REVIEW PAPER

JMS Journal of Medical Science

Exercise as a Non-Pharmacological Therapeutic Strategy in Breast Cancer: An Umbrella Review of Systematic Reviews and Meta-Analyses

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https://doi.org/10.20883/medical.e1320

Keywords: cancer, exercise, CRF, systematic review, umbrella

Received 2025-08-20
Accepted 2026-01-27
Published 2026-03-31

How to Cite: Hendawy M, Abouzid M, Alnajjar AZ, Elnagar M, Rzk FM, Daniel JM, Elshazly H, Saad MM. Exercise as a non-pharmacological therapeutic strategy in breast cancer: an umbrella review of systematic reviews and meta-analyses. Journal of Medical Science. 2026 March;95(1);e1320. doi:10.20883/medical.e1320

ABSTRACT

Background. Breast cancer is the most prevalent cancer diagnosis and a leading cause of cancer-related mortality among women globally. Exercise has gained traction as a promising non-pharmacological strategy to manage cancer-related fatigue, pain, quality of life, anxiety, and depression. However, the current evidence regarding exercise's effects on breast cancer is heterogeneous, with variations in study designs, exercise modalities, and outcome measures. Therefore, this umbrella meta-analysis is conducted to synthesise more robust findings.

Material and method. Adhering to the PRIO and PRIO-harms guidelines, Eligible systematic reviews and meta-analyses published between January 2001 and December 2023 were identified from PubMed, Scopus,

Web of Science, and the Cochrane Library. Using StataMP version 17, Outcomes are reported as standardised mean differences (SMD) with 95% confidence intervals (CI). A p-value ≤ 0.05 was considered statistically significant.

Results. This umbrella review synthesised evidence from 44 systematic reviews, including 31 meta-analyses. These reviews encompassed 906 randomised controlled trials (RCTs) evaluating the effects of exercise interventions on various outcomes in breast cancer patients. Patients undergoing exercise programs demonstrated improvements in fatigue (SMD -0.26, 95% CI [-0.44, -0.08], p < 0.01), pain (SMD -0.65, 95% CI [-1.10, -0.19], p = 0.01), quality of life (SMD 0.28, 95% CI [0.21, 0.36], p < 0.01), and physical activity level (SMD 0.30, 95% CI [0.21, 0.39], p < 0.001). No significant effects were observed for anxiety (SMD 0.00, 95% CI [-0.62, 0.63], p = 1.00) or depression (SMD -0.45, 95% CI [-1.00, 0.10], p = 0.11).

Conclusion. This umbrella meta-analysis provides evidence that exercise in breast cancer patients can reduce fatigue, enhance quality of life, improve physical function, and alleviate pain. However, the impact on depression and anxiety appears limited.

Introduction

Breast cancer is the most commonly diagnosed cancer among women worldwide and a leading cause of cancer-related mortality, with an estimated 2,261,419 new cases and 684,996 deaths reported globally in 2020 [1]. Although advancements in early detection and treatment have significantly improved survival rates, breast cancer patients continue to face substantial physical and psychological challenges [2]. These challenges include fatigue, depression, reduced quality of life (QoL), and heightened anxiety, all of which can profoundly affect patients' well-being and their ability to cope with the disease and its treatments. Women undergoing mastectomy and adjuvant therapies are often exposed to a considerable pharmacological burden, including chemotherapy, endocrine therapy, analgesics, and supportive medications. While these treatments are essential, they are frequently associated with adverse physical and psychological effects [3]. Consequently, non-pharmacological interventions – particularly structured exercise and physiotherapy – have gained increasing attention as safe, accessible, and cost-effective strategies to support rehabilitation and improve survivorship outcomes [4].

Breast cancer patients experience a wide range of physical and psychological symptoms that substantially affect their overall well-being. Cancer-related fatigue (CRF) is among the most prevalent and debilitating outcomes, with up to 99% of patients reporting significant fatigue during and after treatment, leading to impaired physical function, reduced ability to perform daily activities, and diminished QoL [5,6]. Pain is also a common and distressing symptom that further limits physical functioning and negatively influences QoL [7]. In addition to these physical outcomes, psychological disturbances such as depression and anxiety affect a considerable proportion of breast cancer patients, with prevalence rates reaching approximately 30% and 40%, respectively [8], and can exacerbate physical symptoms and overall distress.

Given the substantial burden of these physical and psychological challenges, there is a growing interest in identifying effective interventions to manage these symptoms in the breast cancer population. Exercise has emerged as a promising non-pharmacological approach, with several systematic reviews and meta-analyses examining its impact on fatigue, depression, QoL, and anxiety in breast cancer patients [9–12].

However, the existing evidence on the effects of exercise on breast cancer is diverse, with variations in study designs, exercise modalities, and outcome measures. An umbrella review synthesises the evidence from multiple systematic reviews, and meta-analyses can provide a comprehensive and robust understanding of the current literature on this topic [13]. Therefore, this umbrella review aims to critically appraise and synthesise the available evidence on the effects of exercise on fatigue, depression, QoL, physical activity, pain, and anxiety in breast cancer patients.

Material and methods

This summary of systematic reviews was conducted following the guidelines provided by the Preferred Reporting Items for Overviews of Systematic Reviews (PRIO) checklist [14] and the Preferred Reporting Items for Overviews of Systematic Reviews Harms (PRIO-harms) checklist [15].

Data sources and searches

A systematic approach is employed to identify relevant literature for our umbrella review by searching multiple online databases, including the Cochrane Library, Web of Science (WoS), PubMed, and Scopus. Our search strategy was designed to capture a broad spectrum of information regarding the impact of exercise therapies on CRF in patients with breast cancer. The search terms included a combination of

(Breast Cancers OR Breast Carcinoma OR Mammary Neoplasm OR Mammary Carcinoma OR Human Mammary Carcinomas OR Breast Carcinomas OR Breast neoplasm OR Breast Cancer) AND (fatigue OR tiredness OR weariness OR exhaustion) AND (Internal training OR home training OR internal exercise OR home exercise OR home stretching OR physical exercise OR sedentary OR endurance OR flexibility OR physical activity OR mobility OR aerobic activity OR walking OR resistance OR balance OR home-based exercise).

A combination of Medical Subject Headings (MeSH) and relevant free-text terms is utilised to ensure comprehensive inclusion.

Eligibility criteria

Reviews are included in our Umbrella study if they satisfied the following criteria: Population: Patients diagnosed with breast cancer. Intervention: Any exercise. Comparator: Control group. Outcome: (i) Primary outcomes: Fatigue (ii) Secondary outcomes: Depression, QoL, anxiety, physical function, pain. Study design: We included systematic reviews and meta-analyses.

To ensure an exhaustive evaluation of interventions, we considered a range of exercise interventions, including aerobic exercise, resistance training, and mind-body practices. Also, no restriction was set on the age of the patients or the stage of breast cancer. We excluded primary studies, commentaries, editorials, and letters as they did not fulfil our criteria for a systematic review. Furthermore, reviews that did not explicitly address CRF or did not incorporate patients with breast cancer were excluded from our analysis. In addition, studies that lacked sufficient data to evaluate the quality of the evidence were excluded to maintain the rigour and reliability of the review process.

Data Extraction

A precise, systematic approach was employed to ensure accuracy and reliability during data extraction. Six independent reviewers (ME, MH, FMR, HE, MMS, JMD) extracted data utilising a standardised form to capture information across various domains. Conflicts were resolved through discussion with the senior authors (AZA and MA). The extracted data encompassed vital study characteristics, including the study design, time limit of the search, number of studies included in the systematic review or meta-analysis, type of studies included, number of patients, countries, interventions, study aim, and inclusion and exclusion criteria. Ultimately, the principal findings of each study were summarised to elucidate the impact of exercise interventions on CRF among patients with breast cancer.

Quality assessment

To ensure the reliability and validity of the included systematic reviews with meta-analyses, their methodological quality was assessed using the Assessment of Multiple Systematic Reviews (AMSTAR) tool [16]. This established instrument facilitated a comprehensive evaluation of the review methodology, encompassing study selection, data extraction, and the synthesis of findings. Six independent reviewers (ME, MH, FMR, HE, MMS, JMD) conducted the quality assessment, and any discrepancies were resolved through a comprehensive discussion with the senior author (AZA). When consensus could not be achieved, a third reviewer (MA) was consulted to provide additional insight and facilitate resolution.

