2. BMI

A total of 19 studies [13,27–30,36,38–40,42,43,46,48–50,52,55,56,61] included outcomes for BMI, with 560 participants in the experimental group and 551 in the control group. Analysis using a random effects model showed a significant improvement in BMI with CE (WMD: 0.86; 95% CI: 1.43, −0.29) (Fig. S3) with very high heterogeneity ($I^2 = 70.50\%$, $P < 0.001$). Egger test was similarly non-significance, suggesting that there may be no publication bias ($P_{Egger} = 0.655$) **(Table 2)**.

In subgroup analyses, heterogeneity may have originated from studies where supervision was present in the intervention (WMD: 1.15; 95%CI: 1.89, −0.41; $I^2 = 76.90\%$, $P < 0.001$). In addition, CE significantly affected BMI only in supervised situations (SMD = −1.15, 95%CI, −1.89, −0.41) and after active treatment (SMD = −1.88, 95%CI, −1.88, −0.18). Regression analysis showed a corrected $R^2 = -26.63\%$, which could not account for the variance in the experimental results **(Tables 3 and 4)**.

3.3.3. CRF

A total of 19 RCTs [5,24,27,30,31,33,39,42–44,46–49,54–57,59] reported VO_2max outcomes (participants: 1264), and main effects analysis showed that CE significantly increased VO_2max levels in BCS (WMD:4.55; 95% CI:2.84, 6.26) (Fig. S7). However, heterogeneity between studies was high ($I^2 = 91.90\%$, $P < 0.001$). The Egger test's non-significance suggests there may be no publication bias ($P_{Egger} = 0.584$) **(Table 2)**.

Sources of heterogeneity were found for all variables analyzed in the subgroups. In addition, CE significantly affected VO_2max only in supervised situations (SMD = 4.21, 95%CI, 2.40, 6.02). The regression analysis results showed no significant moderating variables for VO_2max, with a corrected $R^2 = -9.68\%$, which did not explain the variance of the study results **(Tables 3 and 4)**.

3.4. Secondary results

The results of the main effects analysis showed that CE significantly improved BF% (WMD: 2.41, 95%CI: 3.45, −1.37; $I^2 = 71.10\%$, $P < 0.001$), WC (WMD: 4.48, 95%CI: 3.45, −1.37; $I^2 = 80.70\%$, $P < 0.001$), blood pressure (SBP, WMD: 9.14, 95%CI: 13.97, −4.31; $I^2 = 85.80\%$, $P < 0.001$) (DBP, WMD: 7.80, 95%CI: 14.09, −1.51; $I^2 = 86.30\%$, $P < 0.001$), blood lipids (TG, WMD: 75.07, 95%CI: 96.94. −53.20; $I^2 = 88.70\%$, $P < 0.001$) (TC, WMD: 33.21, 95%CI: 59.07, −7.34; $I^2 = 71.10\%$, $P = 0.001$) (HDL, WMD: 14.75, 95%CI: 8.93, 20.56; $I^2 = 94.20\%$, $P < 0.001$) (LDL: WMD: 32.34, 95%CI: 58.69, −5.99; $I^2 = 90.60\%$, $P < 0.001$), FBG (SMD: 0.74, 95%CI: 1.30, −0.19; $I^2 = 87.80\%$, $P < 0.001$), SI levels (SMD: 0.80, 95%CI: 1.24, −0.36; $I^2 = 81.30\%$, $P < 0.001$), HOMA-IR (SMD: 0.65, 95%CI: 0.99, −0.30; $I^2 = 46.70\%$, $P = 0.111$), but not for hip circumference (WMD: 2.37, 95%CI: 3.77, 0.97; $I^2 = 24.20\%$, $P = 0.266$), WHR (WMD: 0.00, 95%CI: 0.01, 0.00; $I^2 = 0\%$, $P = 0.578$) and inflammatory biomarkers (CRP, SMD: 0.79, 95%CI: 1.92, 0.35; $I^2 = 96.00\%$, $P < 0.001$) (IL-6, SMD: 0.32, 95% CI: 1.44, 0.81; $I^2 = 95.30\%$, $P < 0.001$) (TNF-α, SMD: 0.83, 95%CI: 1.94, 0.29; $I^2 = 94.20\%$, $P < 0.001$) The improvement in levels was not statistically different, as detailed in Table 2. Forest plot see Figs. S2–S19. Among the results of >10 studies, only BF% had publication bias (due to high heterogeneity, publication bias was determined using Egger's test) (Figs. S20–S24).

