



# Effects of physical exercise on cognitive function of breast cancer survivors receiving chemotherapy: A systematic review of randomized controlled trials

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## ABSTRACT

**Background:** Cognitive impairment has a great negative impact on quality of life for breast cancer survivors. Emerging evidence suggested that physical exercise can improve cognitive function in order adults with Alzheimer's disease. However, less is known about the effects of physical exercise on cognitive function for breast cancer survivors. The purpose of this meta-analysis was to evaluate the effect of physical exercise on cognitive function in breast cancer survivors.

**Methods:** EMBASE, the Cochrane Library, Web of Science and PubMed were searched from the establishment of the databases to June 2021. Randomized controlled trials were included. All analysis were conducted using the Revman 5.3.

**Results:** 12 studies (936 participants) indicated that exercise improved self-reported cognitive function (MD 10.12, 95% CI [5.49,14.76],  $p < 0.0001$ ), cognitive fatigue (MD -5.41, 95% CI [-10.31,-0.51],  $p = 0.03$ ) and executive function (MD -13.63, 95% CI [-21.86,-5.39],  $p = 0.0001$ ).

**Conclusion:** Physical exercise can improve cognitive function for breast cancer survivors, particularly in self-reported cognitive function, and executive function. Future studies need to explore the effect of exercise on cognitive function from the frequency and duration of exercise.

## 1. Introduction

Breast cancer has become the most common type of cancer and the leading cause of cancer-related death among women around the world. Breast cancer worldwide constituted approximately 2.26 million new cases and 680,000 deaths annually [1]. Largely due to improved treatments [2], such as neoadjuvant chemotherapy, radiotherapy, hormone therapy, there are increasing survival rate for breast cancer in many high-income countries [3], in spite of the decreasing mortality of breast cancer recently [2,4]. However, previous studies have reported that breast cancer survivors can experience a variety of side effects and symptoms of long-term treatment [5–7], of which reduced cognitive function is a common one [7,8].

Cognitive function is the information processing aspect of multiple behavior, including attention, learning, memory, visual memory, visuospatial ability, verbal learning and executive function. Cancer-

related cognitive impairment (CRCI) is reported by 75% of breast cancer survivors [9], especially for those receiving chemotherapy. Among CRCI, attention, processing speed, memory and executive function are the most common areas of impairment after chemotherapy [8,10,11]. Currently, studies have found that chemotherapy, radiation and hormone therapy can cause CRCI in cancer survivors, while cognitive decline in breast cancer survivors is mainly due to chemotherapy [12]. On the one hand, chemotherapeutic drugs can cause structural and functional changes in certain brain regions through the blood-brain barrier, thus leading to cognitive decline [13,14]; on the other hand, chemotherapy drugs may induce the damage of normal cells, cause acute elevation inflammatory cells, accelerate cell aging, and further aggravate the cognitive function of breast cancer survivors [15]. Hence, there is an expression of "Chemobrain", this meta-analysis included breast cancer survivors with CRCI caused by chemotherapy. About 1 in 5 of breast cancer survivors received therapy have difficulties in memory

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and executive function, generally have worse attention than their peers and experienced more cognitive complaints than before treatment [16]. Although this cognitive decline is usually mild to moderate for breast cancer survivors, it can last for months to years after treatment and negatively impact survivors' daily life, mental health, social relationships and work [8,17–20]. At the same time, CRCI can also affect the survivor's ability to make decisions [21,22]. Therefore, effective intervention strategies are urgently needed to improve survivors' cognitive function and quality of life.

There are many factors leading to cognitive dysfunction in breast cancer survivors, including age, hormone levels, social economy, sleep disorders and stress, although these mechanisms are not clear [8,23]. While the optimal intervention that can improve cognitive function of breast cancer survivors is unknown, recent studies have demonstrated that physical exercise may help to maintain or even improve cognitive function [24–26]. There is evidence that, on the one hand, physical exercise can induce the release of neurotrophic factors, neurotransmitters and enzymes, therefore, promoting the nerve growth and development and contributing to the growth of the prefrontal cortex and hippocampus [27–30]. On the other hand, exercise indirectly affects cognitive function by mitigating symptoms of depression and anxiety. Dopaminergic, serotonergic substances caused by depression and anxiety are associated with cognitive impairment, but exercise can relieve depression and anxiety and prevent cognitive deterioration. In recent years, there has been an increasing number of studies on the effects of exercise on cognitive function. However, different types, intensity and duration of exercise have different effects on cognitive function, which has not yet reached a consensus. A meta-analysis showed that moderate-to-strong physical exercise can reduce the risk of cognitive impairment in patients with dementia [30]. Groot's meta-results showed that both combined exercise and aerobic-only exercise had positive effects on patients' cognition, while non-aerobic exercise alone did not [31]. Law's study found that aerobic exercise at moderate-to-high intensity with a total duration of >24 h had pronounced effects on the overall cognition [32]. Práxedes' experiments demonstrated that passing action showed significant differences in decision making and execution between the intervention and experimental groups, but dribbling did not show such differences [33]. At the same time, other studies have shown that dance can improve executive function and episodic memory of Parkinson's disease patients, but the effect on attention language fluency and visuospatial ability was not significant [34]. In contrast, the effects of different types of physical exercise for improving the cognitive function in breast cancer survivors have not been determined.