Statistical analysis

In this Umbrella review, we used StataMP version 17 for statistical analysis. Continuous data were reported as standardised mean differences (SMDs) with 95% confidence intervals (CIs). The

random effect model was applied. It accommodates a larger standard error in the pooled estimate, making it suitable for inconsistent or controversial estimates [17]. When a study used multiple scales within a domain, we first calculated its overall estimate and then pooled the results. For instance, Fong et al. [18] used mental health, physical function, and social function to calculate an overall QoL estimate before incorporating it into the QoL pool analysis. Chi-square and I-square tests are used to evaluate heterogeneity. The Chi-square test determines whether heterogeneity exists, while the I-square test determines the degree of heterogeneity. According to the Cochrane Handbook (Chapter Nine) [19], significant heterogeneity was indicated by an I-square greater than 50%. At the same time, an alpha level of 0.1 or lower for the Chi-square test indicated considerable heterogeneity. Funnel plots and Egger's test were calculated for fatigue and QoL outcomes, and subgroup analyses were performed when possible, depending on the quality of the studies. Lastly, we calculated the Corrected Covered Area (CCA) for the included reviews to inspect the potential impact of overlapping studies using the formula [20]:

$$\mathrm{CCA} = \frac{N - r}{(r \cdot c) - r}$$

where N is the total number of primary studies in all systematic reviews (counting duplicates), r is the number of unique primary studies, and c is the number of systematic reviews.

Results

Characteristics of Included Reviews

This umbrella review synthesised evidence from 44 systematic reviews, of which 31 included meta-analyses published between 2001 and 2023 **(Figure 1)**. A List of studies and their characteristics is presented in **Table 1** [18,21–63]**.**

These reviews encompassed 906 randomised controlled trials (RCTs) evaluating the effects of exercise interventions on various outcomes in breast cancer patients. The included systematic reviews and meta-analyses encompassed breast cancer patients at multiple stages of treatment and survivorship, including those undergoing active treatment (e.g., chemotherapy, radiation therapy).

The included systematic reviews and meta-analyses focused on several outcomes, including 26 on fatigue, 14 on QoL, 7 on physical function, 6 on depression, 4 on anxiety, and 4 on pain. The number of primary studies in each review varied considerably, ranging from 5 RCTs to over 50.

Regarding the types of exercise interventions evaluated, most reviews included aerobic exercise, resistance training, or both. Several reviews also examined the effects of yoga, Tai chi, and pilates.

Quality assessment of the included reviews

According to the AMSTAR 2 evaluation of the 43 systematic reviews, 5 (11.6%) were rated as high quality, 1 (2.3%) as moderate quality, 12 (30.2%) as low quality, and 25 (55.8%) as critically low quality, based on the AMSTAR 2 criteria (**Table 2)**.

The high-quality reviews consistently demonstrated adherence to rigorous systematic review methods, including comprehensive literature searches, duplicate study selection, data extraction, risk-of-bias or methodological-quality assessment of included studies, and appropriate analytical techniques. These reviews provided detailed information on their methods and addressed potential sources of bias and heterogeneity [49,53,56,62,63] **(Table 2)**.

The moderate-quality review had minor limitations, including an inadequate literature search strategy and reporting, and an incomplete assessment of publication bias. However, these limitations were not deemed critical to the overall validity of the review's findings (**Table 2)**.

The low-quality reviews exhibited more substantial methodological flaws, including limited literature searches, lack of duplicate study selection or data extraction, inadequate assessment of the risk of bias or study quality, and potential issues with data synthesis or interpretation [18,22–26,45–47,54,55,59] **(Table 2)**.

Critically low-quality reviews had multiple significant limitations, including failure to register or provide a protocol, inadequate comprehensive literature searches, inability to assess the risk of bias or study quality, and inappropriate data synthesis or meta-analysis methods. These reviews

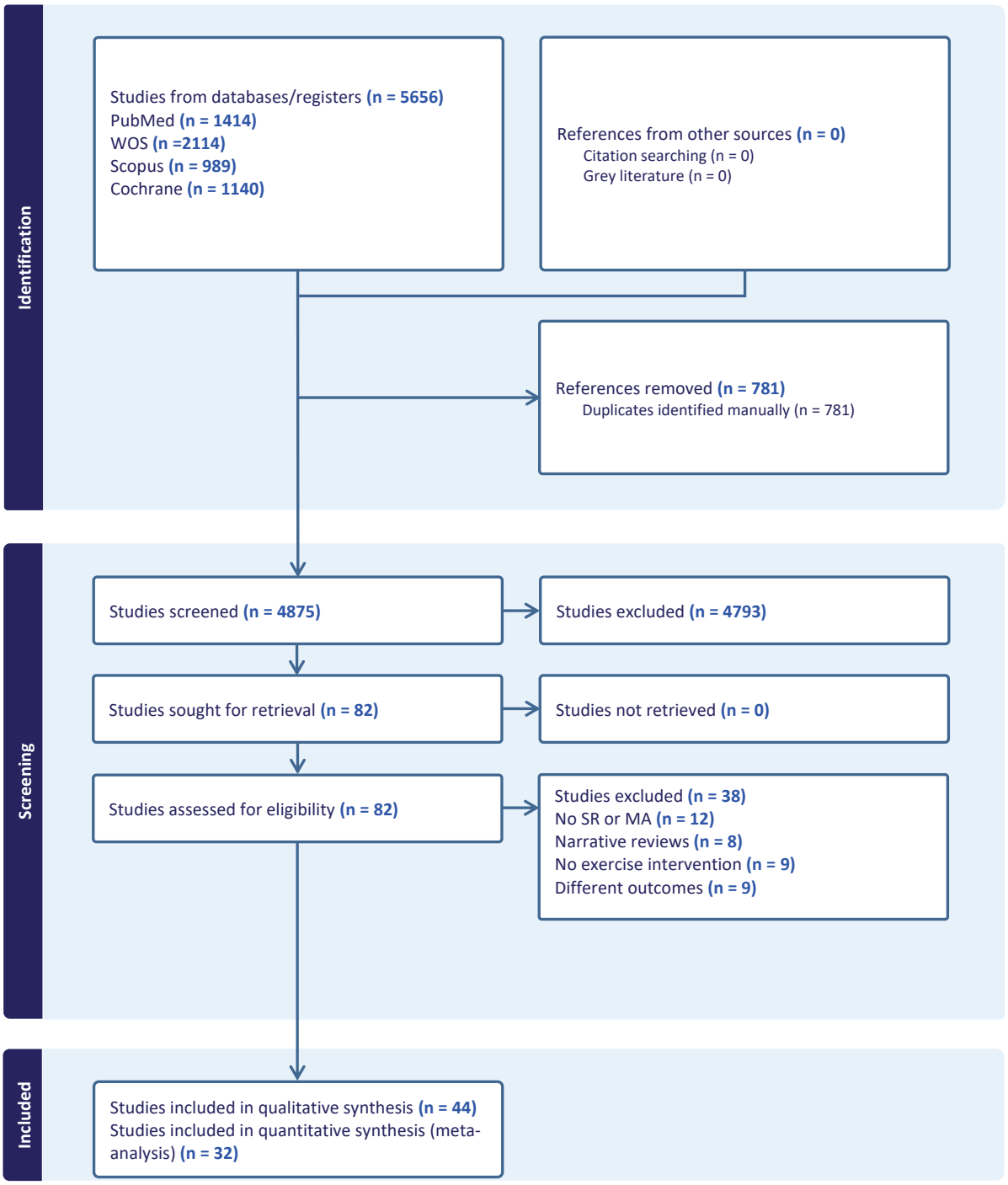

Figure 1. PRISMA chart of the reported studies showing the search selection strategy and exclusion criteria.

Table 1. Characteristics of the included reviews.

