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Effects of different exercise interventions on chemotherapy-related cognitive impairment in patients with breast cancer: a study protocol for systematic review and network meta-analysis

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ABSTRACT

Introduction Breast cancer stands as the most prevalent type of cancer affecting women globally, and chemotherapy plays a pivotal role in its treatment by diminishing tumour recurrence and enhancing the survival rates of patients. However, chemotherapy-related cognitive impairment (CRCI) often occurs in patients undergoing treatment. Although multiple clinical trials have indicated that exercise therapy can improve CRCI in patients with breast cancer, there are variations in the types of exercise interventions and their effectiveness. We aim to perform a pioneering network meta-analysis (NMA) to assess and prioritise the effectiveness of various exercise interventions in enhancing cognitive function in patients with breast cancer undergoing chemotherapy.

Methods and analysis We will search multiple databases, including PubMed, Web of Science, Cochrane, Embase, China National Knowledge Infrastructure, VIP Database for Chinese Technical Periodicals, Wanfang and Sinomed databases, from their inception to May 2023. The main outcome is the cognitive function changes in patients with breast cancer, including subjective and objective results. We will specifically include randomised controlled trials reported in English and Chinese languages, whose primary outcome consists of an assessment of the cognitive function of patients with breast cancer using standardised and validated assessment tools, encompassing both subjective and objective outcomes. The quality of all the trials included will be evaluated based on 'Version 2 of the Cochrane tool for assessing the risk of bias in randomized controlled trials (RoB2)'. We will conduct a Bayesian NMA to thoroughly evaluate and compare the effectiveness of different exercise interventions. We will use cumulative ranking probability plots to estimate the ranking of the best interventions for various exercises. Network plots and funnel plots will be employed to display the study sizes and participants of each exercise intervention, as well as potential publication biases.

Ethics and dissemination The study findings will be shared via peer-reviewed journals to ensure the highest quality and credibility of the research. As the reporting will not include any private patient data, there are no ethical considerations associated with this protocol.

PROSPERO registration number CRD42023406597.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study will use network meta-analysis (NMA) methodology to compare and evaluate the effectiveness of different exercise therapies for alleviating cognitive-related functional impairments in patients with breast cancer.
⇒ The quality assessment of the included trials will be performed using the Risk of Bias V.2. This tool provides a standardised approach to assess the risk of bias in each included trial.
⇒ A rigorous process of developing and evaluating grading recommendations will be undertaken to assess the overall quality of evidence obtained from the NMA.
⇒ The lack of direct comparison results between different exercise methods may lead to discrepancies between the conclusions of future comparative studies and the conclusions of this study.

INTRODUCTION

As per the global cancer statistics report, breast cancer has now surpassed lung cancer in terms of incidence, establishing itself as the foremost malignancy globally.[1] In 2024, there will be 972 060 new cancer cases in women, with breast cancer accounting for 32% of all newly diagnosed cancer cases in women.[2] At present, comprehensive treatment options for breast cancer include surgical intervention, chemotherapy, radiation therapy, hormonal therapy and targeted therapy. Among these, chemotherapy plays a crucial role in the treatment of patients and is deemed one of the pivotal components. Chemotherapy-related cognitive impairment

(CRCI) is a commonly encountered side effect of chemotherapy treatment. This refers to the cognitive impairments that patients with cancer may experience while undergoing or after receiving chemotherapy treatment. These impairments can affect attention, memory, executive function and processing speed.[3 4] This condition can lead to physiological and psychological issues,[5 6] including anxiety, depression and significantly impact the patient's quality of life.[7] Research has revealed that a considerable proportion of patients with breast cancer, ranging from 25% to 75%, encounter chemotherapy-induced cognitive impairment.[5] Multiple studies have provided evidence that cancer and its associated treatments result in continuous cellular damage, leading to the accumulation of unrepaired damaged DNA. Consequently, this accumulation can cause neuronal death and increase the risk of cognitive impairment in patients.[8 9] The occurrence frequency and severity of cognitive impairment are particularly important for patients with cancer undergoing chemotherapy, and potential cognitive damage should be taken seriously.[10] Due to a lack of awareness, patients may not always communicate cognitive impairment symptoms to their doctors. Furthermore, routine assessment of cognitive functions is usually not conducted outside of clinical trial settings.[11] However, restoring normal cognitive function is of vital importance. Interventions for post-chemotherapy cognitive impairment primarily focus on cognitive–behavioural therapy, brain training, exercise and physical activity, psychoeducational, lifestyle changes, occupational therapy, electroencephalography biofeedback and pharmacological interventions.[11 12] Irrespective of the specific type or method of physical activity, engaging in sports and exercise has been shown to enhance oxidative balance and improve memory. Exercise therapy may be a viable and convenient intervention to reduce the risk of cognitive impairments.[13] It can also protect the nerves by improving cognition, learning and memory,[14] while offering economic, sustainable and practical advantages.[15] A network meta-analysis (NMA) revealed that among all non-pharmacological interventions, both Qigong and exercise were found to be more effective in improving objective outcomes of cognitive function compared with music therapy and psychotherapy.[16]