Some studies have shown that individual skills can be transferred and applied to different settings, suggesting that physical exercise therapy for cognitive function in patients with Alzheimer's disease could also be adapted to breast cancer survivors [35]. Previous studies exploring the effect of physical exercise on cognitive function in breast cancer survivors produced conflicting results. Hartman's RCT of moderate-intensity aerobic exercise interventions for 12 weeks in 87 breast cancer survivors, who achieved 150 min of moderate-to-vigorous aerobic exercise per week, found that physical exercise improved processing speed but had no effect on self-reported cognitive function [36]. While, Galiano-Castillo conducted a resistance combined aerobic exercise intervention in 76 breast cancer patients for 8 weeks, asking patients to exercise 90 min per day (3 sessions per week), and found physical exercise improves self-reported cognitive function [6,37]. The conflicting results of previous studies may be due to different modes of physical exercise and duration of intervention [38]. Furthermore, a large number of exercise intervention trials in breast cancer survivors demonstrated that physical exercise has a positive impact on upper limb edema and muscle strength, vascular function, health-related quality of life, fatigue, depression, anxiety, sleep, etc. [18,39–42]. However, few studies focus on the effects of physical exercise and cognitive function on breast cancer survivors, and most studies use self-report and lack

objective, multidimensional measures of cognitive function.

Therefore, the purpose of this meta-analysis randomized controlled trial is to evaluate the effect of physical exercise on cognitive function in breast cancer survivors, and examine the effect of physical exercise interventions on the cognitive domains of processing speed, executive function, and verbal memory.

## 2. Methods

This review followed the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA), and was registered with the International Prospective Register of Systematic Reviews (PROSPERO), and the registration number is CRD42021230372.

### 2.1. Data sources and searches

This systemic review searched five electronic bibliographic databases, including EMBASE (from 1974 to June 2021), the Cochrane Library (the Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials; from the inception to June 2021), Web of Science (from 1900 to June 2021), PubMed (from 1950 to June 2021). MeSH terms and keywords included those relating to breast (eg, mammary), cancer (eg, neoplasm, cancer, carcinoma, tumor, or malignancy), physical exercise (eg, exercise, physical activity, training, sport, aerobic, strength, resistance, endurance, weight, running, walk, cycling, biking, bicycling, yoga, Tai Chi, Qigong, pilate), and cognition (eg, cognitive function, cognitive effect, cognition disorders, cognitive dysfunction neuropsychological tests, learning, memory, attention, executive function) and were combined with an "AND" term. Search terms were modified according to suggestions from the different databases and are reported in full in [Appendix A](#). Only articles published in English were accepted for language restriction. The original published articles of all references, which including relevant articles and additional articles, suitable for inclusion were retrieved for further analysis.

### 2.2. Eligibility criteria and study selection

Population: Adults with breast cancer.

Intervention: Intervention protocols based on physical exercise for adults with breast cancer.

Comparison: Usual care.

Outcome: Cognitive effects from physical exercise.

Study design chosen: Randomized clinical trials.

The inclusion criteria were: 1) Randomized clinical trials; 2) adults, ≥18 years old; 3) diagnosed with stage I–III breast cancer, stage IV breast cancer survivors who may not be able to participate due to their condition and physical condition were not included; 4) receive exercise intervention for at last 6 weeks or more; 5) exercise interventions included high- or moderate-intensity continuous or interval resistance (eg, body weight, machine and free weights), aerobic (eg, walking, cycling, strength training), or mind-body exercise (eg, yoga, Tai Chi, Qigong, Pilates); 6) the intervention could take place in any setting (supervised or homebased); 7) the outcomes of trials must evaluate the cognitive function of breast cancer survivors, the measurement tools include self-reported [43–45] or subjective measures. The exclusion criteria were: 1) co-morbid conditions that could alter cognitive testing results, such as a psychiatric conditions, history of substance use disorder, or other neurological disorder; 2) survivors with other cancer diagnosis; 3) other therapeutic interventions through changing behavior or cognition. The effects of other diseases or interventions on cognitive function were excluded to ensure homogeneity of the study. For studies not reporting relevant data, such as standard deviation and/or mean, the first/corresponding authors of these studies were asked to provide additional information. The studies from authors unable to provide this missing information and grey literature were excluded from this analysis.

### 2.3. Data extraction and quality assessment

Two reviewers screened independently the information of identified studies (title and abstract) in the research and assessed the full texts of potentially eligible articles to determine whether they met the inclusion criteria. Eligible articles were then extracted data by 2 independent reviewers using a unified table to make a last list of identified studies. If the original data were not reported in the eligible studies, contact the author to obtain data or exclude the study. When there is a disagreement, a third reviewer was consulted.

The risk of bias of the RCTs was independently evaluated by 2 reviewers, the Cochrane Handbook for Systematic Reviews of Interventions Version 5.3.0 of the Cochrane Collaboration was used [46]. The following criteria of the Cochrane Handbook was assessed: 1) Random sequence generation, 2) Allocation concealment, 3) Blinding of participants and researchers, 4) Blinding of outcome assessment, 5) Incomplete outcome data, 6) Selective reporting, and 7) Other bias. The results of assessment could be rated as ‘high risk’ (+), ‘low risk’ (–) or ‘unclear risk’ (?). The disagreements were adjudicated by the third reviewers. The methodological quality of the included studies in this meta-analysis was assessed using the 8 criteria from Cuijpers [47], the eight criteria and results are shown in [Appendices B and C](#). In general, when no or insufficient information was provided concerning a quality criterion, we rated it as negative.

For each study included in this meta-analysis, the following data were recorded: first author’s information and publication year, country, sample size, participants (age and number of breast cancer survivors in the control and intervention groups), treatment type, exercise mode, duration, frequency, supervised versus home-based, exercise prescription, type of outcome, outcome measures.