4. Summary

In this study, the minimum period of effective intervention was eight weeks, with a frequency ranging from 1 to 5 times per week. The weekly exercise time ranged from 90 to 270 min, including warm-up and relaxation. The supervised exercise intervention was significantly better than the unsupervised one for both body composition and CRF. In addition, the exercise intervention had a significant intervention effect on BCS both during and after cancer treatment.

5. Discussion

This study is the first meta-analysis to research the effects of CE on cardiopulmonary function and cardiometabolic health in BCS, and we found that CE improved CRF and some outcomes related to cardiometabolic health in BCS significantly but had no statistical difference on inflammatory biomarkers. We also found that CE significantly improved body composition and cardiorespiratory fitness only in the presence of supervision. In addition, significant reductions in BMI were only achieved when CE was performed after active treatment.

As the most prevalent form of cancer in women worldwide, BC is often treated with various approaches, including surgery, radiotherapy, chemotherapy, and targeted therapy. As the clinical field has evolved, survival rates for BCS have improved dramatically, but the cardiotoxicity and cardiovascular disease accompanying the treatment process cannot be ignored. Our study confirmed the effect of CE on promoting VO_2max (WMD = 4.55; 95% CI: 2.84, 6.26; $I^2 = 91.90\%$, $p < 0.001$). CE promotes elevated VO_2max, which in turn enhances BCS resistance, which may be related to the elevated resistance of the organism to oxidative stress [62]. For example, as VO_2max increased, lipid peroxidation, superoxide dismutase/glutathione peroxidase (SOD/GPx) ratio, oxidative stress index (24), and BC risk covariates (hemoglobin, insulin, adipocytokines, inflammatory proteins) all showed varying degrees of

improvement [63–65]. In addition, exercise promotes an increase in VO2max, which modulates changes in the tumor microenvironment, which in turn affects treatment outcome, and studies have shown that the degree of hypoxia in the tumor microenvironment is positively correlated with cancer cell metastasis and mortality [66]. CE increases muscle strength and physical activity levels in BCS while promoting an increase in VO2max, improving their survival quality [67]. Our subgroup analysis showed the same results: only supervised CE had a statistically significant effect on VO_2max. This may be related to the fact that patients can have higher exercise compliance in the presence of supervision. Furthermore, Furthermore, CE on BMI was significant only after active treatment, which may be related to the increased fatigue in BCS during active treatment.

We found a significant improvement effect of CE on BMI (WMD: 0.86; 95% CI: 1.43, −0.29), FBG (SMD: 0.74, 95% CI: 1.30, −0.19) in BCS, in line with previous cohort studies on BCS [68].BMI is a predictor of metabolic and cardiovascular system disease and a risk factor for aggressive biological variation in BCS. The poor prognosis of high BMI in BCS may be associated with the risk of complications from diabetes and heart disease [69,70]. The improvement of BMI and FBG by CE may be related to serum fibroblast growth factor-21, and studies have shown that a three-month CE intervention can regulate glucose metabolic processes in active adults through this factor [71].Moreover, our study found that CE significantly improved blood lipid levels. Previous studies have suggested lipid molecules may be closely linked to cancer development, proliferation, migration, and apoptosis [72]. This may be because CE regulation of lipid metabolism is associated with mRNA expression of post-lipoprotein lipase [73], and increased LPL concentrations promote changes in lipoprotein composition and Apo-E redistribution [74]. Such changes may reduce TG levels and TC/HDL ratios, reducing the risk of concomitant CVD in BC patients [75]. In addition, scheduling AE and RE in the same intervention had a better effect on BMI than non-same intervention. Although no studies have elucidated the mechanisms involved, this may inform the development of future exercise prescriptions.

In terms of insulin improvement, CE significantly reduced insulin secretion and HOMA-IR in BCS, in line with previous studies [76]. obesity in BCS may lead to altered glucose metabolism, higher circulating levels of estrogen, and increased insulin secretion, which in turn promotes the proliferation and growth of cancer cells, an essential cause of BC recurrence. The Messier study noted that overweight and obesity in menopausal women were associated with low cardiorespiratory fitness, low insulin levels, and high blood glucose [77]. The mechanism by which CE reduces insulin and blood glucose may be that the increase in muscle mass and volume promotes gene and protein expression of skeletal muscle amp-activated kinase and glucose transporter proteins [78–80]. In addition, AE in CE improves insulin sensitivity by maintaining or increasing lean body mass, regulating glucose metabolism, and, thus, insulin sensitivity [81].