A randomised clinical trial revealed that engaging in moderate-intensity aerobic exercise can enhance the subjective cognitive function of individuals diagnosed with breast cancer undergoing chemotherapy. However, it did not yield significant impacts on sustained attention, executive function and memory.[17] Two randomised controlled trials (RCTs) indicated that high-intensity aerobic exercise led to improvements in processing speed among patients.[18 19] A RCT demonstrated that after engaging in high-intensity interval resistance training, the rate of decline in cognitive function was slower.[20] Additionally, four RCTs indicated that progressive resistance training led to improvements in cognitive function among patients.[21–24] Yoga,[25–27] Qigong[28 29] and Baduanjin,[30] which are exercise forms combining breath control techniques with physical movements, have also shown some improvement in cognitive function among patients with breast cancer.

It is worth noting that the studies discussed did not directly compare the effectiveness of different exercise interventions. Instead, the comparisons were made between exercise interventions and factors such as no exercise, usual care or general exercise. Consequently, there is currently insufficient evidence to determine the ideal exercise intervention for enhancing cognitive function in patients with breast cancer. In conclusion, the goal of this study is to compare and rank the effectiveness of various exercise interventions to evaluate the most suitable exercise programme. The results of this study will offer clinical nurses valuable evidence regarding the efficacy of various exercise interventions in mitigating cognitive impairments among individuals diagnosed with breast cancer. These findings will enable healthcare professionals to make informed decisions about the most effective types of exercise interventions for managing cognitive difficulties.

METHODS AND ANALYSIS

Our protocol has been officially registered in the PROSPERO database under the registration number CRD42023406597. Throughout this study, we will strictly follow the guidelines provided in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) statement, ensuring comprehensive and transparent reporting of our methods and findings.[31]

Inclusion/exclusion criteria for study selection

Participants

To be eligible for participant selection, individuals must meet the following inclusion criterion: (1) aged 18 years or above; (2) women diagnosed with breast cancer who have undergone or are currently undergoing chemotherapy treatment;(3) no restrictions on factors such as race, educational level, treatment type, clinical stage or pathological stage. The exclusion criteria encompass the following: (1) the presence of cognitive impairment before chemotherapy; (2) the inclusion of comorbid conditions like psychiatric disorders, prior substance use disorders or any other neurological abnormalities which could potentially influence the results of cognitive tests.

Interventions

Exercise interventions encompass a wide range of activities, including but not limited to high-intensity or moderate-intensity continuous or interval resistance training, aerobic exercises such as walking or cycling, and mind–body exercises like yoga, Tai Chi or Qigong. These interventions can be implemented in various environments, including supervised settings or in the comfort of one's own home. Other therapeutic interventions that incorporate cognitive–behavioural therapy will be excluded.

Comparators

In comparison to exercise interventions, general physical activity, lack of physical activity or usual care will be included.

Outcome measures

The primary outcome measures considered for this systematic review and NMA are subjective or objective changes in cognitive function in patients with breast cancer, assessed using standardised and validated cognitive function measurement tools.

Type of studies

The inclusion criteria for the study are RCTs conducted in either Chinese or English language that assess the effects of exercise interventions on patients with breast cancer. The following types of studies will be excluded from our analysis: non-randomised controlled studies, observational cohort studies, case-control studies, qualitative studies, pilot studies, duplicate reports and reviews. Only RCTs will be considered for inclusion in our analysis.

