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A systematic review and meta-analysis of interventions to reduce perceived stress in breast cancer patients

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ABSTRACT

Purpose: Breast cancer (BC) patients commonly face stress that causes severe psychological and physiological problems. The main objective of the review was to confirm the effect of interventions on breast cancer patients' perceived stress, and the secondary objective was to explore the impact of interventions on anxiety, depression, and inflammatory markers.

Methods: A systematic and comprehensive search for randomized controlled trials (RCTs) that reported interventions' effects on perceived stress in breast cancer patients was performed in nine databases.

Results: Twenty-four RCTs, including 1887 participants, met the inclusion criteria, summarizing six categories for the intervention group: mindfulness and yoga, exercise, cognitive-behavioral stress management, self-regulation, relaxation training, and acupuncture. Compared with usual care or other types of care, mindfulness and yoga had excellent effects against perceived stress, anxiety, and depression; self-regulation could reduce perceived stress and anxiety; exercise could reduce perceived stress; acupuncture could reduce the level of depression; mindfulness could improve the TNF-α level, and yoga can reduce the level of salivary cortisol and DNA damage.

Conclusion: This systematic review indicated that nondrug interventions, such as mindfulness and yoga, effectively reduce perceived stress, anxiety, and depression. Rigorous studies with large sample sizes are needed to address the limitations of small sample sizes and shortcomings in methodology in this area.

1. Introduction

The global cancer statistics in 2022 expect breast cancer (BC) to account for 31 % of all newly diagnosed tumors in women, and the mortality rate will account for 15 % of all cancers in women [1]. According to the American Cancer Society, the 5-year survival rate of BC patients from different races varies from 80 % to 92 % [2,3]. BC patients face the stress of a cancer diagnosis, a "fatal disease," and experience the pressure of surgery, chemotherapy, radiotherapy, and other treatment methods. It is noteworthy that BC patients with intense psychological stress, such as fear of cancer recurrence, will be more doubtful about their disease and future life, exhibit severe symptom burden, and develop serious mental illnesses such as posttraumatic stress disorder [4]. Moreover, BC patients need to invest in a more extended period of treatment costs due to the improvement of the 5-year survival rate, which brings a severe economic burden to patients and their families.

Some studies have shown that financial distress in younger cancer patients was severe [5], and four years after the cancer diagnosis, 12 % of early BC patients had medical debt [6], which had a remarkable impact on the patient's mental health and quality of life [7]. In addition, as a threatening illness, BC challenges women's identity, body image, relationships with children and husbands, and self-esteem [8], thus aggravating stress, anxiety, and depression.

Increasing evidence has shown that stress is closely related to various psychological and physiological problems [9,10], but only when individuals feel environmental stimuli is stress, that is, perceived stress

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[11]. Perceived stress refers to the subjective feeling or psychological response that occurs when a stressful event in the environment acts on an individual and is evaluated through the integrated perception process (sensation, perception organization, judgment, and recognition stages) [12]. It is the level of subjective psychological stress that an individual experiences [11]. Compared with stress, only by focusing on the perceived stress of BC patients can we understand the impact of stress on health more deeply. Consequently, it is vital to reduce BC patients' perceived stress.

In recent years, some scholars have carried out intervention research on reducing the perceived stress of BC patients, such as yoga [13], mindfulness-based stress reduction [14], body-mind-spirit [15], exercise [16], cognitive-behavioral stress management [17], enhanced self-regulation [18], and auricular acupuncture [19]. Nevertheless, the effects of interventions are contradictory. For example, Taylor et al. [13] explored the effect of yoga on BC patients and showed no significant change in perceived stress compared to the control group. In contrast, another RCT [20] displayed the opposite result. Moreover, most RCTs have small sample sizes, such as 24 [21], 28 [22], 31 [23], and 44 [14], which limits statistical efficiency to a certain extent. Due to the heterogeneity of results, it is necessary to elucidate the impact of interventions on perceived stress and comprehensively identify effective interventions in BC patients.