### 2.4. Data synthesis and analysis

A quantitative synthesis for the effect size of each study was calculated as the outcomes were continuous data. The mean difference (MD) was calculated as an effect method when the included studies used the same scale, and the standardized mean difference (SMD) was calculated when the included studies used different scales to evaluate intervention effects. This study adopted random effect model as the main analysis method.  $I^2$  statistic were used to assess statistical heterogeneity, with  $I^2$  values of 0%, 25%, 50% and 75% represented no, low, moderate and high heterogeneity, respectively [48,49]. Subgroup analysis was performed if significant heterogeneity was found, and subgroup analysis was conducted based on type of training (resistance or aerobic) or training time of each exercise. The stability of the results was tested by sensitivity analysis. Publication bias were presented by funnel plots. All analysis was conducted using the Review Manager Software (Revman 5.3).

## 3. Results

### 3.1. Search results and study selection

The initially research retrieved 1752 references, along with one additional reference identified from other sources. First, 280 duplicates were removed. Subsequently, 1422 articles were excluded due to irrelevant interventions and the population after screening the abstracts and titles. Then, the full text of 51 articles were received for review and 37 were excluded. After further review of the remaining 14 articles, we found that four articles actually reported the results of two studies at different follow-up time points. Finally, 12 studies were included in this study [6,36,37,39,50–59]. The results of the search progress and study selection are depicted in [Fig. 1](#).

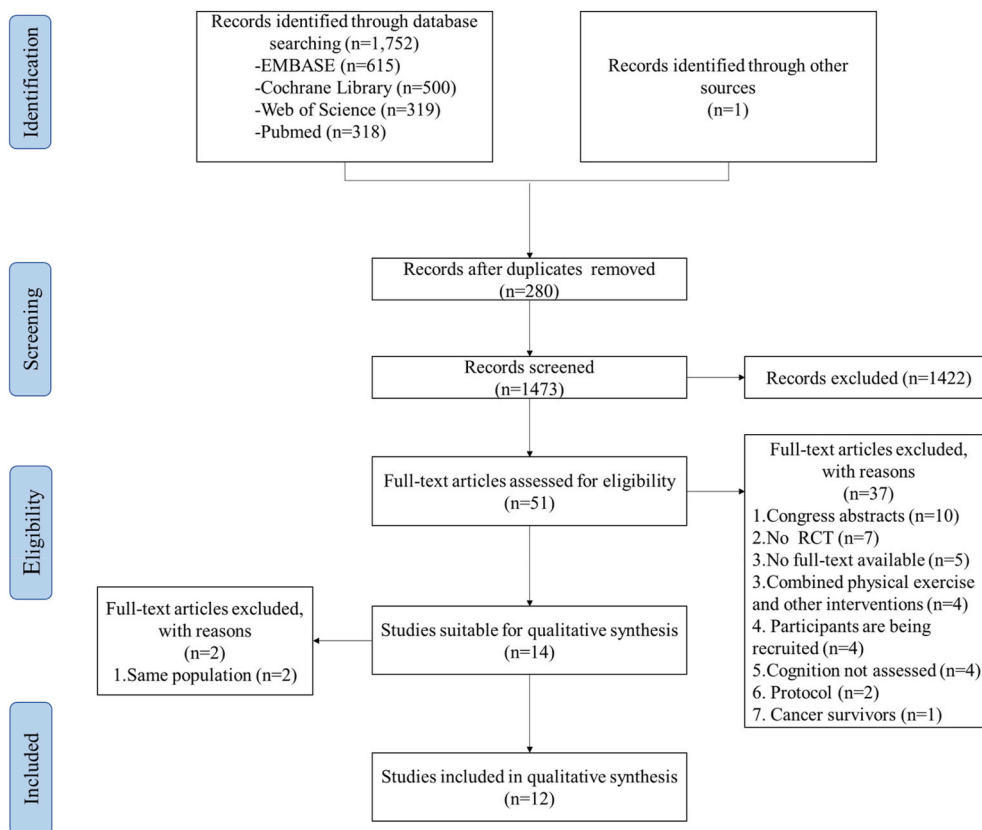


Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of the literature search used.

### 3.2. Characterization of the included studies

The characteristics of the 12 RCTs are shown in Table 1. Included trials were distributed in the United States ( $n = 2$ ) [36,54], England ( $n = 2$ ) [52,53], Sweden ( $n = 1$ ) [50,51], Germany ( $n = 2$ ) [56,58], Australia ( $n = 1$ ) [55], Ireland ( $n = 1$ ) [57], Spain ( $n = 1$ ) [6,37], Iran ( $n = 1$ ) [39] and India ( $n = 1$ ) [59] during the period of 2009–2021. Cognitive function data were available for 523 survivors who participated in the physical exercise intervention and 402 survivors who served as a control group. The breast cancer survivors all received chemotherapy, and some also received other treatments such as surgery, radiation and hormone therapy.

One trial may include 1 or 2 interventions. Kate conducted a study with two interventions: the AT-HIIT (Concurrent aerobic high-intensity interval training and continuous moderate-intensity aerobic exercise training) and RT-HIIT (Concurrent aerobic high-intensity interval training and resistance exercise training) [50,51]. Jamie's trial consisted of two interventions, Qigong and gentle exercise, while Joseph's interventions were moderate and high intensity exercise [54]. Overall, the most common physical exercise was aerobic exercise ( $n = 6$ ), followed by yoga ( $n = 2$ ), qigong ( $n = 1$ ) and combination exercise (aerobic and resistance exercise,  $n = 2$ ), and resistance exercise ( $n = 1$ ). The total duration of intervention ranged from 6 to 24 weeks, with 8–12 weeks selected for most trials. The exercise frequency of the majority of trials were 12 weeks, with 2–3 times per week as the most frequent, and some experiments also required exercise every day. Each exercise duration ranged from 20 min to 90 min, 30–60 min was the most popular. Some trials stipulated that the intensity of exercise was 60–80% ( $n = 6$ ) [36, 50–52,56–58], and some experiments were not reported in detail ( $n = 5$ ) [6,37,39,53,54,59]. More than half of the trials had permanent staff supervising survivors to complete the exercise at a fixed location ( $n = 9$ ) [36,39,50–52,55–59], and others were supervised with a home-based ( $n = 3$ ) [6,37,53,54].