Data sources and search strategy

We will conduct a thorough search across eight electronic databases, namely PubMed, Web of Science, Embase, Cochrane, Wanfang Database, China National Knowledge Infrastructure, VIP Database for Chinese Technical Periodicals and Sinomed Database, from the inception of the databases until May 2023. To ensure a comprehensive retrieval of relevant literature, a combination of controlled vocabulary and free-text terms will be employed. The complete search strategies for all databases can be found in the online supplemental file 1.

Selection of studies

Two researchers, Yu Dong and Hao Huang, will import the retrieved literature into EndNote V.X9 (https://www.endnote.com/) and perform a deduplication process. They will independently read the titles and abstracts for initial screening and conduct a comprehensive review and assessment of the full texts of all relevant studies. Excluded studies will be documented and explained. In case of any disagreements, a third researcher will be invited for discussion and a voting decision will be made. For duplicate studies, only the most comprehensive trials with the richest data will be included. The screening process will be presented using a PRISMA flow chart, as depicted in figure 1.

Risk of bias in included studies

We will use the Cochrane Risk of Bias V.2 (RoB2) to evaluate the potential bias in the studies that are included. This tool enables the classification of bias levels into 'low risk', 'high risk', or 'some concerns' categories. Researchers will independently assess all study results using the RoB2 tool, compare and negotiate any differences in opinions. They will compare the bias risk of each module and discuss the discrepancies to reach a consensus, in order to evaluate the overall bias risk of the article. If there are still disagreements that cannot be resolved, a third researcher will be consulted and will make a conclusive voting decision to ultimately reach a consensus on the overall bias risk assessment of the article.

Data extraction

Two researchers, Yu Dong and Hao Huang, will extract the pertinent data from the included studies independently and record it in an Excel 2019 database. If there are any doubts or inconsistencies, a third investigator will serve as a judge, and any disagreements will be resolved through discussion. We will extract information including: (1) general information (author name, country, publication year, recruitment period and sample size); (2) participants (age, education level, occupation, tumour stage, type of treatments, treatment duration, time elapsed between treatment and the RCT and adherence to the intervention); (3) intervention (type of exercise, exercise intensity, frequency of exercise sessions per week, exercise duration in minutes, follow-up period and measurement methods used to assess the primary outcome indicators).

Grading the quality of evidence

The evidence quality of primary outcomes will be graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. Two reviewers (Yu Dong and Hao Huang) will independently assess the evidence quality for each outcome and assign a grade of 'high', 'moderate', 'low' or 'very low' based on the GRADE rating criteria.

Statistical analysis

To analyse continuous outcomes, we will compute the weighted mean differences accompanied by their corresponding 95% CIs. Regarding binary outcomes, we will compute the ORs along with their corresponding 95% CIs. To conduct the traditional meta-analysis, we will employ the RevMan V.5.3 software. The extent of heterogeneity among the studies will be evaluated using the I^2 statistic. If the p value is greater than 0.1 and I^2 is less than 50%, this suggests the absence of significant heterogeneity. In such cases, a fixed-effect model will be employed. If the p value is less than or equal to 0.1 and I^2 is equal to or greater than 50%, it suggests substantial heterogeneity and a random-effect model will be employed. R Studio software will be used to compute and present league tables, showing direct and mixed comparisons of different interventions. Network plots will be created using STATA software (V.14.0) and the 'network' package. Each outcome will have a corresponding network plot, where node size represents the sample size of each exercise intervention and edge thickness indicates the number of studies included in direct comparisons. In cases where loop closures occur, the node-split model will be used to assess consistency. A consistency model will be adopted for NMA when there is no statistically significant difference ($p > 0.05$) observed between direct and indirect comparisons. Alternatively, if heterogeneity is detected, we will