First author [Ref.]	Year	Country	No. of studies	Treatment	Control	Quality assessment	Measurement tools	Meta-analysis	Main conclusion
Fraser [22]	2023	Canada, USA, Italy, Turkey, Netherlands, UK, India, Puerto Rico, Germany, Denmark	17	Home-based exercise: aerobic only, resistance only, aerobic + resistance, walking, other (yoga, exergaming, gardening)	No exercise	RoB	FACT-B, FACT-G, FACT-P, SF-36, IBCSG, EORTC, PORPUS, PFS	Yes	Home-based exercise slightly improves QoL in breast/prostate cancer survivors, independent of cancer type, duration, or age. Also improves PA and CRF.
Coughlin [23]	2019	USA	15	Home-based PA: walking, self-selected, aerobic + resistance	Routine exercise	-	-	No	Home-based PA reduces symptoms and improves physical functioning.
Vulpen [24]	2016	Australia, Germany	5	Physical exercise: resistance, resistance + aerobic, home-based PA	Routine exercise	RoB	FAQ, MFI	Yes	Physical exercise significantly reduces body fatigue.
Mok [25]	2022	-	18	Combined: resistance + endurance	Resistance alone, endurance alone	-	-	Yes	Combined exercise provides enduring fatigue benefits during adjuvant therapy in breast cancer.
Fong [18]	2012	-	34	PA: aerobic, weight/strength, yoga/stretching	No exercise	-	-	Yes	PA improves physiology, body composition, function, psychology, and QoL post-breast cancer treatment.
Singh [26]	2018	-	60	Resistance, yoga, aerobics	No exercise	PEDro, fatigue/ depression scales	-	Yes	Exercise is safe, feasible, effective for stage II+ breast cancer.
O'Neill [27]	2020	Canada	24	Yoga	Routine care, health education, no exercise	RoB	FACIT-F, FSI, BFI, EORTC QLQ-C30	Yes	Yoga reduces CRF in breast cancer, comparable to aerobic exercise.
Mcneely [28]	2006	-	14	Aerobic + resistance	Usual care	-	FACIT-F, PFS	Yes	Exercise improves CRF in breast cancer.
Velthuis [29]	2010	-	18	Aerobic + resistance	Usual care (no PA emphasis)	-	-	-	Supervised aerobic during treatment manages CRF.
Hashimi [30]	2019	-	8	Yoga	Stretching	-	-	-	Yoga improves QoL like other exercises.
Fontein [31]	2013	USA (3), Turkey (2), India, Germany, UK	17	Yoga	No exercise	-	Cancer Fatigue Scale	No	PA improves survival outcomes.
Buffart [32]	2012	-	16	Yoga	No exercise	-	Breast-cancer subscale	Yes	Yoga feasible, benefits physical/ psychosocial symptoms.
Lee [33]	2018	USA, Canada, France, UK, Sweden, Brazil, Netherlands, Australia	29	Exercise during adjuvant therapy	Routine care, no exercise	Quality assessment of controlled studies	MFI, RPFS	Yes	Aerobic, resistance, combined reduce CRF; high-intensity best.
Reverte-Pagola [34]	2022	-	31	Supervised/unsupervised exercise	No exercise	-	VAS	-	Both reduce CRF severity.

Table 1 continuued.

First author [Ref.]	Year	Country	No. of studies	Treatment	Control	Quality assessment	Measurement tools	Meta--analysis	Main conclusion
Samuel [35]	2020	-	3	Pedometer-based	Usual care	PEDro	-	No	Feasible, beneficial during chemotherapy.
Jurado [36]	2020	Spanish, French, English, Italian, Portuguese	13	Therapeutic exercise post-treatment	No exercise	AGREE II	-	No	Optimal for alleviating treatment effects.
Wu [37]	2023	-	78	Aerobic, resistance, yoga, combined, stretching	Non-exercise	-	-	Yes	Yoga most effective, then combined aerobic/resistance.
Battaglini [38]	2014	-	51	Aerobic or aerobic + resistance	Usual care	-	-	No	Safe, improves physiological/ psychological parameters.
Chen [39]	2023	Iran, Finland, Turkey, China, Germany, Spain	8	Exercise	-	-	EORTC QLQ-C30	Yes	Improves physical health, reduces fatigue/nausea/insomnia.
Zomkowski [40]	2017	Australia, USA, Netherlands, Canada, Finland, Italy	13	Work activity	Standard care	-	-	No	Symptoms limit work; higher unemployment.
Arnold [41]	2010	-	5	Aerobic	Standard care	-	-	No	Positive trends in reducing CRF in hospitalized patients.
Kärki [42]	2001	-	33	Shoulder exercise post-axillary dissection	Standard care	SAS	-	No	Benefits psychological outcomes.
Lin [43]	2020	NA	-	Yoga, mixed aerobic, horseback, cycle	Standard care	Quality assessment	-	Yes	Low-moderate intensity (20 min, 3x/ week, â‰¤12 weeks) reduces fatigue.
Jacobsen [44]	2008	NA	-	Psychological/activity-based	Standard care	-	-	Yes	Limited support for non-pharmacological CRF management.
Lu [45]	2019	USA, China, UK, Spain	30	Combined (walking, aquatic, strength), aerobic	Standard care	RoB	-	Yes	Limited support; need heightened fatigue criteria studies.
Dijck [46]	2016	NA	9	Home-based, web-based, info sessions/booklets	Standard care	RoB	-	Yes	Relieves musculoskeletal symptoms, improves QoL.
Juvet [47]	2017	USA, Canada, Australia, UK, Spain, Germany, Netherlands, Norway	24	Aerobic + resistance	Standard care	RoB	BPI, WOMAC, VAS, FACT, SF-36	Yes	Yoga improves HRQoL, reduces fatigue/ sleep issues.
Espíndula [48]	2017	Turkey, Iran, USA	13	Pilates, combined	Standard care	RoB	SF-36, HADS, STAI, FSI, CFS, FSS, VAS	Yes	Self-management increases QoL post-adjuvant.
Carayol [49]	2014	NA	25	Walking, running, sports, resistance, dance, yoga, tai chi, pilates	Standard care	RoB	SF-36, 6MWT, FACT-B, PAL, EORTC C30, MFI	Yes	Improves functioning, reduces fatigue (post > during treatment).
Smits [50]	2015	NA	4	6-month behavioral PA	Standard care	RoB	FACT, SF-36, EORTC QLQ-30, PFS, FACT-F, SCFS, MFI, POMS, FACIT, PFI	Yes	Pilates/home-based encouraged.
Lof [51]	2012	North America, Spain	33	Aerobic, resistance, stretching, tai chi	Standard care	RoB	EORTC QLQ-C30, BR23	Yes	Improves fatigue/QoL/anxiety/depression despite biases.

Table 1 continued.

First author [Ref.]	Year	Country	No. of studies	Treatment	Control	Quality assessment	Measurement tools	Meta--analysis	Main conclusion
Peng [52]	2022	Australia, China, Spain, USA, Korea	8	Telehealth: stretching, yoga, qigong, pilates	Standard care	RoB	FACT-B, FACT-G, FACT-An, SF-36	Yes	Improves QoL, reduces fatigue in endometrial/ovarian survivors.
Lipsett [53]	2017	NA	12	Aerobic, resistance, yoga, qigong, tai chi, pilates	Standard care	RoB	Generic/cancer-specific QoL scales	Yes	Beneficial changes in insulin/IGF/ inflammation.
Zhu [54]	2021	USA, Australia, UK, Brazil	9	Acupuncture, exercise (vibratory, walking, training)	Sham acupuncture, no treatment	RoB	EORTC QLQ-C30, FACT-B+4, SF-36	Yes	Telehealth superior for PA/capacity/QoL/ fatigue.
Dong [55]	2019	NA	9	Yoga	Standard care	RoB	FAQ, PFS-R, FACT-F, BFI	Yes	Supervised aerobic-resistance promising during RT.
Shen [56]	2020	Canada, USA, Brazil, China, Germany, Korea, India	10	Post-RT: yoga, stretching, resistance, qigong, Nia, upper limb, aerobic	Standard care	RoB	FACIT-F, SF-36, FACT-G	Yes	Acupuncture/exercise reduce pain/ improve QoL; mixed for fatigue.
Huizinga [57]	2021	NA	17	Home-based walking	Standard care	RoB	Exercise parameters, scales, RT dose	-	Alternative for fatigue relief.
Belloni [58]	2021	NA	13	Aerobic + resistance	Standard care	RoB	Exercise parameters, scales, RT dose	-	Efficacy on clinical outcomes.
Ehlers [59]	2020	USA, China, Germany, Netherlands, Australia, Canada, England, France, Norway, Sweden, Thailand	11	Aerobic, mind-body	Standard care	RoB	Exercise parameters, scales, RT dose	-	Home-based PA reduces fatigue up to 9 months.
Montaño-Rojas [60]	2020	NA	11	Resistance	Standard care	RoB	Exercise parameters, scales, RT dose	-	Implement during/after treatment.
Luo [61]	2020	China, USA, Thailand	41	Pedometer-based, tai chi	Standard care	RoB	Exercise parameters, scales, RT dose	-	Improves QoL.
Cataldi [62]	2021	NA	15	PA: aerobic (AE), resistance (RE), endurance (EN), combined (warm-up + RE + AE + cooldown)	Standard care	RoB	Exercise parameters, scales, RT dose	-	Effective for symptoms/QoL; needs more RCTs.
Cheng [63]	2017	NA	78	Home-based: education, exercise, diet	Standard care	RoB	Exercise parameters, scales, RT dose	-	Yoga best, then combined aerobic/ resistance.
Cramer [21]	2017	USA, Brazil, Germany, Slovenia, Australia, India, Turkey, China, Taiwan	24	Yoga: complex, exercise-based, meditation-based	Standard care	RoB	HRQoL, depression, anxiety, fatigue scales	Yes	Improves HRQoL/fatigue/sleep short-term.