### 3.3. Quality assessment

Risk of bias are shown for all included studies in Fig. 2 and for each study in Fig. 3. In general, the risk of random sequence generation ( $n = 9$ ), full reporting of results ( $n = 11$ ), and selection offset ( $n = 9$ ) for most trials were low. 10 trials described the generation of random sequences in detail, used the computer automatic sequence generation method ( $n = 5$ ), permuted blocks ( $n = 3$ ) and random number table ( $n = 1$ ). 8 trials were allocated in appropriate ways, those random numbers were grouped in sealed opaque envelopes ( $n = 2$ ), or randomly grouped to ensure participants were comparable by block randomization method ( $n = 5$ ) or random list numbers ( $n = 1$ ). Due to the specific nature of exercise interventions, some studies did not blind to investigators or participants. Only 4 trials blinded survivors and participants and 6 of the trials also blinded the outcome measurement. 4 trials did not lose participants and 2 did not report the reasons for the loss of follow-up, 6 trials had the following reasons: 1) death, 2) cancer recurrence, 3) changes in treatment, 4) side effects of chemotherapy, 5) personal scheduling conflicts. And there were 4 trials performed the intent-to-treat analysis. 5 of the trials may have high risk of other bias, possibly caused by the higher educational level of the study population, the participants' preference for sports, and the fact that the sports data were not obtained through objective means.

Overall, the included studies were of moderate quality with an average score of 5.33 (SD = 0.42), the results are shown in Appendices C. and the distribution of the quality scores was generally normal. No studies had a quality score of zero, one or two, two trials had a low score of three, three had a medium score, seven had above average scores, most of the articles had a quality score of 6 ( $n = 6$ ), and only one trial met all eight quality criteria. Therefore, we determined that this meta-analysis was of moderate quality.

### 3.4. Effects of physical exercise on cognitive function

#### 3.4.1. Self-report cognitive function

A total of 12 RCTs of self-reported cognitive function, which involving 497 participants in physical exercise group and 448 participants in control group, including 6 aerobic exercise, 3 mind-body exercise, 2 combined aerobic exercise and resistance exercise, and 1 resistance exercise (Fig. 4) [6,36,37,39,50,51,54,56–59]. 8 trials used the self-reported EORTC QLQ-C30 (The European Organisation for Research and Treatment of Cancer quality of life questionnaire) cognitive function subscale [6,37,39,50,51,57–59], 2 trials used the FACT-Cog (Functional Assessment of Cancer Therapy-Cognitive Function) subscale [52,54], and 2 trials used other self-reported scales [36, 54]. The meta-analysis showed that exercise intervention improved cognitive function scores in breast cancer survivors (MD 10.12, 95% CI [5.49,14.76],  $p < 0.0001$ ). Subgroup analysis was conducted to reduce clinical heterogeneity, and the results showed that aerobic exercise could improve cognitive function (MD 16.22, 95% CI [11.58,20.86],  $p < 0.00001$ ), but body-mind exercise, resistance exercise and combined exercise did not significantly improve cognitive function (MD 7.48, 95% CI [-4.81,19.77],  $p = 0.23$ ; MD 2.76, 95% CI [-5.63,11.22],  $p = 0.11$ ; MD 10.70, 95% CI [4.50,16.89],  $p = 0.0007$ ). Sensitivity analysis showed that the results were stable and reliable.

#### 3.4.2. Self-report cognitive fatigue

A total of 4 RCTs of self-reported cognitive fatigue, which involving 272 participants in exercise group and 244 participants in control group (Fig. 5) [50,51,56,58]. Of the 2 trials used the PFS (Piper Fatigue Scale) [50,51], 2 trials used the FAQ (Fatigue Assessment Questionnaire) [56, 58]. The meta-analysis showed that there was low heterogeneity among studies for cognitive fatigue ( $I^2 = 0\%$ ,  $p = 0.86$ ), and exercise significantly improve cognitive fatigue in breast cancer survivors (MD -5.41, 95% CI [-10.31,-0.51],  $p = 0.03$ ). Sensitivity analysis showed that the results were stable and reliable.

#### 3.4.3. Processing speed

In 6 trials, there were 97 participants in the experimental group and 81 participants in the control group in which TMT-A was objectively neuropsychological (Fig. 7) [6,37,52,54,55]. The results showed that the exercise intervention did not improve the overall processing speed of breast cancer survivors (MD -2.77, 95% CI [-8.13,2.58],  $p = 0.31$ ). However, subgroup analysis was performed and showed that aerobic exercise improved cognitive function (MD -10.01, 95% CI [-17.86,-2.15],  $p = 0.01$ ), but both mind-body exercise and combined exercise did not significantly improve cognitive function (MD 2.90, 95% CI [-1.58,7.38],  $p = 0.20$ ; MD -2.71, 95% CI [-7.31,1.89],  $p = 0.25$ ). Sensitivity analysis showed that the results were stable and reliable.

#### 3.4.4. Executive function

TMT-B was tested in 6 trials, there were 160 participants in the experimental group and 140 participants in the control group (Fig. 8) [6, 37,50–52,54,56]. There was no heterogeneity in executive function among studies ( $I^2 = 0\%$ ,  $p = 0.55$ ) Meta-analysis showed that exercise intervention significantly improved cognitive function in breast cancer survivors (MD -13.63, 95% CI [-21.86,-5.39],  $p = 0.0001$ ). Sensitivity analysis showed that the results were stable and reliable.