CE also showed a significant improvement in blood pressure (SBP, WMD: 9.14, 95% CI:13.97, −4.31) (DBP, WMD: 7.80, 95% CI:14.09, −1.51), similar to the results of previous studies [61]. This may be related to increased blood flow to the body and the release of more nitric oxide from endothelial cells during the CE intervention. Furthermore, exercise decreased mRNA for angiotensin II receptors [82], type I and III collagen, smooth muscle α-actin, and transforming growth factor-β1, which improved vascular structure and modulated vasoconstriction [68]. In addition, the control of the autonomic nervous system during exercise plays an important role in regulating blood pressure [82].

The effect of exercise on inflammatory factors has long been shown to have mixed results. Inflammation levels significantly predict obesity and poor health outcomes in BCS [83]. WHEL reported an 18% increase in BC-specific mortality for each unit increase in CRP. A meta-analysis showed that exercise interventions significantly reduced IL-6, TNF-a, and CRP levels in overweight and obese people, with CE, in particular, being the most effective as the optimal exercise intervention for reducing IL-6 and TNF-a levels [84]. It has been shown that CE reduces the expression of toll-like receptor 4 (TLR4) on the surface of $CD14^+$ cells and reduces lipopolysaccharide (LPS) stimulated IL-6 production [85]. Our study found no ameliorative effect of CE on inflammatory factors. A meta-analysis was consistent with our results [86], which may be related to the small sample size of BCS and the broad characteristics of the treatment and disease, and may also be due to the differences in treatment and the stage of the disease in which patients were treated in these studies. This is because there is evidence that the duration of exercise is a determinant of whole-body IL-6 anti [87]. The strength of CE in reducing inflammatory factors in BCS lies in the fact that this combined mode of exercise can both improve cardiorespiratory fitness and blood circulation through AE and increase muscle strength and bone density through RE while increasing basal metabolic rate and further reducing inflammation levels, but our findings did not show this improved effect. Based on our findings, a larger number of RCT trials may be needed in the future to validate the ameliorative effect of CE on biomarkers of inflammation in BCS.

6. Strengths and limitations

This study is the first meta-analysis to examine the effect of CE on cardiopulmonary function and cardiometabolic health in BCS, and we collected studies using a more extensive database than the literature included in previous meta-analyses. Second, we performed subgroup and regression analyses of variables that may have influenced the results, taking account of the effects of age, region, sample size, and year of publication to account for sources of heterogeneity to the extent possible. In addition, we examined the training patterns of CE, which have not been covered in previous studies. This study provides clinical practitioners, BCS, and caregivers with additional treatment options, and the results may help guide decision-making and facilitate more in-depth research in the future.

Several limitations should be addressed in this study. First, the moderately low quality of the literature in our study may have affected the overall quality of the research and the imprecision of the results. Second, although we conducted subgroup and regression analyses, we did not determine the heterogeneity of some of the outcomes. Third, most of the studies we included did not account for diet, a moderating variable that cannot be ignored and could potentially affect the accuracy of some of the results. Given these limitations, we should be cautious in interpreting the results.

7. Conclusion

CE improved BCS's CRF and cardiometabolic health-related outcomes, and the effects on body composition and CRF may not be modulated by age and duration of intervention. Considering the multiple benefits and safety of CE in BCS, it is necessary to recommend CE as an adjunct to the clinical management of BCS and to perform it under supervision whenever possible. In addition, there will be a need for many larger RCTs to explore the effects of CE on inflammatory biomarkers in BCS.

CRediT authorship contribution statement

Linjie Cheng: Writing – original draft, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Wenxiang Tian:** Writing – original draft, Resources, Data curation. **Hua Mu:** Writing – review & editing, Visualization, Validation, Supervision, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e26318.