Lazarus and Folkmans' transactional model of stress and coping clarified that when individuals perceive stress, the neuroendocrine system activates the hypothalamus-pituitary-adrenal (HPA) axis, increasing the release of inflammatory markers [24]. Considering that inflammatory markers can also reflect changes in stress, several included studies explored the impact of interventions on perceived stress and verified the impact on inflammatory markers. In addition, anxiety and depression are common in breast cancer patients, so most of the included studies verified the impact of anxiety and depression simultaneously. Therefore, this study used perceived stress as the primary outcome and anxiety, depression, and inflammatory factors as secondary outcomes. Several interventions, such as mindfulness-based stress reduction [14] and auricular acupuncture [19], explored the effectiveness of inflammatory makers but were limited to a small sample size. At the same time, interventions targeted at reducing anxiety or depression, such as mindfulness and yoga [14,15], cognitive-behavioral stress management [17], and self-regulation [18], showed different effects, even opposite results [14,15]. Hence, it is necessary to integrate results from different RCTs to verify the effects of interventions on inflammatory factors, anxiety, and depression.

A rigorous meta-analysis is necessary to address the lower statistical efficiency and inconsistent results in previous studies. However, to our knowledge, systematic reviews and meta-analyses on the effect of interventions on perceived stress in breast cancer patients are limited. Thus, this study adopts a meta-analysis method, aiming to confirm the impact of interventions on perceived stress, anxiety, depression, and inflammatory markers to identify effective interventions. This systematic review can enable practitioners to understand the current interventions for improving perceived stress, which interventions are effective or ineffective, and the limitations of current research, which can provide a reference for future new intervention research and clinical trials.

2. Methods

2.1. Protocol and registration

The protocol was enrolled in the international prospective register of systematic reviews (PROSPERO), and the register number was CRD42023402993. The review used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [25] and Cochrane Handbook [26] to guide the process.

2.2. Eligibility criteria

Studies were required to meet the following criteria:

(1) P (Population): BC patients with any treatment, such as chemotherapy, radiotherapy, hormonal therapies, or surgery, will be included.
(2) I (Intervention): any interventions to reduce stress.
(3) C (Control): routine care or other types of stress management intervention. (4) O (Outcome): the primary outcome was perceived stress, and the secondary outcomes were depression, anxiety, or inflammatory cytokines.
(5) S (Study Design): randomized controlled trials (RCTs).
(6) Studies retrieved from the English and Chinese databases.

2.3. Databases and search strategies

Two researchers (XTD and MYZ) independently searched databases following the eligibility criteria. The search terms included "stress," "perceived stress," "breast cancer," and "randomized controlled trial". We searched the Cochrane Library, PubMed, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Embase, Web of Science, China National Knowledge Infrastructure (CNKI), Chinese Biomedical literature database (CBM), China Science and Technology Journal Database (VIP), and Wanfang Data Knowledge Service Platform from inception until 26 February 2023. In addition, we also reviewed the bibliographies of relevant review papers for additional articles. This process was conducted iteratively until no new papers were identified. The search strategies are listed in Appendix A. The study used NoteExpress software for initial duplication and Rayyan QCRI (Qatar Computing Research Institute) for final duplication and screening. The selection process is illustrated in Fig. 1.

2.4. Quality appraisal

The Cochrane Risk of Bias 2 (RoB 2) was used to evaluate the risk of bias in the included trials. This assessment tool consists of five domains: the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Following the judgment criteria, each domain was carefully assessed as "high risk of bias," "some concern of bias," or "low risk of bias". Two evaluators (XTD and MYZ) independently evaluated the risk bias of each study and consulted the third evaluator (QW) for any discrepancies.

2.5. Data extraction

The review used a homemade data extraction table that contained authors, publication year, country, participants, sample size, mean age, interventions, delivery method, duration, interventionist, measures, and critical findings. Before extraction, pretests were used. The two researchers (XTD and SFW) extracted data independently and sorted it into Microsoft Excel. If there were discrepancies between the two researchers, they tracked the study back to the original study and discussed until an agreement was reached.

2.6. Data synthesis and analysis

The general information of all eligibility studies is shown in Table 1. For analysis, the data extracted from the included publications were input into Review Manager (RevMan) 5.4 software. Heterogeneity was assessed using the I^2 statistic. Values of 25 %, 50 %, and 75 % indicate low, moderate, and high heterogeneity, respectively. The random-effects model was used to analyze data with high heterogeneity.