#### 3.4.5. Verbal memory

Verbal memory was tested in 6 trials, there were 90 participants in the experimental group and 85 participants in the control group (Fig. 8) [36,52,54,55]. There was moderate heterogeneity among verbal memory studies ( $I^2 = 55\%$ ,  $p = 0.05$ ) Meta-analysis showed that exercise intervention did not significantly improve cognitive function in breast cancer survivors (MD 0.58, 95% CI [-2.34,3.50],  $p = 0.70$ ). Sensitivity analysis showed that the results were stable and reliable.

**Table 1**  
Characteristics of included studies.

Author, year	Country	Sample Size	Participants	Treatment type	Mode	Duration	Frequency	Supervised versus home-based	Exercise prescription	Type of outcome	Outcome measures
Sara et al., [50,51]	Sweden	206	UC = 60, age = 52.6 ± 10.2 RT-HIIT = 74, age = 52.7 ± 10.3 AT-HIIT = 72, age = 54.4 ± 10.3	Chemotherapy	Aerobic exercise, resistance exercise	16 weeks	2/week	Supervised	60min; RT-HIIT: 2 sets of 8–12 reps at 70–80% HRR AT-HIIT: 20 min + 2 sets of 8–12 reps at 70–80% HRR	Self-report	EORTC-QLQ; PFS
Campbell et al. [52]	England	19	Con = 9, age = 51.4 ± 5.1 Ex = 10, age = 53.2 ± 7.0	Chemotherapy; radiation	Walking, machine-based, aerobic exercise	24 weeks	4/week	Supervised, home-based	150 min/week; 20–45min at 60–80% HRR & 4 sets of HIIT (5–10 min) by week 12	Self-report Objective;	FACT-Cog TMT; Verbal learning
Noelia et al. [6, 37]	Spain	81	Con = 41, age = 49.2 ± 7.9 Ex = 40, age = 47.4 ± 9.6	Chemotherapy surgery; radiation;	Aerobic exercise, resistance exercise	8 weeks	3/week	Home-based	AER: 90min	Self-report Objective	EORTC-QLQ TMT
Kajal et al. [53]	England	50	Con = 25, age = 52.36 ± 8.9 Ex = 25, age = 52.1 ± 11.7	Chemotherapy	Walking	12 weeks	3/week	Home-based	AER: 30 min;	Self-report Objective	CFQ Executive function;
Sheri et al. [36]	America	87	Con = 44, age = 56.2 ± 9.3 Ex = 43, age = 58.2 ± 11.37	Chemotherapy surgery;	Aerobic exercise	12 weeks	3-5/week	Supervised, home-based	30–45 min; Walking at 65%–75% HRR	Self-report Objective	PROMISE Verbal learning
Jamie et al. [54]	America	50	Con = 11, age = 56.2 ± 11.3 GE = 20, age = 53.1 ± 10.7 Qigong = 19, age = 52.9 ± 11.9	Chemotherapy radiation; ; hormonal-therapy	Qigong; gentle exercise;	8 weeks	7/week	Home-based	QG: 30min	Self-report Objective	FACT-Cog; PROMIS TMT; Verbal learning
Joseph et al. [55]	Australia	17	Con = 6, age = 61.5 ± 7.8 MOD = 5, age = 67.8 ± 7.0 HIIT = 6, age = 60.3 ± 8.1	Chemotherapy surgery; radiation; hormonal-therapy;	Cycling, aerobic exercise	12 weeks	3/week	Supervised	MOD: 20–30 min at 50% HRR; HIIT: 20–30 min at 105% HRR	Objective	Executive function, Verbal learning
Nilofar et al. [39]	Iran	40	Con = 20, age = 51.8 ± 11.4 Ex = 20, age = 51.6 ± 10.5	Chemotherapy radiation;	Yoga	8 weeks	3/week	Supervised, home-based	Unclear	Self-report	EORTC QLQ_C30
Martina et al. [56]	Germany	101	Con = 46, age = 53.3 ± 10.2 RE = 49, age = 53.3 ± 10.2	Chemotherapy; surgery; hormonal-	Machine-based, resistance exercises	12 weeks	2/week	Supervised	60 min: 3 sets of 8–12 repetitions at 60–80% HRR	Self-report Objective	FAQ; EORTC QLQ-C30 TMT
Patricia et al. [57]	Ireland	37	Con = 18, age = 56.3 ± 2.0 Ex = 19, age = 53.9 ± 2.3	Chemotherapy surgery; radiation;	Exercise	10 weeks	1-2/week	Supervised, home-based	1–5 weeks: 2/week at 65%–85% HRR, 6–10 weeks: 1/week at 65%–85% HRR	Self-report	EORTC QLQ-C30
Steindorf et al. [58]	Germany	160	Con = 78, age = 56.4 ± 8.7	Chemotherapy; surgery; radiation;	Machine-based, resistance exercise	12 weeks	2/week	Supervised	60 min: 3 sets, 8–12 reps at 60%–80% HRR	Self-report Objective	FAQ; EORTC QLQ-C30 TMT

(continued on next page)



Table 1 (continued)

Author, year	Country	Sample Size	Participants	Treatment type	Mode	Duration	Frequency	Supervised versus home-based	Exercise prescription	Type of outcome	Outcome measures
Vadiraja et al. [59]	India	88	RE = 77, age = 55.2 ± 9.5 Con = 44, age = 48.5 ± 10.2 Yoga = 44, age = 46.7 ± 9.3	Chemotherapy; surgery; radiation;	Yoga	6 weeks	7/week	Supervised, home-based	YOGA:60 min:	Self-report	EORTC QLQ-C30

Con, control; CFQ, Cognitive Failures Questionnaire; Ex, exercise; EORTC-QLQ, The European Organisation for Research and Treatment of Cancer quality of life questionnaire; FACT-Cog, Functional Assessment of Cancer Therapy-Cognitive Function; FAQ, Fatigue Assessment Questionnaire; HIIT, High-intensity interval training; HRR, heart rate reserve; MOD, moderate; PFS, Piper fatigue scale; PROMIS, Patient-Reported Outcomes Measurement Information System scales; QG/TCE, Qigong/Tai Chi Easy intervention; REP, repetitions; SQG, Sham Qigong Control; TMT, Trail Making A/B test; UC, usual care.