References

[1] R.L. Siegel, K.D. Miller, N.S. Wagle, A. Jemal, Cancer statistics, 2023, CA A Cancer J. Clin. 73 (1) (2023) 17–48.
[2] A.G. Waks, E.P. Winer, Breast cancer treatment: a review, JAMA 321 (3) (2019) 288–300.
[3] S.A.M. Gernaat, P.J. Ho, N. Rijnberg, M.J. Emaus, L.M. Baak, M. Hartman, et al., Risk of death from cardiovascular disease following breast cancer: a systematic review, Breast Cancer Res. Treat. 164 (3) (2017) 537–555.
[4] M.T. Knobf, S. Jeon, Metabolic syndrome, exercise, and cardiovascular fitness in breast cancer survivors, Journal of the advanced practitioner in oncology 11 (1) (2020) 98–102.
[5] C.M. Dieli-Conwright, K.S. Courneya, W. Demark-Wahnefried, N. Sami, K. Lee, F.C. Sweeney, et al., Aerobic and resistance exercise improves physical fitness, bone health, and quality of life in overweight and obese breast cancer survivors: a randomized controlled trial, Breast Cancer Res. 20 (1) (2018) 124.
[6] T.M. Zagar, D.M. Cardinale, L.B. Marks, Breast cancer therapy-associated cardiovascular disease, Nat. Rev. Clin. Oncol. 13 (3) (2016) 172–184.
[7] A. Padegimas, S. Clasen, B. Ky, Cardioprotective strategies to prevent breast cancer therapy-induced cardiotoxicity, Trends Cardiovasc. Med. 30 (1) (2020) 22–28.
[8] A.J. Smuder, Exercise stimulates beneficial adaptations to diminish doxorubicin-induced cellular toxicity, Am. J. Physiol. Regul. Integr. Comp. Physiol. 317 (5) (2019). R662-r72.
[9] C.E. Garber, B. Blissmer, M.R. Deschenes, B.A. Franklin, M.J. Lamonte, I.M. Lee, et al., American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise, Med. Sci. Sports Exerc. 43 (7) (2011) 1334–1359.
[10] K.H. Schmitz, K.S. Courneya, C. Matthews, W. Demark-Wahnefried, D.A. Galvão, B.M. Pinto, et al., American College of Sports Medicine roundtable on exercise guidelines for cancer survivors, Med. Sci. Sports Exerc. 42 (7) (2010) 1409–1426.
[11] S.J. Foulkes, E.J. Howden, A. Bigaran, K. Janssens, Y. Antill, S. Loi, et al., Persistent impairment in cardiopulmonary fitness after breast cancer chemotherapy, Med. Sci. Sports Exerc. 51 (8) (2019) 1573–1581.
[12] L. Kong, R. Gao, Aerobic exercise combined with resistance exercise training improves cardiopulmonary function and blood lipid of patients with breast cancer: a systematic review and meta-analysis, Medicine 101 (51) (2022) e32391.
[13] C.M. Dieli-Conwright, K.S. Courneya, W. Demark-Wahnefried, N. Sami, K. Lee, T.A. Buchanan, et al., Effects of aerobic and resistance exercise on metabolic syndrome, sarcopenic obesity, and circulating biomarkers in overweight or obese survivors of breast cancer: a randomized controlled trial, J. Clin. Oncol. : official journal of the American Society of Clinical Oncology 36 (9) (2018) 875–883.
[14] M.J. Page, J.E. McKenzie, P.M. Bossuyt, I. Boutron, T.C. Hoffmann, C.D. Mulrow, et al., The PRISMA 2020 statement: an updated guideline for reporting systematic reviews, Br. Med. J. 372 (2021) n71.
[15] Cancer survivors–United States, MMWR Morbidity and mortality weekly report 60 (9) (2007) 269–272, 2011.
[16] H. Jp, Cochrane Handbook for Systematic Reviews of Interventions, The Cochrane Collaboration, 2009. Available from:, Version 5.0. 2. https://training.cochrane.org/handbook/archive/v5.0.2/.
[17] L.V. Hedges, Distribution theory for glass's estimator of effect size and related estimators, J. Educ. Stat. 6 (2) (1981) 107–128.
[18] X. Wan, W. Wang, J. Liu, T. Tong, Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range, BMC Med. Res. Methodol. 14 (1) (2014) 135.
[19] J.P. Higgins, S.G. Thompson, Quantifying heterogeneity in a meta-analysis, Stat. Med. 21 (11) (2002) 1539–1558.
[20] M. Egger, P. Juni, C. Bartlett, F. Holenstein, J. Sterne, How important are comprehensive literature searches and the assessment of trial quality in systematic reviews? Empirical study, Health Technol. Assess. 7 (1) (2003) 1–76.
[21] J.A. Sterne, A.J. Sutton, J.P. Ioannidis, N. Terrin, D.R. Jones, J. Lau, et al., Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials, Br. Med. J. (2011) 343.
[22] Lipsey MW WD. Practical Meta-Analysis. Vol vol. 49. Thousand Oaks, CA: Sage publications2001.
[23] K. Lee, D. Tripathy, W. Demark-Wahnefried, K.S. Courneya, N. Sami, L. Bernstein, et al., Effect of aerobic and resistance exercise intervention on cardiovascular disease risk in women with early-stage breast cancer: a randomized clinical trial, JAMA Oncol. 5 (5) (2019) 710–714.
[24] C.M. Dieli-Conwright, F.S. Fox, D. Tripathy, N. Sami, J. Van Fleet, T.A. Buchanan, et al., Hispanic ethnicity as a moderator of the effects of aerobic and resistance exercise on physical fitness and quality-of-life in breast cancer survivors, Journal of cancer survivorship : research and practice 15 (1) (2021) 127–139.
[25] W.P. Chung, H.L. Yang, Y.T. Hsu, C.H. Hung, P.Y. Liu, Y.W. Liu, et al., Real-time exercise reduces impaired cardiac function in breast cancer patients undergoing chemotherapy: a randomized controlled trial, Ann Phys Rehabil Med 65 (2) (2022) 101485.