In contrast, a fixed-effects model was used. For the effects of interventions on perceived stress and other negative emotions (e.g.,

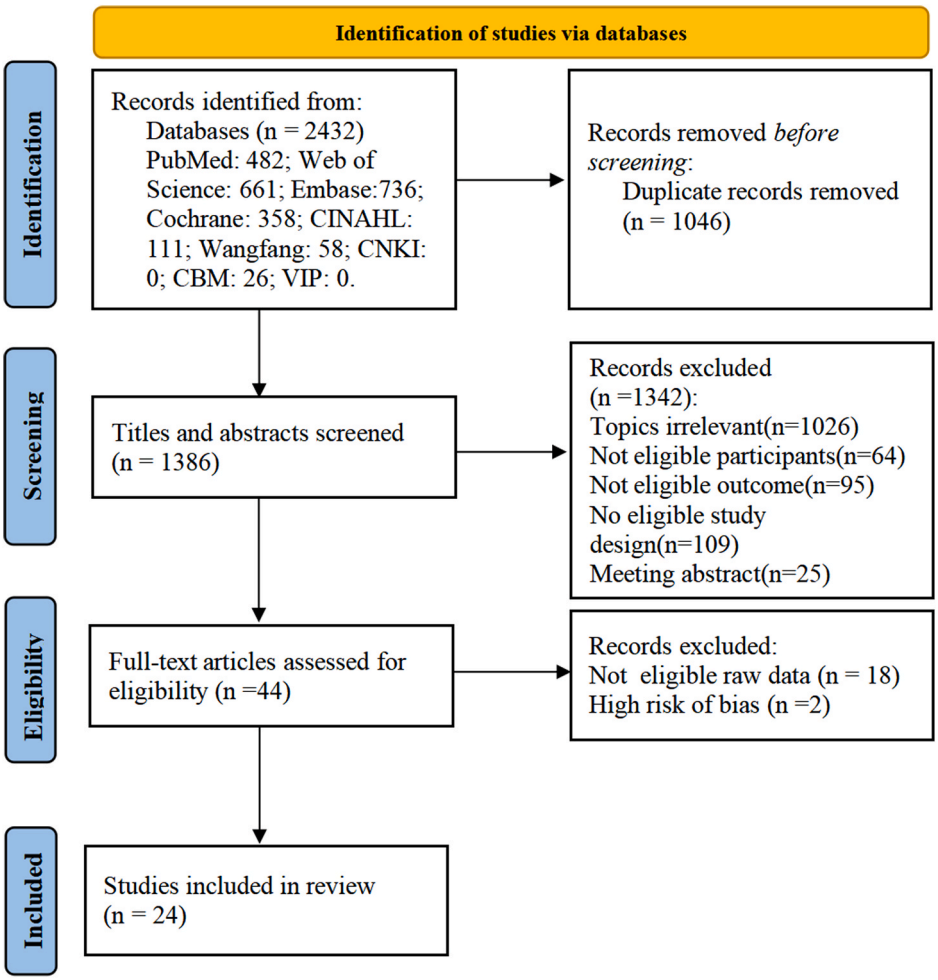

Fig. 1. PRISMA flow diagram of study selection.

depression, anxiety), the weighted mean difference (WMD) was calculated when outcomes were measured using the same scale or indicator. The standardized mean difference (SMD) was used when different scales or indicators were used among various trials, with a corresponding 95 % confidence interval (CI). Subgroup analysis was completed to explore the potential sources of heterogeneity. In stratified meta-analyses, the literature data were divided into subgroups according to the interventions (mindfulness and yoga, cognitive-behavioral stress management, self-regulation, exercise, relaxation training, and acupuncture). If the combined results showed high heterogeneity, each study's effect size and 95 % CI were measured and revealed a narrative description. A *P* value less than 0.05 implies statistical significance. A funnel plot was used to inspect the enrolled literature to detect publication bias.

3. Results

3.1. Search results

A total of 2432 potential publications were retrieved, and 1046 duplicates were deleted. After screening the titles and abstracts, 44 studies were selected, and 24 studies remained after 20 were disqualified for insufficient raw data and high risk of bias (Fig. 1). The sample size of the 24 RCTs ranged from 24 to 322, and the patients' ages were between 43.0 and 61.0 years. All 24 studies were published in English, and from the United States (n = 11), China (n = 4), India (n = 2), Ireland (n = 1), Singapore (n = 1), United Kingdom (n = 1), Germany (n = 1), South Korea (n = 1), Iran (n = 1), and Slovenia (n = 1). Breast cancer patients receive chemotherapy, surgery, radiotherapy, hormonal therapies, or other treatments.

3.2. Study characteristics

For interventions from the intervention group, the study summarized the interventions into six categories, including mindfulness and yoga [13–15,20,22,23,27–32] (n = 12), exercise [16,33–36] (n = 5), cognitive-behavioral stress management [17,37] (n = 2), self-regulation [18,21,38] (n = 3), relaxation training [39] (n = 1), and acupuncture [19] (n = 1). The control interventions were classified into four categories: supportive care [15,17–20,30–33,39] (n = 10), wait-list control (n = 7) [13,16,21,22,34,35,38], usual care [14,27,29,37] (n = 4), and active control [23,28,36] (n = 3).