Abbreviations: RoB, Cochrane Risk-of-Bias criteria; NOKC, Norwegian Knowledge Centre for the Health Services Handbook for Systematic Reviews; PEDro, Physiotherapy Evidence Databases Scale; NOS, Newcastle–Ottawa Scale; JBI-MAStARI, Joanna Briggs Institute-Critical Appraisal Tool for Randomized Controlled Trials; RoB 2.0, Revised Risk-of-Bias Tool for Randomized Trials; FAQ, Fatigue Assessment Questionnaire; RPFS, Revised Piper Fatigue Scale; PFI, Piper Fatigue Instrument; SCFS-6, Schwartz Cancer Fatigue Scale-6; POMS-F, Profile of Mood States Fatigue Scale; FS, Fatigue Scale; LAS-F, Linear Analog Scale for Fatigue; CFS, Cancer Fatigue Scale; FSI, Fatigue Symptom Inventory; PFS-R, Revised Piper Fatigue Scale; EORTC-QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 Fatigue Subscale; FSS, Fatigue Severity Scale; MFSI-SF, Multidimensional Fatigue Symptom Inventory-Short Form; VO2 peak, peak oxygen uptake.

Table 2. Quality assessment of 44 systematic reviews/meta-analyses.

First author [Ref.]	AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews)																Overall quality
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	
Fraser [22]	N	P	N	P	Y	Y	Y	Y	P	Y	Y	Y	N	N	N	Y	Low quality review
Coughlin [23]	Y	N	N	P	N	N	Y	P	N	N	N	N	N	N	N	Y	Low quality review
Vulpen [24]	Y	Y	Y	P	Y	N	P	Y	Y	N	Y	Y	N	Y	N	Y	Low quality review
Mok [25]	Y	N	Y	P	N	N	P	Y	Y	Y	Y	N	N	N	Y	Y	Low quality review
Fong [18]	Y	N	Y	Y	Y	Y	Y	P	N	Y	Y	N	N	Y	Y	Y	Low quality review
Singh [26]	Y	N	Y	P	N	Y	N	Y	N	Y	Y	N	N	Y	Y	Y	Low quality review
O'Neill [27]	Y	N	N	Y	Y	Y	N	P	Y	N	Y	Y	N	N	Y	Y	Critially low quality review
Mcneely [28]	Y	N	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	Y	N	Y	Critially low quality review
Velthuis [29]	Y	N	N	Y	Y	Y	N	P	Y	Y	N	Y	N	N	N	N	Critially low quality review
Hashimi [30]	Y	N	Y	Y	Y	Y	N	N	Y	Y	N	Y	N	Y	Y	N	Critially low quality review
Fontein [31]	Y	N	N	Y	Y	Y	N	Y	N	N	N	N	N	Y	N	N	Critially low quality review
Buffart [32]	Y	N	Y	Y	N	N	Y	P	N	N	Y	N	N	N	N	N	Critially low quality review
Lee [33]	Y	N	N	P	N	N	N	Y	N	N	Y	Y	N	Y	Y	N	Critially low quality review
Reverte-Pagola [34]	Y	Y	N	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	N	N	Critially low quality review
Samuel [35]	Y	N	Y	N	Y	N	Y	Y	N	Y	N	N	N	N	Y	Y	Critially low quality review
Jurado [36]	Y	N	Y	Y	Y	Y	N	Y	N	Y	N	N	N	N	Y	Y	Critially low quality review
Wu [37]	Y	N	Y	Y	Y	Y	N	Y	N	N	N	N	N	N	Y	Y	Critially low quality review
Battaglini [38]	N	P	N	P	Y	Y	N	N	N	N	N	N	Y	N	N	Y	Critially low quality review
Chen [39]	N	N	N	Y	Y	Y	N	N	Y	N	Y	N	Y	N	N	N	Critially low quality review
Zomkowski [40]	Y	N	N	Y	N	Y	N	N	Y	N	Y	N	Y	N	N	N	Critially low quality review
Arnold [41]	Y	N	N	P	Y	Y	N	N	P	N	Y	N	Y	N	N	Y	Critially low quality review
Kärki [42]	N	P	Y	P	N	N	N	N	N	N	N	N	N	Y	N	N	Critially low quality review
Lin [43]	Y	P	N	P	Y	Y	N	P	P	N	Y	Y	Y	Y	Y	Y	Low quality review
Jacobsen [44]	Y	P	N	P	Y	N	N	P	N	Y	N	N	N	N	N	Y	Low quality review
Lu [45]	N	N	N	N	Y	N	N	N	P	N	Y	Y	Y	Y	N	Y	Low quality review
Dijck [46]	N	N	N	P	Y	Y	N	N	Y	N	Y	Y	Y	Y	N	Y	Critially low quality review
Juvet [47]	Y	Y	Y	P	Y	Y	Y	Y	P	N	Y	Y	Y	Y	Y	Y	High quality review
Espíndula [48]	N	P	Y	P	Y	Y	P	P	N	Y	Y	Y	Y	Y	N	N	Low quality review
Carayol [49]	N	N	Y	P	N	N	N	N	N	N	N	N	N	N	N	Y	Critially low quality review
Smits [50]	Y	P	Y	P	Y	Y	Y	P	P	N	Y	Y	Y	N	N	N	Low quality review
Lof [51]	Y	Y	Y	P	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	High quality review
Peng [52]	Y	P	Y	P	Y	Y	P	Y	P	N	Y	Y	N	Y	Y	N	Low quality review
Lipsett [53]	Y	P	Y	P	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Low quality review
Zhu [54]	Y	P	Y	P	Y	Y	P	P	P	N	Y	Y	Y	Y	Y	Y	High quality review
Dong [55]	Y	P	Y	P	Y	Y	Y	Y	P	N	Y	Y	N	N	Y	N	Low quality review
Shen [56]	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	N	N	N	N	Y	Critially low quality review
Huizinga [57]	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Low quality review
Belloni [58]	Y	Y	N	Y	Y	Y	N	P	Y	Y	Y	Y	Y	Y	N	Y	Critially low quality review
Ehlers [59]	N	N	N	Y	N	N	Y	P	N	Y	N	N	N	N	N	Y	Critially low quality review
Montaño-Rojas [60]	Y	P	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Moderate quality review
Luo [61]	Y	N	N	Y	Y	Y	Y	P	Y	Y	N	Y	Y	Y	Y	Y	Critially low quality review
Cataldi [62]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	High quality review
Cheng [63]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	High quality review
Cramer [21]	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Critially low quality review

Q1. „Did the research questions and inclusion criteria for the review include the components of PICO?"; Q2. „Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?"; Q3. „Did the review authors explain their selection of the study designs for inclusion in the review?" ; Q4. „Did the review authors use a comprehensive literature search strategy?; Q5. „Did the review authors perform study selection in duplicate?"; Q6. „Did the review authors perform data extraction in duplicate?"; Q7. „Did the review authors provide a list of excluded studies and justify the exclusions?"; Q8. „Did the review authors describe the included studies in adequate detail?"; Q9. „Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?" ; Q10. „Did the review authors report on the sources of funding for the studies included in the review?" ; Q11. „If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?" ; Q12. „If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?"; Q13. „Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?" ; Q14. „Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?" ; Q15. „If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?" ; Q16. „Did the review authors report any potential sources of con- flict of interest, including any funding they received for conducting the review?" (Shea BJ,2017 [26] p.3–5)
Answers: Y, yes; P, partial yes; N, no

may have reported biased or unreliable results due to methodological shortcomings [21,27–44,48,50–52,57,58,60,61] **(Table 2)**.