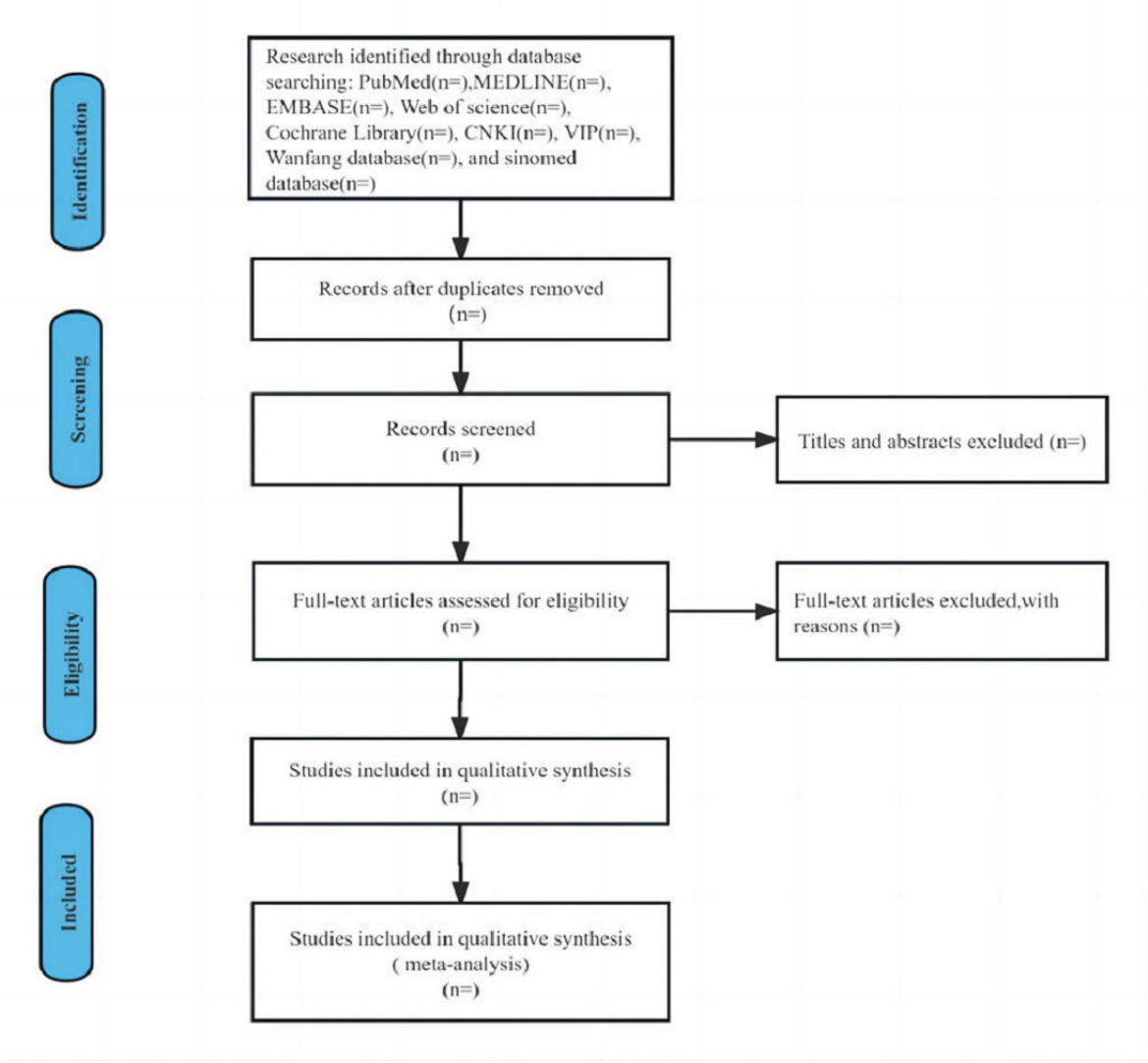

Figure 1 PRISMA flow chart of the study.

employ a random-effect model to combine the effect sizes. Any absence of inconsistency will result in using a fixed-effect model. For ranking the interventions, we will employ Stata software (V.14.0) to compute the surface under the cumulative ranking curve (SUCRA). SUCRA values indicate the efficacy of the treatments, with higher values indicating better outcomes. Funnel plots will be employed to examine any potential publication bias.

DISCUSSION

Exercise may have a certain role in improving cognitive dysfunction in patients with cancer, particularly those undergoing chemotherapy. However, there is currently a lack of supporting empirical evidence. The primary objective of this systematic review is to conduct an extensive literature search and compile existing research to analyse the impacts of exercise interventions on cognitive dysfunction among those who have undergone or are undergoing chemotherapy treatment. The objective is to provide patients with the latest and most comprehensive evidence for exercise interventions and rank their effectiveness. The NMA approach employed in this study facilitates the incorporation of both direct and indirect evidence, enabling comparisons between exercise interventions that have not been directly assessed. It is considered the optimal approach to address the current research question.