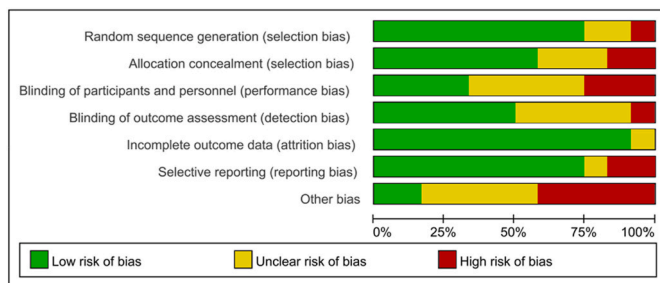


Fig. 2. Risk of bias graph.

4. Discussion

This meta-analysis evaluated the effects of physical exercise on overall self-reported cognitive function in breast cancer survivors, and then explored the effects of self-reported cognition, cognitive fatigue, processing speed, executive function, and verbal memory. A total of 12 RCTs published between 2009 and 2021 were included in the meta-analysis.

The results of this meta-analysis highlight the potential of physical exercise to positively affect overall self-reported cognitive function, cognitive fatigue and executive function in breast cancer survivors. The significant effects of aerobic exercise and combined exercise intervention on self-cognition report was found. These results suggested that physical exercise, especially moderate to high-intensity aerobic exercise and combined exercise, can improve overall cognitive function. However, the current results did not show significant effects of exercise interventions on specific cognitive areas of processing speed and verbal memory.

4.1. Interpretation of results and comparison with previous research

To our knowledge, this is the first meta-analysis to examine the impact of physical exercise intervention on cognitive function in breast cancer survivors. Campbell et al. evaluated the benefits of physical exercise on cognitive function in cancer survivors in a systematic review [60]. Twelve of the 29 trials reported a significant effect of physical exercise on self-reported cognitive function. Importantly, only three of the 10 trials that used neurocardiological tests to assess cognitive function showed a significant effect of physical exercise, and only the three trials used cognitive function as the primary outcome. This meta-analysis confirmed the results of Campbell’s study, which used self-report and objective tests to evaluate the cognitive function of breast cancer survivors and determine the efficacy of exercise intervention on the cognitive function. The underlying mechanisms between physical exercise and cognitive function are as follows: firstly, exercise can induce the increase of neurotrophic factors, neurotransmitters and

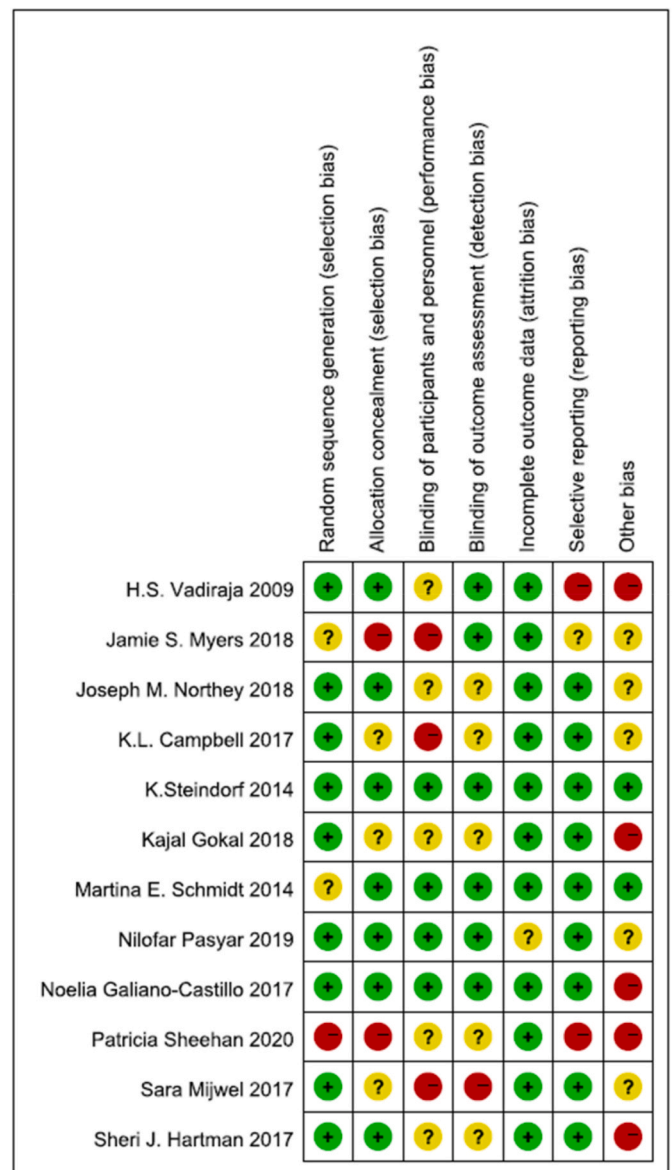


Fig. 3. Risk of bias summary.

enzymes (such as brain-derived neurotrophic factors, dopamine, tyrosine hydroxylase) to promote nerve growth and development [27]. Secondly, both animal studies and human studies have shown that exercise contributes to the growth of the prefrontal cortex and