[26] A.M. Gómez, C. Martínez, C. Fiuza-Luces, F. Herrero, M. Pérez, L. Madero, et al., Exercise training and cytokines in breast cancer survivors, Int. J. Sports Med. 32 (6) (2011) 461–467.
[27] L.M. Jones, L. Stoner, J.C. Baldi, B. McLaren, Circuit resistance training and cardiovascular health in breast cancer survivors, Eur. J. Cancer Care 29 (4) (2020) e13231.
[28] J.S. Chang, T.H. Kim, I.D. Kong, Exercise intervention lowers aberrant serum WISP-1 levels with insulin resistance in breast cancer survivors: a randomized controlled trial, Sci. Rep. 10 (1) (2020) 10898.
[29] N. Mutrie, A.M. Campbell, F. Whyte, A. McConnachie, C. Emslie, L. Lee, et al., Benefits of supervised group exercise programme for women being treated for early stage breast cancer: pragmatic randomised controlled trial, Br. Med. J. 334 (7592) (2007) 517.
[30] S. Casla, S. López-Tarruella, Y. Jerez, I. Marquez-Rodas, D.A. Galvão, R.U. Newton, et al., Supervised physical exercise improves VO2max, quality of life, and health in early stage breast cancer patients: a randomized controlled trial, Breast Cancer Res. Treat. 153 (2) (2015) 371–382.
[31] V. De Luca, C. Minganti, P. Borrione, E. Grazioli, C. Cerulli, E. Guerra, et al., Effects of concurrent aerobic and strength training on breast cancer survivors: a pilot study, Publ. Health 136 (2016) 126–132.
[32] M. Ergun, S. Eyigor, B. Karaca, A. Kisim, R. Uslu, Effects of exercise on angiogenesis and apoptosis-related molecules, quality of life, fatigue and depression in breast cancer patients, Eur. J. Cancer Care 22 (5) (2013) 626–637.
[33] F. Herrero, A.F. San Juan, S.J. Fleck, J. Balmer, M. Pérez, S. Cañete, et al., Combined aerobic and resistance training in breast cancer survivors: a randomized, controlled pilot trial, Int. J. Sports Med. 27 (7) (2006) 573–580.
[34] K. Hojan, D. Procyk, D. Horyńska-Kęstowicz, E. Leporowska, M. Litwiniuk, The preventive role of regular physical training in ventricular remodeling, serum cardiac markers, and exercise performance changes in breast cancer in women undergoing trastuzumab therapy-an REH-HER study, J. Clin. Med. 9 (5) (2020).
[35] A. Monazzami, R. Momenpur, E. Alipour, K. Yari, M. Payandeh, Effects of eight-week combined resistance and endurance training on salivary interleukin-12, tumor necrosis factor, cortisol, and testosterone levels in patients with breast cancer, Int. J. Cancer Manag. 14 (2) (2021) e109039.
[36] J.A. Ligibel, N. Campbell, A. Partridge, W.Y. Chen, T. Salinardi, H. Chen, et al., Impact of a mixed strength and endurance exercise intervention on insulin levels in breast cancer survivors, J. Clin. Oncol. : official journal of the American Society of Clinical Oncology 26 (6) (2008) 907–912.
[37] T.H. Kim, J.S. Chang, K.S. Park, J. Park, N. Kim, J.I. Lee, et al., Effects of exercise training on circulating levels of Dickkpof-1 and secreted frizzled-related protein-1 in breast cancer survivors: a pilot single-blind randomized controlled trial, PLoS One 12 (2) (2017) e0171771.
[38] A.E. Hiensch, S. Mijwel, D. Bargiela, Y. Wengström, A.M. May, H. Rundqvist, Inflammation mediates exercise effects on fatigue in patients with breast cancer, Med. Sci. Sports Exerc. 53 (3) (2021) 496–504.