Primary and secondary outcomes

The patient went on exercise programs and showed an improvement in fatigue (SMD -0.26, 95% CI [-0.44, -0.08], p < 0.01) **(Figure 2)**, pain (SMD -0.65, 95% CI [-1.10, -0.19], p = 0.01) **(Figure 3)**, QoL (SMD 0.28, 95% CI [0.21, 0.36], p < 0.01) **(Figure 4)** and physical activity level (SMD 0.30, 95% CI [0.21, 0.39], p < 0.001) **(Figure 5)**. No significant differences were found in anxiety (SMD 0.00, 95% CI [-0.62, 0.63], p = 1.00) **(Figure 6)** and depression (SMD -0.45, 95% CI [-1.00, 0.10], p = 0.11) **(Figure 7)**.

Concerning heterogeneity, results were homogenous for pain (I^2 = 31.52%, p = 0.21), and heterogeneous for fatigue (I^2 = 94.24%, p < 0.01), QoL (I^2 = 46.48%, p < 0.001), physical activity level (I^2 = 23.33%, p = 0.02), anxiety (I^2 = 97.79%, p < 0.01) and depression (I^2 = 94.03%, p < 0.01).

Sensitivity analysis did not alter the outcomes except for pain **(Figures S1–S6)**. Removing the Shen et al. study [56] resulted in an insignificant reduction in pain (SMD -0.76, 95% CI [-1.64, 0.12], p = 0.092).

Sup group analysis

Subgroup analysis was performed for fatigue and QoL according to the methodological quality of the included reviews **(Figures S7** and **S8)**. For

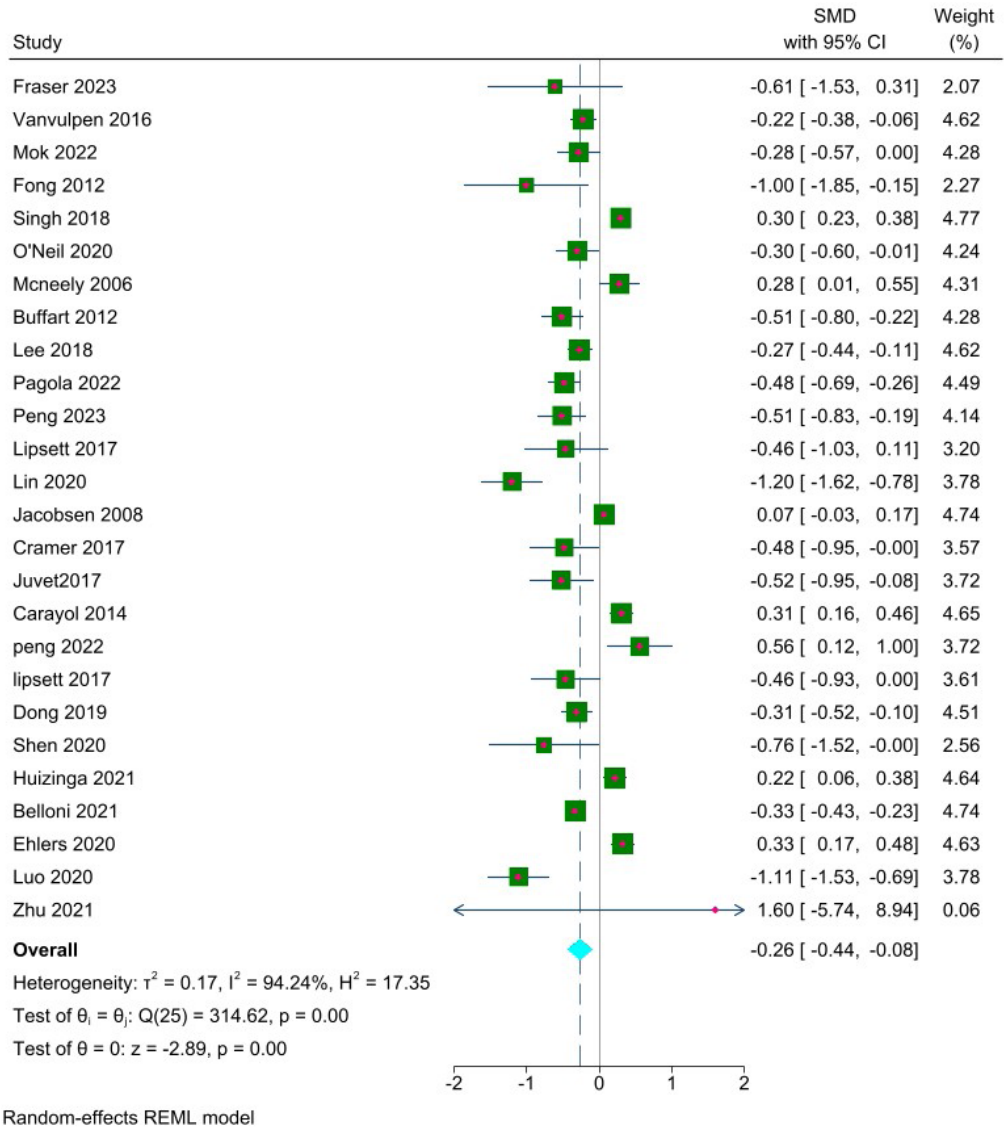

Figure 2. Forest plot of fatigue. SMD = standardized mean difference; CI = confidence interval; REML = restricted maximum likelihood.

fatigue, critically low-quality reviews (SMD -0.27, 95% CI [-0.53, -0.00], p < 0.001) and low-quality reviews (SMD -0.24, 95% CI [-0.51, 0.02], p < 0.001) showed significant results. For QoL, critically low-quality reviews showed an insignificant association (SMD 0.19, 95% CI [0.09, 0.30], p = 0.06), whereas low-quality reviews showed a significant association (SMD 0.35, 95% CI [0.27, 0.44], p < 0.01).

Overlap assessment

We calculated the Corrected Covered Area (CCA) as 0.54%, indicating very low overlap [20]. After removing duplicates, 719 unique RCTs remained out of a total of 903 records.

Risk of bias

The funnel plots for fatigue (θ = -0.26, 95% CI -0.439 to -0.084, p = 0.0038) and QoL (θ = 0.284,

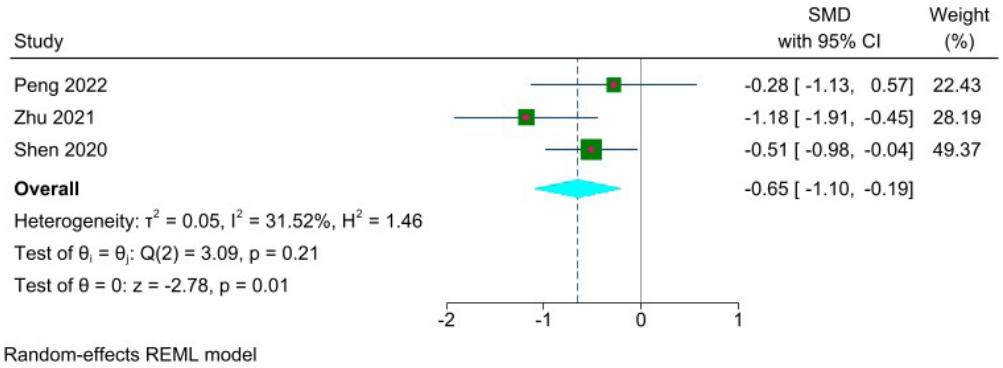

Figure 3. Forest plot of pain. SMD = standardized mean difference; CI = confidence interval; REML = restricted maximum likelihood.