However, it is essential to recognise and acknowledge the potential limitations of this study. Some original studies may have implementation and measurement biases in their research design, leading to publication bias in the results of this study. The limited number of studies and small sample sizes in some exercise interventions may introduce bias in the research results. The participants included in the study may have differences in their daily exercise habits, exercise areas, intensity and frequency, which could lead to potential heterogeneity. In this study, the patients' education level, occupation, tumour stage, type of treatments, treatment duration, time elapsed between treatment and the RCT, and

adherence to the intervention need to be analysed as potential sources of bias affecting the outcome measures. Subsequent research should rigorously and comprehensively eliminate confounding factors to further validate the effectiveness of the exercise intervention. The lack of direct comparison results between different exercise methods may lead to discrepancies between the conclusions of future comparative studies and the conclusions of this study. To ensure the reliability and objectivity of the research conclusions, further confirmation through multicentre, large-sample, high-quality collaborative RCTs is necessary to validate the study results. The results of NMA will offer healthcare professionals a comprehensive body of evidence regarding the efficacy of various exercise interventions in mitigating cognitive dysfunction among patients with breast cancer. The research results will remind healthcare professionals in the clinical practice of patients with breast cancer to not only focus on the treatment of the tumour itself, but also to pay attention to the intervention and management of CRCIs. By incorporating exercise intervention into the comprehensive treatment plan for patients with breast cancer, personalised exercise plans will be designed for patients, guiding them to choose appropriate types, frequencies and intensities of exercise, as well as monitoring the impact of exercise on cognitive function to improve their cognition and quality of life. Based on the current research findings, future studies can further explore the long-term effects of different types, frequencies and intensities of exercise interventions on CRCIs in patients with breast cancer. Additionally, there is potential for in-depth investigation into the mechanisms by which exercise impacts breast cancer treatment, in order to provide scientific evidence for the development of more targeted exercise intervention strategies. This will further enhance comprehensive care and treatment plans for patients with breast cancer.

Contributors YD drafted the manuscript. YD and HH will conduct literature search, study selection, data extraction, quality assessment of included randomised controlled trials and data analysis. AP will oversee the review process for each procedure and be responsible for quality control. All authors have read and approved the publication of the protocol.