[39] L.Q. Rogers, A. Fogleman, R. Trammell, P. Hopkins-Price, S. Vicari, K. Rao, et al., Effects of a physical activity behavior change intervention on inflammation and related health outcomes in breast cancer survivors: pilot randomized trial, Integr. Cancer Ther. 12 (4) (2013) 323–335.
[40] G.A. Thomas, B. Cartmel, M. Harrigan, M. Fiellin, S. Capozza, Y. Zhou, et al., The effect of exercise on body composition and bone mineral density in breast cancer survivors taking aromatase inhibitors, Obesity 25 (2) (2017) 346–351.
[41] C.M. Dieli-Conwright, J.H. Parmentier, N. Sami, K. Lee, D. Spicer, W.J. Mack, et al., Adipose tissue inflammation in breast cancer survivors: effects of a 16-week combined aerobic and resistance exercise training intervention, Breast Cancer Res. Treat. 168 (1) (2018) 147–157.
[42] R. Nuri, M.R. Kordi, M. Moghaddasi, N. Rahnama, A. Damirchi, F. Rahmani-Nia, et al., Effect of combination exercise training on metabolic syndrome parameters in postmenopausal women with breast cancer, J. Cancer Res. Therapeut. 8 (2) (2012) 238–242.
[43] T. Cornette, F. Vincent, S. Mandigout, M.T. Antonini, S. Leobon, A. Labrunie, et al., Effects of home-based exercise training on VO2 in breast cancer patients under adjuvant or neoadjuvant chemotherapy (SAPA): a randomized controlled trial, Eur. J. Phys. Rehabil. Med. 52 (2) (2016) 223–232.
[44] K.A. Bolam, S. Mijwel, H. Rundqvist, Y. Wengström, Two-year follow-up of the OptiTrain randomised controlled exercise trial, Breast Cancer Res. Treat. 175 (3) (2019) 637–648.
[45] T.R.S. de Paulo, K.M. Winters-Stone, J. Viezel, F.E. Rossi, R.R. Simões, G. Tosello, et al., Effects of resistance plus aerobic training on body composition and metabolic markers in older breast cancer survivors undergoing aromatase inhibitor therapy, Exp. Gerontol. 111 (2018) 210–217.
[46] C. Dethlefsen, C. Lillelund, J. Midtgaard, C. Andersen, B.K. Pedersen, J.F. Christensen, et al., Exercise regulates breast cancer cell viability: systemic training adaptations versus acute exercise responses, Breast Cancer Res. Treat. 159 (3) (2016) 469–479.
[47] N. Travier, M.J. Velthuis, C.N. Steins Bisschop, B. van den Buijs, E.M. Monninkhof, F. Backx, et al., Effects of an 18-week exercise programme started early during breast cancer treatment: a randomised controlled trial, BMC Med. 13 (2015) 121.
[48] F. Vincent, E. Deluche, J. Bonis, S. Leobon, M.T. Antonini, C. Laval, et al., Home-based physical activity in patients with breast cancer: during and/or after chemotherapy? Impact on cardiorespiratory fitness. A 3-arm randomized controlled trial (apac), Integr. Cancer Ther. 19 (2020) 1534735420969818.
[49] A.D. Reis, P. Pereira, R.R. Diniz, J.G.L. de Castro Filha, A.M. Dos Santos, B.T. Ramallo, et al., Effect of exercise on pain and functional capacity in breast cancer patients, Health Qual. Life Outcome 16 (1) (2018) 58.
[50] D. Long Parma, D.C. Hughes, S. Ghosh, R. Li, R.A. Treviño-Whitaker, S.M. Ogden, et al., Effects of six months of Yoga on inflammatory serum markers prognostic of recurrence risk in breast cancer survivors, SpringerPlus 4 (2015) 143.
[51] K. Lee, N. Sami, D. Tripathy, W. Demark-Wahnefried, M.K. Norris, K.S. Courneya, et al., Aerobic and resistance exercise improves Reynolds risk score in overweight or obese breast cancer survivors, Cardio-oncology (London, England) 6 (1) (2020) 27.
[52] C.M. Dieli-Conwright, F.C. Sweeney, K.S. Courneya, D. Tripathy, N. Sami, K. Lee, et al., Hispanic ethnicity as a moderator of the effects of aerobic and resistance exercise in survivors of breast cancer, Cancer 125 (6) (2019) 910–920.