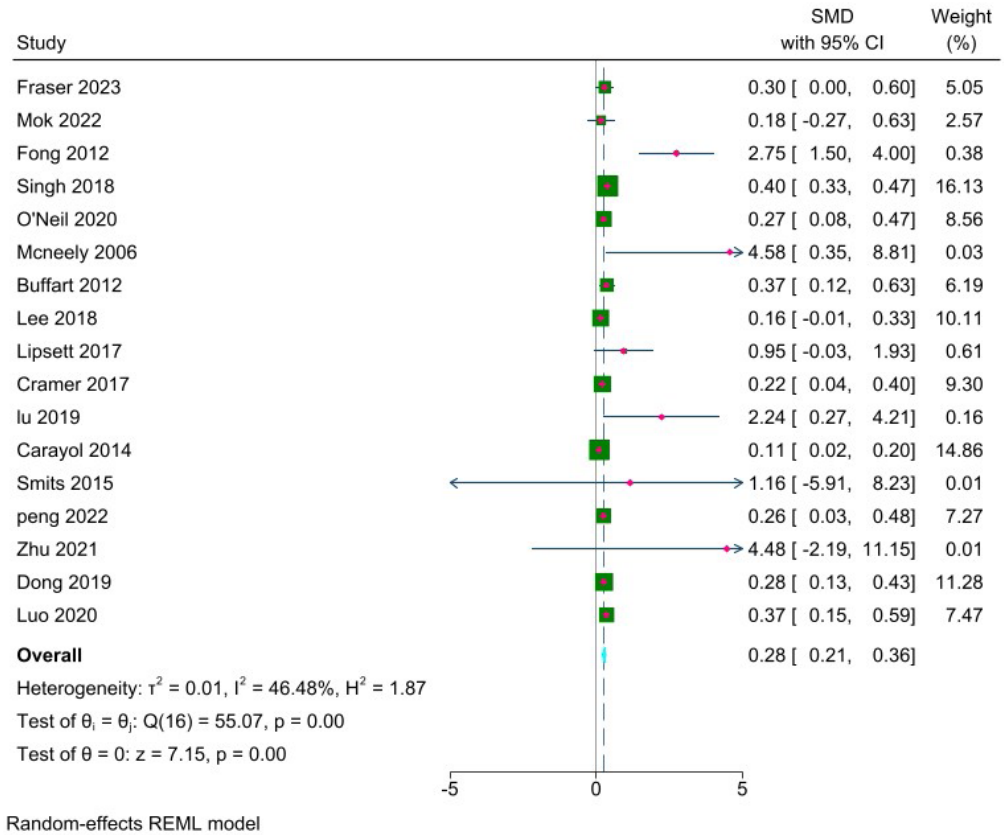

Figure 4. Forest plot of quality of life. SMD = standardized mean difference; CI = confidence interval; REML = restricted maximum likelihood.

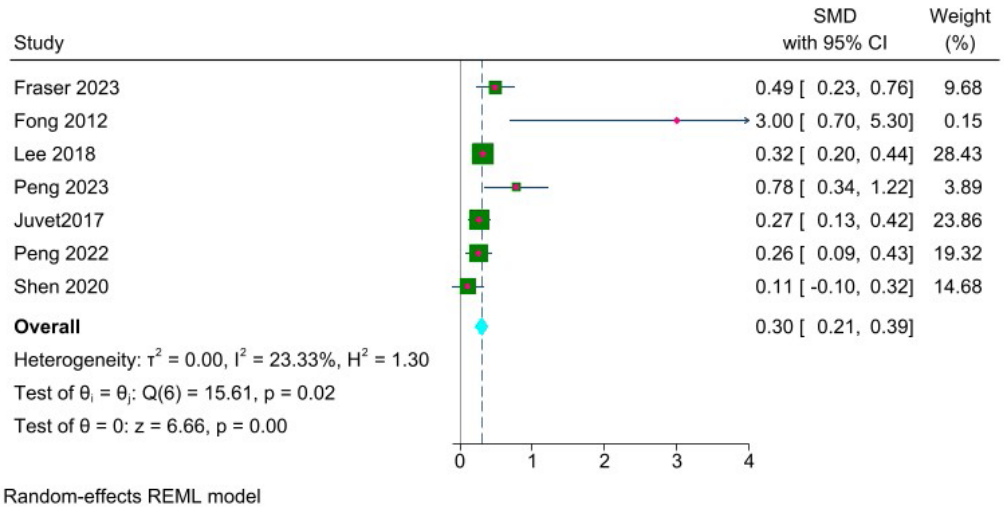

Figure 5. Forest plot of physical activity level. SMD = standardized mean difference; CI = confidence interval; REML = restricted maximum likelihood.

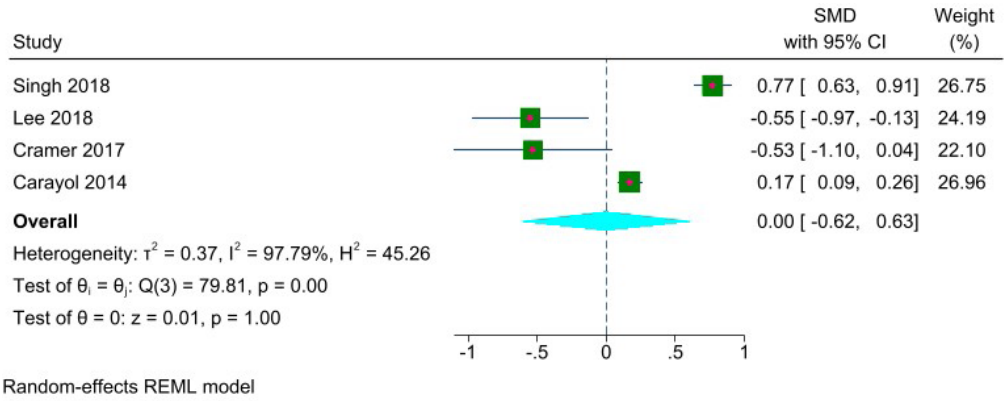

Figure 6. Forest plot of anxiety. SMD = standardized mean difference; CI = confidence interval; REML = restricted maximum likelihood.

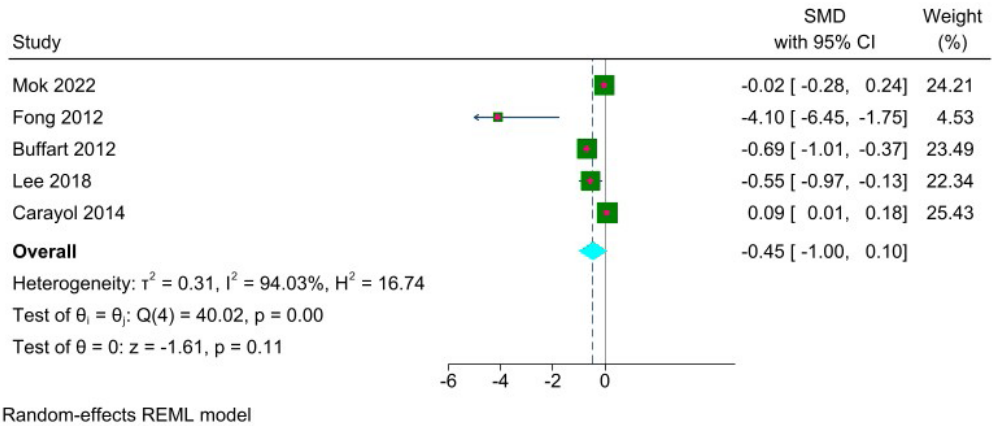

Figure 7. Forest plot of depression. SMD = standardized mean difference; CI = confidence interval; REML = restricted maximum likelihood.

95% CI 0.206 to 0.362, p < 0.005) are presented in **Figures S9** and **S10**. Visual inspection of the fatigue funnel plot reveals a largely symmetrical distribution of studies around the pooled effect estimate, with most clustered at higher precision and a single small-study outlier, suggesting no strong evidence of publication bias. In contrast, the quality-of-life funnel plot shows greater dispersion and some asymmetry among less precise studies, suggesting small-study effects or publication bias.

Discussion

In this umbrella review, we systematically synthesised evidence from 44 systematic reviews and meta-analyses to investigate the effects of exercise on multiple outcomes, including fatigue, QoL, physical function, pain, depression, and anxiety in breast cancer patients. Our findings reinforce the well-established therapeutic benefits of exercise, demonstrating significant improvements in fatigue, QoL, physical function, and pain outcomes [5]. These results align with the growing body of evidence supporting the integration of exercise as a crucial component of comprehensive cancer care [64,65].

Fatigue, one of the most prevalent and debilitating symptoms experienced by cancer patients, was consistently improved with exercise interventions across multiple meta-analyses included in our review [11,12,66,67]. The positive effects of exercise on fatigue were observed across various cancer types, treatment modalities, and exercise regimens [67,68]. However, our meta-analysis did not conduct subgroup analyses based on intervention characteristics, such as duration, type, frequency, and supervision level. A recent systematic review by Dennett et al. highlighted that these factors can have varying degrees of influence on the effects of exercise on cancer-related fatigue [69]. Future research should explore these potential moderators to optimise exercise prescriptions for managing fatigue in patients with breast cancer.

Regarding QoL, our review found robust evidence supporting the beneficial impact of exercise interventions on overall well-being and various QoL domains, including physical, emotional, and functional aspects [39,68,70]. These findings underscore the importance of integrating exercise as a critical component of supportive care for breast cancer patients, as it can mitigate the detrimental effects of cancer and its treatments on multiple aspects of QoL.