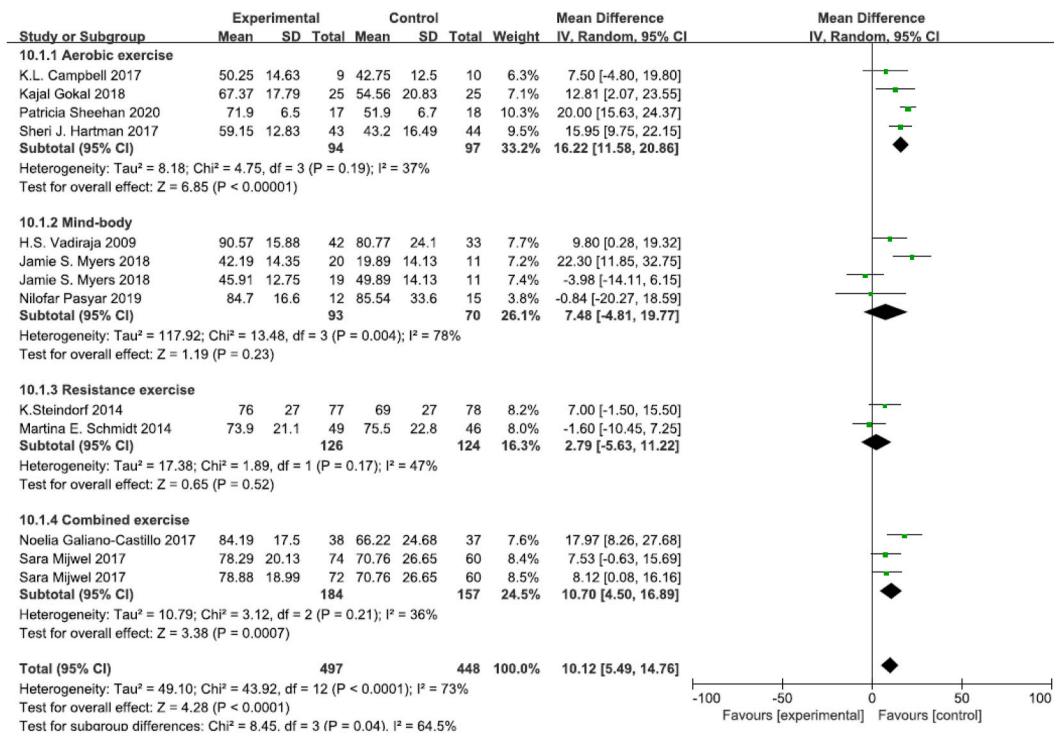


Fig. 4. Effects of physical exercise training on self-reported cognition.

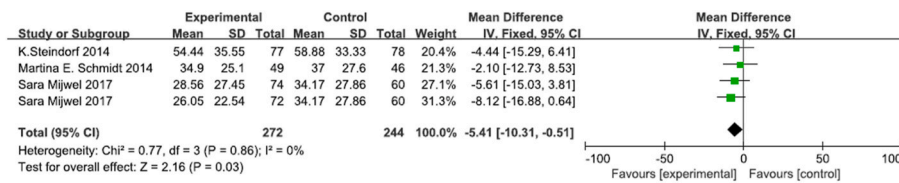


Fig. 5. Effects of physical exercise training on self-report cognitive fatigue.

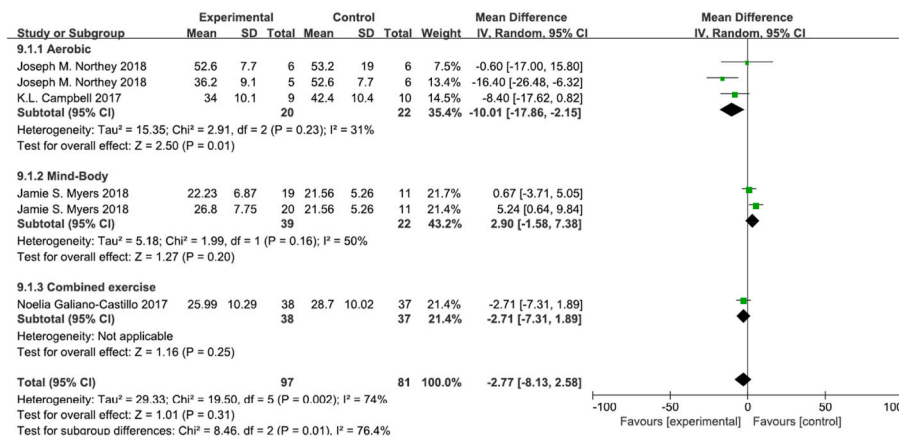


Fig. 6. Effects of physical exercise training on processing speed.

hippocampus, and promotes cerebrovascular generation by enhancing cerebral perfusion, especially when physical exercise is combined with an enriched environment [29]. Thirdly, physical exercise is effective in enhancing cognitive function by regulating blood sugar, inflammation and hormone levels [30]. Although there are many mechanisms between physical exercise and cognitive function, further studies are needed to explore regulatory pathways among them. Future studies should use objective tests or other more accurate methods to detect

subtle changes in cognitive function in breast cancer survivors, and explore the regulation of physical exercise and cognitive functions.

The current results are comparable to a recent systematic review by Erickson et al. [30]. They investigated the effects of physical exercise interventions investigated the effects of physical exercise intervention on cognitive function throughout the life cycle and found that moderate-to-vigorous physical exercise improved cognitive function in healthy individuals and even patients with cognitive impairment.