The perceived stress scale (PSS) is the most frequently used measurement tool for perceived stress, and the 4-item PSS and Chinese version of the PSS were also used. Other validated measurement tools were used in the RCTs, including the Beck Anxiety Inventory (BAI), the Self-rating Anxiety Scale (SAS), the State-Trait Anxiety Inventory (STAI), the Patient- Reported Outcomes Measurement Information System (PROMIS)-Anxiety, PROMIS-Depression, the Beck Depression Inventory (BDI), the Center for Epidemiological Studies Depression Scale (CES-D), and the Hospital Anxiety and Depression Scale (HADS). In addition, four studies also measured inflammatory cytokines, including C-reactive protein (CRP) [14], interleukin-6 (IL-6) [28], tumor necrosis factor-α (TNF-α) [28], cortisol [14,31], total leukocyte count, neutrophil count, and lymphocyte count [33] to reflect the effect of interventions from another perspective. Table 1 lists the characteristics

Table 1
Characteristics of the included randomized controlled trials.

Author, year, country	Participants	Sample Size (I/C)	Mean Age, y	Interventions		Measures	Critical findings
				Intervention Group (IG)	Control Group (CG)		
Groarke A, 2013, Ireland [37]	Breast cancer with surgery, the majority received adjuvant therapy	87/92	IG: 53.30 ± 9.86 CG: 54.10 ± 10.62	CBSM 5 weeks 3 h, per week groups of 8–12 a clinical psychologist	Usual care oncology nurses	PSS HADS	The CBSM can reduce global stress and anxiety compared to CG, but not maintained at 12 months.
Henneghan AM, 2020, United States [23]	Breast cancer with chemotherapy, or received hormonal therapies, anti-human epithelial receptor 2 therapy	16/15	ML: 48.93 ± 10.69 KK: 50.00 ± 9.52	KK delivered remotely consumer-based audio platform 12 min a day, every day, 8 weeks a host	ML four audio files containing 12-min clips of classical music 12 min a day, every day, 8 weeks a host	PSS PROMIS-Anxiety PROMIS-Depression	The ML group reported lower stress after intervention.
Birendranath Banerjee, 2007, Singapore [32]	Breast cancer with radiotherapy, and some received chemotherapy	35/23	Yoga: 47.00 ± 1.10 -CG: 43.00 ± 1.50	Yoga 6 weeks each session, 90 min a group of expert yoga trainers	Supportive counseling group 6 weeks	PSS HADS DNA damage	PSS was decreased in the yoga group, while CG did not show any change pre- and post- radiotherapy.
Zhang JY, 2022, China [35]	Stage I–III breast cancer	29/29	MTCC: 47.79 ± 5.14 CG: 47.20 ± 7.65	MTCC 8-week, twice a week, 1 h per day clinical nurses who has the psychological consultant qualification	Wait-list control group	PSS SAS	MTCC reduces the level of stress and anxiety.
Zhang JY, 2016, China [27]	Stages I–III breast cancer, within 2–6 months after surgery	30/30	MBSR: 48.67 ± 8.49 CG: 46.00 ± 5.12	MBSR 8 weeks weekly 2 h sessions a psychologist who was certified and qualified in mindfulness skills	Usual care	CPSS STAI	MBSR can decrease perceived stress and anxiety, and the results persisted at three months after intervention.
Saxton JM, 2014, United Kingdom [33]	Overweight stage I-III breast cancer, who had completed treatment	44/41	IG: 55.80 ± 10.00 CG: 55.30 ± 8.80	Lifestyle intervention 24 weeks three supervised exercise session each week an individually tailored hypocaloric healthy eating programme	a healthy eating booklet three exercise sessions	PSS BDI Total leukocyte count Neutrophil count Lymphocyte count	The IG exhibited a reduction in depressive symptoms at the 6-month follow-up but no significant decrease in perceived stress.Compared to IG, the CG had higher total leukocyte, neutrophil and lymphocyte counts at the 6-month follow-up.
Witek Janusek L, 2019, United states [28]	Early stage breast cancer	84/80	MBSR: 55.00 ± 10.10 ACC: 55.20 ± 10.10	MBSR 8 weeks 2.5 h weekly 6 h silent mindful retreat after the fifth week a licensed clinical psychologist	ACC 8 weeks 2.5 h weekly four content experts (oncology clinicians) and two breast cancer survivors	PSS CES-D Inflammatory cytokines (IL-6, TNF-α)	Compared to the ACC group, MBSR lowers stress, depression, TNF-α levels, and IL-6 in women with breast cancer.
Höxtermann MD, 2021, Germany [19]	Stage I-III breast cancer with insomnia	26/26	Auricular Acupuncture: 56.58 ± 7.90 Psycho-education: 54.80 ± 8.30	Auricular Acupuncture 5 weeks twice weekly two licensed acupuncturists	Psychoeducation a single 90-min psychoeducation group session an experienced psychologist	PSS IL-6 HADS	Compared to the psychoeducation group, the auricular acupuncture group can improve stress and anxiety at week 5. No significant differences were found in any other results from week 5, or in any results from weeks 17 or 29.
Yun MR, 2017, South Korea [30]	Stage I-III breast cancer, who had completed treatment	26/26	MSM: 49.04 ± 8.70 SME: 47.85 ± 7.71	MSM 8 weeks twice a week, 2 h per session 1 main and 3 assistant instructors certified in MSM	SME education sessions once per week for 2 h each session over 4 weeks a lecture format	PSS CES-D BAI	Compared with the SME group, the MSM group reported a significant decrease in depression, anxiety, perceived stress.
Mirmahmoodi M, 2020, Iran [14]	Breast cancer without metastasis, received at least 1 chemotherapy period or surgery, and no use of corticosteroids, psychoactive and hormonal drugs	22/22	MBSR: 44.14 ± 11.19 CG: 45.64 ± 10.11	MBSR 8 weeks 90-min sessions one researcher skillful in MBSR	Usual care	PSS BAI BDI-II Cortisol CRP	Compared with CG, MBSR can lower anxiety, but no significant difference in reducing perceived stress, depression, and levels of CRP and cortisol.