[53] N.J. D'Alonzo, L. Qiu, D.D. Sears, V. Chinchilli, J.C. Brown, D.B. Sarwer, et al., WISER survivor trial: combined effect of exercise and weight loss interventions on insulin and insulin resistance in breast cancer survivors, Nutrients 13 (9) (2021).
[54] M.L. Irwin, B. Cartmel, C.P. Gross, E. Ercolano, F. Li, X. Yao, et al., Randomized exercise trial of aromatase inhibitor-induced arthralgia in breast cancer survivors, J. Clin. Oncol. : official journal of the American Society of Clinical Oncology 33 (10) (2015) 1104–1111.
[55] N. Rahnama, R. Nouri, F. Rahmaninia, A. Damirchi, H. Emami, The effects of exercise training on maximum aerobic capacity, resting heart rate, blood pressure and anthropometric variables of postmenopausal women with breast cancer, J. Res. Med. Sci. : the official journal of Isfahan University of Medical Sciences 15 (2) (2010) 78–83.
[56] S. Mijwel, A. Jervaeus, K.A. Bolam, J. Norrbom, J. Bergh, H. Rundqvist, et al., High-intensity exercise during chemotherapy induces beneficial effects 12 months into breast cancer survivorship, Journal of cancer survivorship : research and practice 13 (2) (2019) 244–256.
[57] C. Mostarda, J. Castro-Filha, A.D. Reis, M. Sevílio Jr., C.J. Dias, A.C. Silva-Filho, et al., Short-term combined exercise training improves cardiorespiratory fitness and autonomic modulation in cancer patients receiving adjuvant therapy, J. Exerc. Rehabil. 13 (5) (2017) 599–607.
[58] K.M. Sturgeon, J.C. Brown, D.D. Sears, D.B. Sarwer, K.H. Schmitz, WISER survivor trial: combined effect of exercise and weight loss interventions on inflammation in breast cancer survivors, Med. Sci. Sports Exerc. 55 (2) (2023) 209–215.
[59] A. Soriano-Maldonado, D.M. Díez-Fernández, A. Esteban-Simón, M.A. Rodríguez-Pérez, E. Artés-Rodríguez, M.A. Casimiro-Artés, et al., Effects of a 12-week supervised resistance training program, combined with home-based physical activity, on physical fitness and quality of life in female breast cancer survivors: the EFICAN randomized controlled trial, Journal of cancer survivorship : research and practice 17 (5) (2023) 1371–1385.
[60] S. Mijwel, M. Backman, K.A. Bolam, E. Olofsson, J. Norrbom, J. Bergh, et al., Highly favorable physiological responses to concurrent resistance and high-intensity interval training during chemotherapy: the OptiTrain breast cancer trial, Breast Cancer Res. Treat. 169 (1) (2018) 93–103.
[61] C. Mostarda, J. Castro-Filha, A.D. Reis, M. Sevílio, C.J. Dias, A.C. Silva-Filho, et al., Short-term combined exercise training improves cardiorespiratory fitness and autonomic modulation in cancer patients receiving adjuvant therapy, J. Exerc. Rehabil. 13 (5) (2017) 599–607.
[62] K.Y. An, A.R. Morielli, D.W. Kang, C.M. Friedenreich, D.C. McKenzie, K. Gelmon, et al., Effects of exercise dose and type during breast cancer chemotherapy on longer-term patient-reported outcomes and health-related fitness: a randomized controlled trial, Int. J. Cancer 146 (1) (2020) 150–160.
[63] American College of Sports Medicine Position Stand, The recommended quantity and quality of exercise for developing and maintaining cardiorespiratory and muscular fitness, and flexibility in healthy adults, Med. Sci. Sports Exerc. 30 (6) (1998) 975–991.