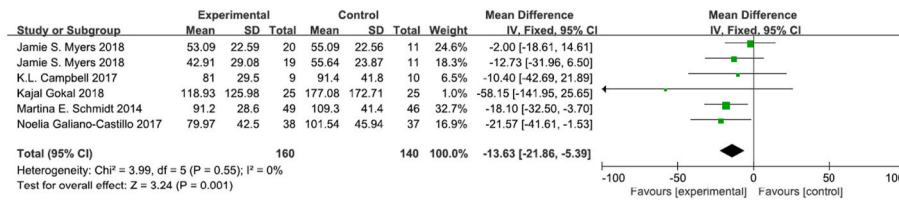


Fig. 7. Effects of physical exercise training on executive function.

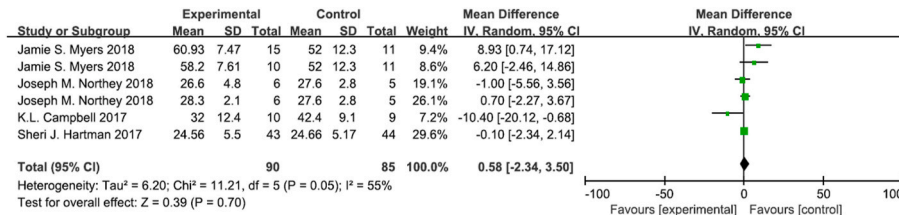


Fig. 8. Effects of physical exercise training on verbal memory.

Studies in their specific field have shown that exercise interventions can improve processing speed, memory and executive function, which are partly similar to the results of the current study. Our study did not show any significant effects on processing speed and verbal memory, but aerobic exercise improved processing speed in breast cancer patients, which consistent with Smith’s findings [61]. Some studies suggested that combined exercise improves memory in patients more than exercise alone, explained by changes in brain structure, brain function and brain connectivity [62]. The reason for the different results may be that included studies that involved different intensities and different modes of exercise [38]. This emphasizes the need for more detailed and accurate research into specific cognitive domains.

A meta-analysis by Northey suggested that physical exercise improves cognitive function in adults older than 50 [38]. They found that interventions of aerobic exercise, resistance training and tai chi, all had significant effects on cognitive function, with each exercise lasting 45–60 min and at least moderate intensity having cognitive benefits, which similar to those observed in the current study. And the American Heart Association recommends 70% HRR exercise of more than 30 min three times a week, or 150 min of moderate-intensity exercise and 75 min of high-intensity exercise per week to prevent cognitive decline. Participants in seven of the 12 RCTs included in the current study participated in 30–60 min of resistance/aerobic exercise at 50–80% HRR. However, our results need to be interpreted with caution, since the results of tai Chi and resistance training were based on two trials. Assessing more modes of physical exercise should be a the focus of future research.

4.2. Strengths and limitations

There are several advantages in this study. This meta-analysis is the first systematic review to evaluate the effect of physical exercise on cognitive function in breast cancer survivors, and found that physical exercise can improve cognitive function in breast cancer survivors. Second, only RCT studies were included in this meta-analysis. Third, this study adopted a combination of subjective and objective measurements, provided stronger evidence of beneficial effects of physical exercise on cognitive function in breast cancer survivors. Nevertheless, this study has some limitations. Firstly, the meta-analysis only searched studies published in English, which may lead to incomplete literature review. Secondly, this study included 12 studies, and some of which had varying degrees of heterogeneity. In addition, due to publication bias, this study may be biased towards positive results. Therefore, the results of study need to be cautiously interpreted. Thirdly, this study lacks the

exploration of exercise parameters, such as duration and frequency. Furthermore, this meta-analysis didn’t provide evidence that physical exercise affects other cognitive functions, such as attention, working memory, visuospatial ability and so on, further studies need explore other areas of cognitive function.

4.3. Implications for future research

Future studies are needed to investigate different patterns and durations of physical exercise. We recommend a multi-arm design that includes single exercise training, combined exercise training, and a control group to distinguish the contributions of different exercise types. In addition, future research should focus on using objective measures such as neuropsychological tests to examine the positive effects of physical exercise. Finally, it is important to detect exercise modes in different cognitive domains. And different physical exercises can provide different kinds of stimulation, including duration, frequency, intensity and type or type of physical exercise. Moreover, Den Heijer’s study has shown that physical exercise at a young age can better promote the proliferation and positive response of nerve cells [28], and Fabel’s animal experiments have shown that physical activity combined with a rich environment can induce hippocampal neurogenesis [63], suggesting that the timing and combination of physical exercise interventions should also be the focus of future research. In conclusion, more objective measures are needed to confirm the effects of physical exercise on cognitive function in the future.

5. Conclusion

This meta-analysis found that physical exercise can improve cognitive function in breast cancer survivors, particularly in self-reported cognitive function, cognitive fatigue and executive function, but did not seem to improve processing speed and verbal memory. There was methodological heterogeneity in included study samples, thus the results of the present study need to be cautiously interpreted. Meanwhile, this meta-analysis showed that aerobic exercise and combined exercise were more effective than resistance exercise, mind-body exercise. Physical therapists can start exercise interventions earlier, and combine exercise with other measures to be more effective in reducing cognitive decline in breast cancer survivors. Future studies need to focus on the effect of physical exercise on cognitive function, which can be explored from the frequency and duration of physical exercise.



## Author contributions

Xiaohan Ren: contributed to conception, design of the work, the acquisition and analysis of data, writing the original draft, and review and editing of the paper. Xiaoqin Wang: contributed to writing the original draft, and review and editing of the paper. Jiuru Sun, Zhaozhao Hui, Shuangyan Lei, Caihua Wang: contributed to the acquisition and analysis of data, review the paper. Mingxu Wang: contributed to review and editing of the paper. All authors read and approved the final manuscript.

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## 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.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.breast.2022.03.014>.

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