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Table 1 (*continued*)

Author, year, country	Participants	Sample Size (I/C)	Mean Age, y	Interventions		Measures	Critical findings
				Intervention Group (IG)	Control Group (CG)		
Lu Q, 2023, United States [18]	Chinese American breast cancer who had completed treatment within the past 5 years	CF: 36 ESR: 54	57.80 ± 9.20	ESR 3 weeks once time, weekly	CF	PSS CES-D BSI	Compared with the CF, the ESR reduced depressive and anxiety symptoms at all follow-up time points (1, 3, and 6-months) through reductions in perceived stress.
Ho RT1, 2016, China [15]	Stages I-III breast cancer who had completed active treatment	BMS: 51 CG:57	47.70 ± 7.00	BMS 8 weeks 2 h weekly sessions two experienced social workers, who had received standard training in BMS treatment	Social support 8 weeks 2 h weekly sessions a social worker and a group member	PSS HADS	Compared to CG, BMS can reduce perceived stress, but could not improve anxiety and depression.
Ho RT2, 2016, China [34]	Breast Cancer with radiotherapy	69/70	48.90 ± 8.20	DMT 3 weeks six1.5-h DMT sessions, twice a week a qualified dance movement therapist	Wait-list control group	PSS HADS	DMT showed significant effects on hinder the deterioration in perceived stress, but no difference in anxiety, depression.
Reich RR, 2017, United States [29]	Stage 0-III breast cancer	167/155	56.60	MBSR 6 weeks 2 h per week sessions a psychologist trained in MBSR	Usual care	PSS CES-D STAI	MBSR can improve psychological (anxiety, depression, perceived stress).
Dodds SE, 2015, United States [22]	Breast Cancer with adjuvant chemotherapy	12/16	CBCT: 54.70 ± 12.10 CG: 55.80 ± 9.70	CBCT 8 weeks 2 h classes weekly a clinically trained Ph.D. social work researcher and experienced 20-year meditator fulfilling requirements for CBCT teacher certification of the Emory University-Tibet Science Initiative	Wait-list control group	PSS CES-D Salivary cortisol	Compared to CG, the CBCT can improve the patients depression in post-intervention and reduce the level of perceived stress in follow-up.
Lechner SC, 2014, United States [17]	Breast cancer	57/57	CBSM: 50.16 ± 7.89 CG: 52.07 ± 9.93	CBSM 10 weeks a licensed clinical psychologist	Wellness and Education Condition 10 weeks 90-min sessions a graduate level black female interventionist	PSS CES-D	Participants in both groups showed improvement on depressive symptoms and stress levels over the 6-month post-intervention follow-up.
Taylor TR, 2018, United States [13]	African-American breast cancer, who received surgery and treatment (excluding hormone therapy) at least 12 months	18/15	Yoga: 54.90 ± 8.80 CG: 52.60 ± 8.20	Yoga 8 weeks 75 min per session, 1 day per week a certified yoga instructor at Howard University	Wait-list control group	PSS CES-D	Compared to CG, yoga can reduce depression, but no significant group differences in perceived stress.
Kovačič T, 2011, Slovenia [39]	Stages I-II breast cancer after surgery	16/16	Not reported.	a standard physiotherapy plus relaxation training according to the YIDL system 1-week standard physiotherapy program plus 1 h group relaxation session per day the physiotherapists	a standard physiotherapy	PSS	The relaxation training according to yoga in Daily Life ® system could be useful clinical physiotherapy intervention for breast cancer patients.
Gao Z, 2022, United States [16]	Breast cancer had undergo treatment at least 3 months ago	20/15	IG: 56.85 ± 9.79 CG: 55.27 ± 11.47	Tai Chi intervention condition using an app to practice Tai Chi 12 weeks three times a day, at least five days/week	Wait-list control group	PSS	No significant time × group interaction effects emerged for stress.
Knoerl R, 2022, United States [36]	Stages I-III breast cancer, who plan to receive surgery	21/26	Exercise: 52.30 ± 9.60 Mind-body: 53.40 ± 8.00	an exercise prehabilitation intervention 40 min strength training and 180 min aerobic exercise each week a certified trainer	a mind–body prehabilitation intervention	PSS HADS	There were no significant differences between groups.