Furthermore, our review demonstrated that exercise interventions significantly improved physical function and alleviated pain among breast cancer patients [70–72]. These outcomes are particularly relevant, as cancer treatments and disease progression can lead to functional impairments and chronic pain, adversely affecting activities of daily living and overall independence. By enhancing physical function and reducing pain, exercise can play a crucial role in facilitating rehabilitation and improving the overall well-being of breast cancer survivors.

Notably, our meta-analyses revealed a negligible impact of exercise interventions on depression and anxiety levels in this patient population. These findings align with previous research suggesting that exercise alone may not be sufficient to alleviate psychological distress in cancer survivors [10,68,73]. The multifactorial nature of depression and anxiety, influenced by biological, psychological, and social factors, necessitates a multidisciplinary approach to address these complex conditions [74–76].

Given the limited efficacy of exercise interventions in improving depression and anxiety, alternative lifestyle modifications should be explored and integrated into comprehensive care plans. Cognitive-behavioural therapy and mindfulness-based interventions have shown promising results in reducing depression and anxiety symptoms among breast cancer patients [71,77,78]. Incorporating these evidence-based psychosocial interventions alongside exercise programs may yield synergistic benefits by addressing both physical and psychological aspects of cancer survivorship. Furthermore, emerging evidence suggests that dietary interventions, such as the Mediterranean diet or anti-inflammatory dietary patterns, may benefit mental health outcomes across various populations [79–81]. Incorporating dietary counselling and education into comprehensive lifestyle interventions for breast cancer patients could potentially alleviate depression and anxiety symptoms, further enhancing overall well-being.

Strengths and limitations

This umbrella review synthesised a substantial body of evidence from numerous systematic reviews and meta-analyses, offering a comprehensive evaluation of the effects of exercise interventions on various patient-reported outcomes in patients diagnosed with breast cancer. The diversity of the included reviews underscores the complex and multifaceted nature of this topic, underscoring the importance of a thorough synthesis and critical appraisal of the available evidence. In interpreting the findings, greater emphasis was placed on the results from high-quality reviews. In contrast, findings from low- and critically low-quality reviews were interpreted cautiously, while accounting for potential methodological limitations.

Regarding limitations, it is crucial to acknowledge that the included reviews may have employed different inclusion criteria, study designs, and analytical methods, potentially introducing heterogeneity in the findings. Our review did not assess the long-term sustainability of the observed effects or the potential adverse events associated with exercise interventions. The quality assessment was based solely on the information reported in the published reviews. Some reviews may have employed more rigorous methods than those explicitly described in the published reports. Additionally, some reviews may have included overlapping primary studies, leading to double-counting of evidence. Hence, we calculated the CCA, which showed a very low overlap. The varying methodological quality of the included reviews underscores the importance of critical appraisal and the need for transparent, rigorous reporting in systematic reviews and meta-analyses. Future research in this area should adhere to established guidelines and methodological standards to ensure the reliability and validity of the findings. It should also explore aspects related to the safe and effective implementation of exercise programs in clinical practice.

Conclusions

This umbrella review provides compelling evidence for the beneficial role of exercise in ameliorating fatigue, enhancing QoL, improving physical function, and alleviating pain in patients diagnosed with breast cancer. However, the impact on depression and anxiety appears to be limited, underscoring the need for complementary interventions that target psychological well-being. Future research should concentrate on developing and evaluating comprehensive lifestyle interventions that integrate exercise, psychosocial support, and dietary modifications to optimise overall health and QoL in this patient population. Furthermore, the exploration of potential moderators of exercise effects on fatigue and other outcomes is crucial to refining exercise prescriptions and maximising the therapeutic benefits for patients with breast cancer.

Declarations

Acknowledgment
Mohamed Abouzid is a participant in STER Internationalisation of Doctoral Schools. Program from NAWA, the Polish National Agency for Academic Exchange, No. PPI/STE/2020/1/00014/DEC/02.

Authors contribution
MH and AZA: conceptualisation and methodology. MH, AZA, ME, FMR, JMD, HE, MMS and MA: investigation and data curation. MAzid: formal analysis. MH, AZA and MAzid: Writing – Original Draft. MAzid: Supervision. MH: Project administration. MAzid: Writing – Review & Editing. All authors read and approved the final content.

Availability of data and materials
All data generated or analysed during this study are included in this published article

Ethical approval
Not applicable

Conflict of interest statement
The authors declare no conflict of interest.

Funding sources
There are no sources of funding to declare.

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Supplementary figures

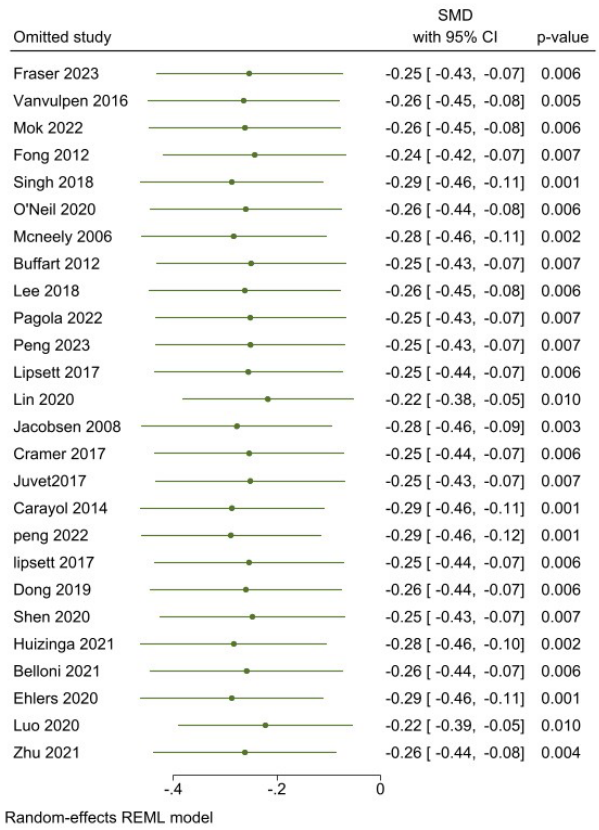

Figure S1. Sensitivity analysis for fatigue.

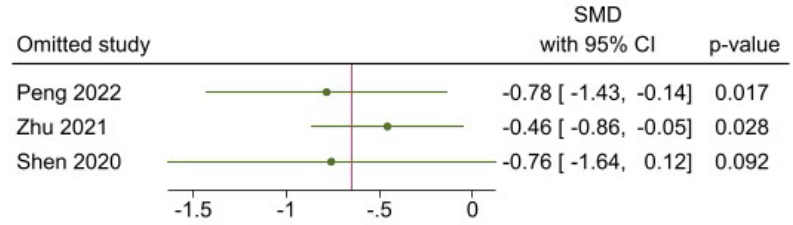

Figure S2. Sensitivity analysis for pain.

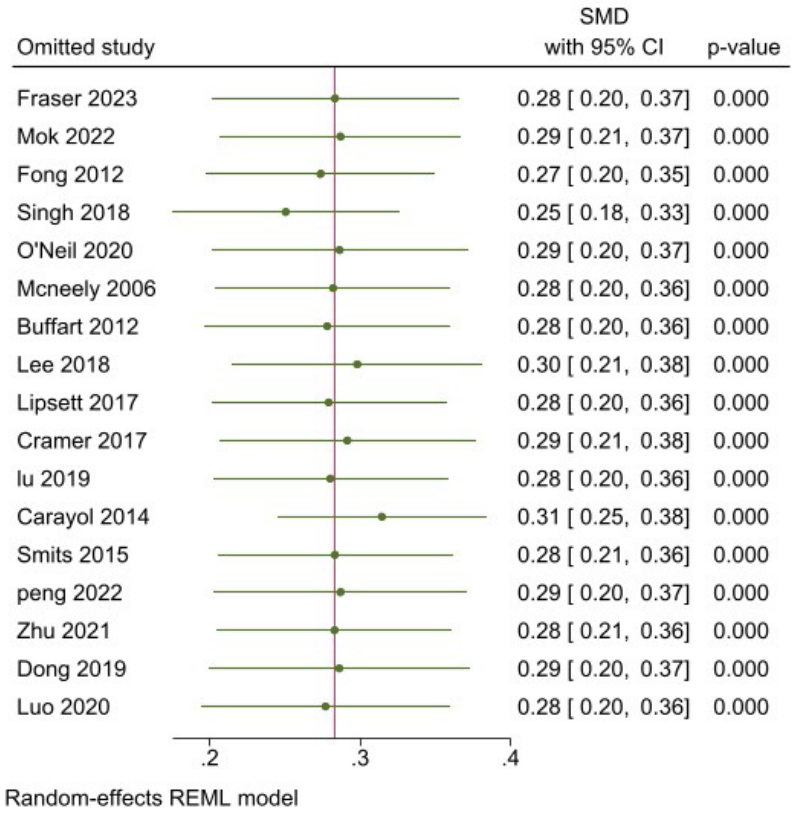

Figure S3. Sensitivity analysis for quality of life.