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REFERENCES

1 Sung H, Ferlay J, Siegel RL, *et al*. Global cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021;71:209–49.
2 Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. *CA Cancer J Clin* 2024;74:12–49.
3 Craig CD, Monk BJ, Farley JH, *et al*. Cognitive impairment in gynecologic cancers: a systematic review of current approaches to diagnosis and treatment. *Support Care Cancer* 2014;22:279–87.
4 Lv L, Mao S, Dong H, *et al*. Pathogenesis, assessments, and management of chemotherapy-related cognitive impairment (CRCI): an updated literature review. *J Oncol* 2020.:3942439.
5 Bender CM, Merriman JD, Sereika SM, *et al*. Trajectories of cognitive function and associated Phenotypic and Genotypic factors in breast cancer. *Oncol Nurs Forum* 2018;45:308–26.
6 Von Ah D, Habermann B, Carpenter JS, *et al*. Impact of perceived cognitive impairment in breast cancer survivors. *European Journal of Oncology Nursing* 2013;17:236–41.
7 Lee JR, Oh PJ. A structural model for chemotherapy related cognitive impairment and quality of life in breast cancer patients. *J Korean Acad Nurs* 2019;49:375.
8 Wang H, Lautrup S, Caponio D, *et al*. DNA damage-induced neurodegeneration in accelerated ageing and Alzheimer's disease. *IJMS* 2021;22:6748.
9 Bird A. DNA methylation patterns and epigenetic memory. *Genes Dev* 2002;16:6–21.
10 Minisini A, Atalay G, Bottomley A, *et al*. What is the effect of systemic anticancer treatment on cognitive function *Lancet Oncol* 2004;5:273–82.
11 Di Nardo P, Lisanti C, Garutti M, *et al*. Chemotherapy in patients with early breast cancer: clinical overview and management of long-term side effects. *Expert Opin Drug Saf* 2022;21:1341–55.
12 Oldacres L, Hegarty J, O'Regan P, *et al*. Interventions promoting cognitive function in patients experiencing cancer related cognitive impairment: A systematic review. *Psychooncology* 2023;32:214–28.
13 Erickson KI, Hillman C, Stillman CM, *et al*. Physical activity, cognition, and brain outcomes: A review of the 2018 physical activity guidelines. *Med Sci Sports Exerc* 2019;51:1242–51.
14 Vilela TC, de Andrade VM, Radak Z, *et al*. The role of exercise in brain DNA damage. *Neural Regen Res* 2020;15:1981–5.
15 Jia R-X, Liang J-H, Xu Y, *et al*. Effects of physical activity and exercise on the cognitive function of patients with Alzheimer disease: a meta-analysis. *BMC Geriatr* 2019;19:181.
16 Liu Y, Liu J-E, Chen S, *et al*. Effectiveness of Nonpharmacologic interventions for chemotherapy-related cognitive impairment in breast cancer patients: A systematic review and network meta-analysis. *Cancer Nurs* 2023;46:E305–19.
17 Schmitz KH, Courneya KS, Matthews C, *et al*. American college of sports medicine Roundtable on exercise guidelines for cancer survivors. *Med Sci Sports Exerc* 2010;42:1409–26.
18 Campbell KL, Kam JWY, Neil-Sztramko SE, *et al*. Effect of aerobic exercise on cancer-associated cognitive impairment: A proof-of-concept RCT. *Psychooncology* 2018;27:53–60.
19 Salerno EA, Rowland K, Kramer AF, *et al*. Acute aerobic exercise effects on cognitive function in breast cancer survivors: a randomized crossover trial. *BMC Cancer* 2019;19:371.
20 Mijwel S, Backman M, Bolam KA, *et al*. Adding high-intensity interval training to conventional training modalities: optimizing health-related outcomes during chemotherapy for breast cancer: the Optitrain randomized controlled trial. *Breast Cancer Res Treat* 2018;168:79–93.
21 Schmidt ME, Wiskemann J, Armbrust P, *et al*. Effects of resistance exercise on fatigue and quality of life in breast cancer patients undergoing adjuvant chemotherapy: A randomized controlled trial. *Int J Cancer* 2015;137:471–80.
22 Steindorf K, Schmidt ME, Klassen O, *et al*. Randomized, controlled trial of resistance training in breast cancer patients receiving adjuvant radiotherapy: results on cancer-related fatigue and quality of life. *Ann Oncol* 2014;25:2237–43.

23 Baumann FT, Drosselmeyer N, Leskaroski A, *et al*. 12-week resistance training with breast cancer patients during chemotherapy: effects on cognitive abilities. *Breast Care* 2011;6:142–3.
24 Baumann FT, Drosselmeyer N, Knicker A, *et al*. Effects of a 3-month resistance training intervention on the cognitive abilities of breast cancer patients during chemotherapy. *Deutsche Zeitschrift Fur Onkologie* 2009;41:70–5.
25 Derry HM, Jaremka LM, Bennett JM, *et al*. Yoga and self-reported cognitive problems in breast cancer survivors: a randomized controlled trial. *Psychooncology* 2015;24:958–66.
26 Pasyar N, Barshan Tashnizi N, Mansouri P, *et al*. Effect of yoga exercise on the quality of life and upper extremity volume among women with breast cancer related Lymphedema: a pilot study. *Eur J Oncol Nurs* 2019;42:103–9.
27 Vadiraja HS, Rao MR, Nagarathna R, *et al*. Effects of yoga program on quality of life and affect in early breast cancer patients undergoing adjuvant radiotherapy: a randomized controlled trial. *Complement Ther Med* 2009;17:274–80.
28 Larkey L, Goel N, Rogers C, *et al*. Effects of gentle exercise on fatigue, perceived cognitive function and metabolic equivalents. *Psycho-Oncology* 2009;18:S59–60.
29 Myers JS, Mitchell M, Krigel S, *et al*. Qigong intervention for breast cancer survivors with complaints of decreased cognitive function. *Support Care Cancer* 2019;27:1395–403.
30 Wei X, Yuan R, Yang J, *et al*. Effects of Baduanjin exercise on cognitive function and cancer-related symptoms in women with breast cancer receiving chemotherapy: a randomized controlled trial. *Support Care Cancer* 2022;30:6079–91.
31 Moher D, Shamseer L, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.