[64] T.S. Church, S.N. Blair, S. Cocreham, N. Johannsen, W. Johnson, K. Kramer, et al., Effects of aerobic and resistance training on hemoglobin A1c levels in patients with type 2 diabetes: a randomized controlled trial, JAMA 304 (20) (2010) 2253–2262.
[65] J. Rosado-Pérez, V.M. Mendoza-Núñez, Relationship between aerobic capacity with oxidative stress and inflammation biomarkers in the blood of older Mexican urban-dwelling population, Dose Response : a publication of International Hormesis Society 16 (2) (2018) 1559325818773000.
[66] V.S. Paramanandam, V.S. Prema, Exercise training may improve the tumour microenvironment after breast cancer (PEDro synthesis), Br. J. Sports Med. 51 (21) (2017) 1564–1565.
[67] I.M. Lahart, G.S. Metsios, A.M. Nevill, A.R. Carmichael, Physical activity, risk of death and recurrence in breast cancer survivors: a systematic review and meta-analysis of epidemiological studies, Acta Oncol. 54 (5) (2015) 635–654.
[68] G.K. Reeves, K. Pirie, V. Beral, J. Green, E. Spencer, D. Bull, Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study, Br. Med. J. 335 (7630) (2007) 1134.
[69] B.L. Ecker, J.Y. Lee, C.J. Sterner, A.C. Solomon, D.K. Pant, F. Shen, et al., Impact of obesity on breast cancer recurrence and minimal residual disease, Breast Cancer Res. 21 (1) (2019) 41.
[70] P. Poirier, T.D. Giles, G.A. Bray, Y. Hong, J.S. Stern, F.X. Pi-Sunyer, et al., Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss, Arterioscler. Thromb. Vasc. Biol. 26 (5) (2006) 968–976.
[71] J. Goh, L. Lim, B. Kennedy, S.C. Lee, Combined aerobic and strength exercise maintains circulating fgf-21 in asian breast cancer patients: 3544 board #365 may 29 2:30 PM - 4:00 PM, Med. Sci. Sports Exerc. 52 (7S) (2020) 985.
[72] R. Guo, Y. Chen, H. Borgard, M. Jijiwa, M. Nasu, M. He, et al., The function and mechanism of lipid molecules and their roles in the diagnosis and prognosis of breast cancer, Molecules 25 (20) (2020) 4864.
[73] M.T. Hamilton, J. Etienne, W.C. McClure, B.S. Pavey, A.K. Holloway, Role of local contractile activity and muscle fiber type on LPL regulation during exercise, Am. J. Physiol. 275 (6) (1998) E1016–E1022.
[74] M.S. Liu, F.R. Jirik, R.C. LeBoeuf, H. Henderson, L.W. Castellani, A.J. Lusis, et al., Alteration of lipid profiles in plasma of transgenic mice expressing human lipoprotein lipase, J. Biol. Chem. 269 (15) (1994) 11417–11424.
[75] L.B. Oscai, R.W. Tsika, D.A. Essig, Exercise training has a heparin-like effect on lipoprotein lipase activity in muscle, Can. J. Physiol. Pharmacol. 70 (6) (1992) 905–909.
[76] C.M. Dieli-Conwright, K.S. Courneya, W. Demark-Wahnefried, N. Sami, K. Lee, T.A. Buchanan, et al., Effects of aerobic and resistance exercise on metabolic syndrome, sarcopenic obesity, and circulating biomarkers in overweight or obese survivors of breast cancer: a randomized controlled trial, J. Clin. Oncol. 36 (9) (2018) 875–883.
[77] V. Messier, F.M. Malita, R. Rabasa-Lhoret, M. Brochu, A.D. Karelis, Association of cardiorespiratory fitness with insulin sensitivity in overweight and obese postmenopausal women: a Montreal Ottawa New Emerging Team study, Metabolism 57 (9) (2008) 1293–1298.
[78] M.J. Gibala, S.L. McGee, A.P. Garnham, K.F. Howlett, R.J. Snow, M. Hargreaves, Brief intense interval exercise activates AMPK and p38 MAPK signaling and increases the expression of PGC-1alpha in human skeletal muscle, J. Appl. Physiol. 106 (3) (2009) 929–934.
[79] J.K. Brown, T. Byers, C. Doyle, K.S. Coumeya, W. Demark-Wahnefried, L.H. Kushi, et al., Nutrition and physical activity during and after cancer treatment: an American Cancer Society guide for informed choices, CA A Cancer J. Clin. 53 (5) (2003) 268–291.
[80] M.C. Towler, D.G. Hardie, AMP-activated protein kinase in metabolic control and insulin signaling, Circ. Res. 100 (3) (2007) 328–341.
[81] E. Bruno, E. Roveda, J. Vitale, A. Montaruli, F. Berrino, A. Villarini, et al., Effect of aerobic exercise intervention on markers of insulin resistance in breast cancer women, Eur. J. Cancer Care 27 (2) (2018) e12617.
[82] M. Hamer, The anti-hypertensive effects of exercise, Sports Med. 36 (2) (2006) 109–116.
[83] F. Balkwill, A. Mantovani, Inflammation and cancer: back to Virchow? Lancet 357 (9255) (2001) 539–545.
[84] S. Wang, H. Zhou, C. Zhao, H. He, Effect of exercise training on body composition and inflammatory cytokine levels in overweight and obese individuals: a systematic review and network meta-analysis, Front. Immunol. 13 (2022) 921085.
[85] L.K. Stewart, M.G. Flynn, W.W. Campbell, B.A. Craig, J.P. Robinson, B.K. McFarlin, et al., Influence of exercise training and age on CD14+ cell-surface expression of toll-like receptor 2 and 4, Brain Behav. Immun. 19 (5) (2005) 389–397.
[86] T.J. Bruinsma, A.M. Dyer, C.J. Rogers, K.H. Schmitz, K.M. Sturgeon, Effects of diet and exercise-induced weight loss on biomarkers of inflammation in breast cancer survivors: a systematic review and meta-analysis. Cancer epidemiology, biomarkers & prevention : a publication of the American association for cancer research, American Society of Preventive Oncology 30 (6) (2021) 1048–1062, cosponsored by the.
[87] C.P. Fischer, Interleukin-6 in acute exercise and training: what is the biological relevance? Exerc. Immunol. Rev. 12 (2006) 6–33.