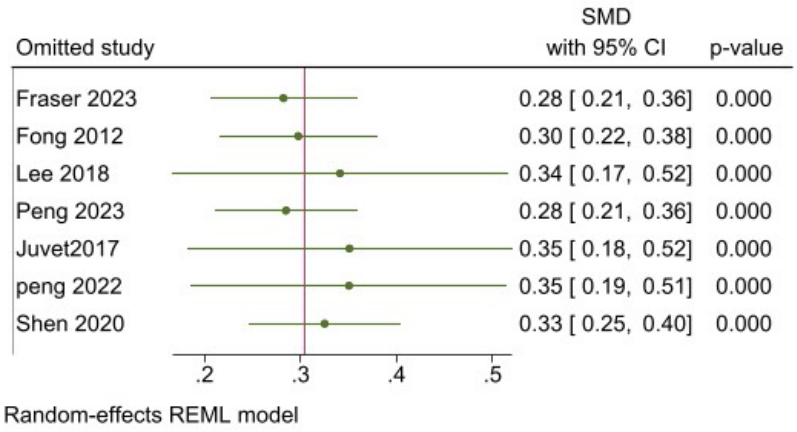

Figure S4. Sensitivity analysis for physical activity level.

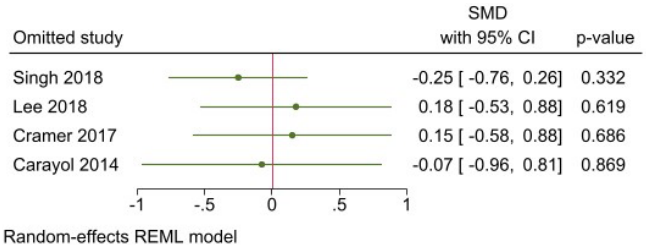

Figure S5. Sensitivity analysis for anxiety.

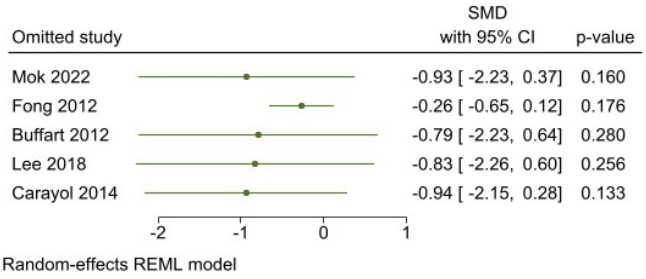

Figure S6. Sensitivity analysis for depression.

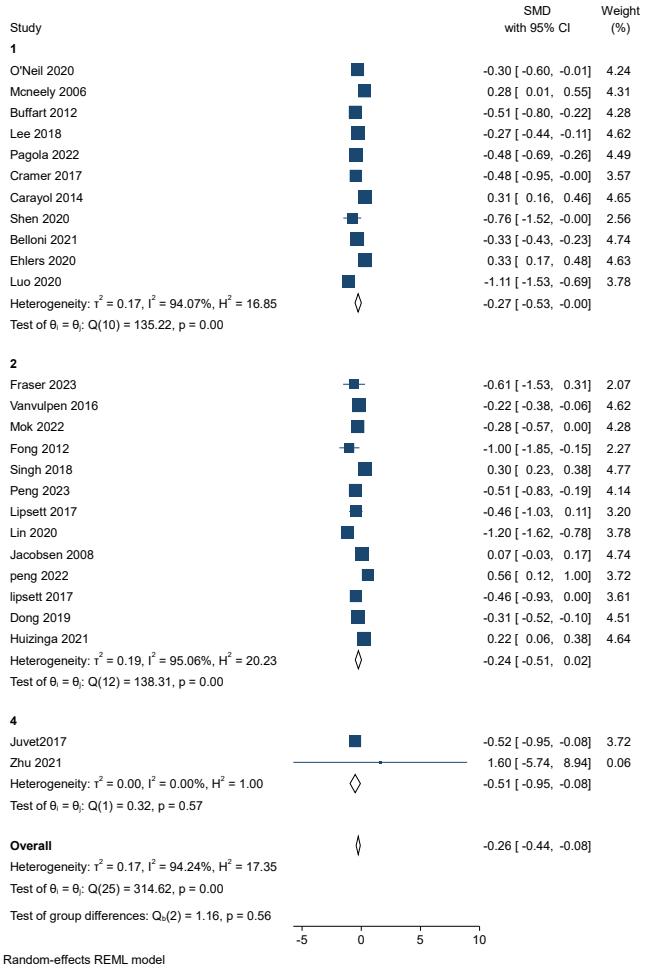

Figure S7. Subgroup forest plot for the fatigue outcome, stratified by methodological quality of the included reviews. Subgroups are defined as follows: (1) critically low-quality review; (2) low-quality review; and (4) high-quality review.

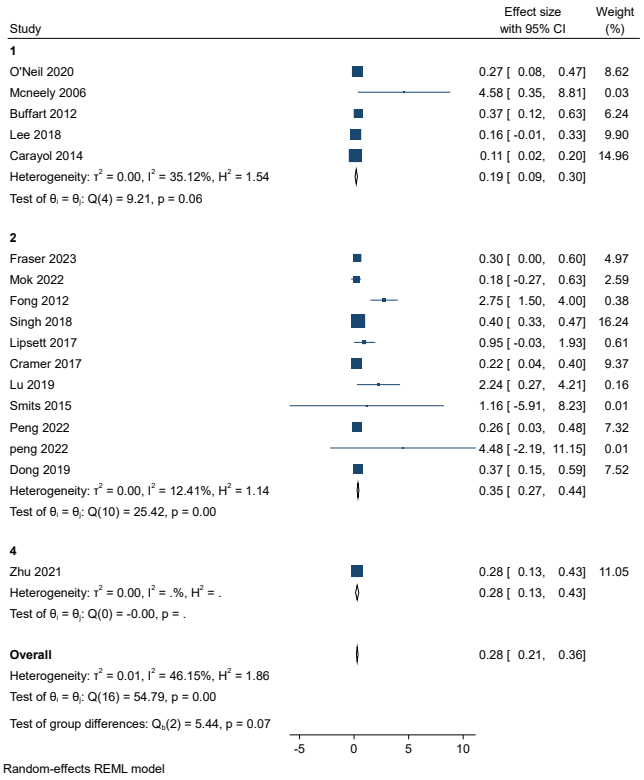

Figure S8. Subgroup forest plot for the quality of life outcome, stratified by methodological quality of the included reviews. Subgroups are defined as follows: (1) critically low-quality review; (2) low-quality review; and (4) high-quality review.

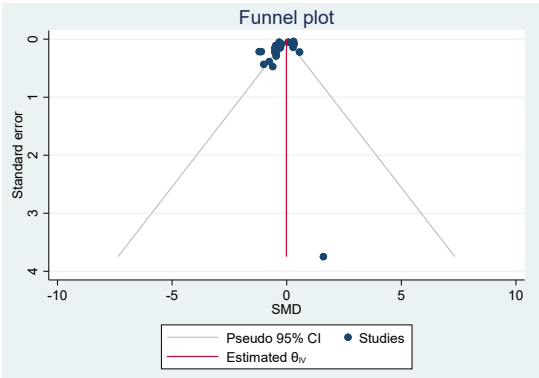

Figure S9. Funnel plot assessing publication bias for the fatigue outcome.

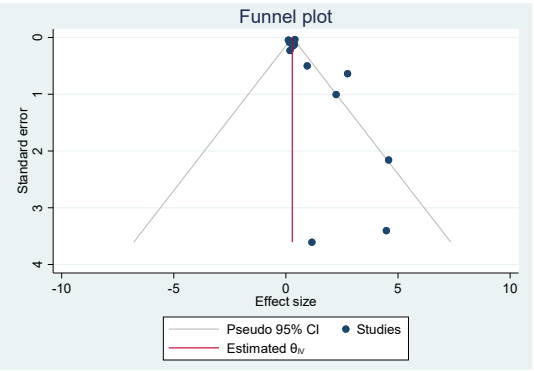

Figure S10. Funnel plot assessing publication bias for the quality of life outcome.