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Table 1 (*continued*)

Author, year, country	Participants	Sample Size (I/C)	Mean Age, y	Interventions		Measures	Critical findings
				Intervention Group (IG)	Control Group (CG)		
Vadiraja HS, 2017, India [20]	Metastatic breast cancer	33/31	50.54 ± 8.53	integrated yoga program 3 months an instructor	supportive therapy and education 3 months	PSS	Compared to supportive therapy, yoga reduces perceived stress.
Vadiraja HS, 2009, India [31]	Breast cancer with adjuvant radiotherapy	44/44	Yoga: 46.00 ± 9.13 CG: 48.45 ± 10.21	Yoga 6 weeks 1 h, per week a trained yoga therapist	Brief supportive therapy with education 6 weeks	PSS HADS Diurnal Salivary Cortisol	Compared to CG, yoga can reduce depression, perceived stress, anxiety, 6 a.m. salivary cortisol.
Loprinzi CE, 2011, United States [21]	Breast cancer	12/12	SMART: 61.00 ± 6.00 CG: 61.00 ± 7.25	SMART 90-min sessions in the SMART program and 3 follow-up telephone calls 12 weeks study investigators	Wait-list control group	PSS SAS	Compared with baseline, a statistically significant improvement in perceived stress, anxiety at 12 weeks in SMART.
Winzelberg AJ, 2003, United States [38]	Breast cancer	36/36	49.50 ± 6.20	Bosom Buddies structured, web-based support group one topic per week 12 weeks a mental health professional	Wait-list control group	PSS STAI CES-D	TheIG group can reduce depression and perceived stress in breast cancer.

Note: ACC: Active control condition; BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory; BSI: Brief Symptom Inventory; BMS: Body-Mind-Spirit; CF: Cancer-Facts; CBCT: Cognitively Based Compassion Training; CBSM: Cognitive-Behavioral Stress Management; CES-D: Center for Epidemiological Studies Depression Scale; CG: Control Group; CPSS: Perceived Stress Scale of Chinese version; CRP: C-reactive protein; DMT: Dance Movement Therapy; ESR: Enhanced Self-Regulation; HADS: Hospital Anxiety and Depression Scale; IG: Intervention Group; IL-6: Interleukin-6; KK: Kirtan Kriya meditation; MBSR: Mindfulness-based stress reduction; ML: Music listening; MTCC: Mindfulness-based Tai Chi Chuan program; MSM: Mind subtraction meditation; PSS: Perceived Stress Scale; PROMIS: Patient-Reported Outcomes Measurement Information System; SAS: Self-rating Anxiety Scale; STAI: State-Trait Anxiety Inventory; SMART: Stress Management and Resiliency Training; SME: Self-management education.

of the eligible studies.

3.3. Risk of bias

The study applied RoB 2.0 for the risk of bias assessment of the 24 RCTs. Since the current study focused on the effect of interventions on perceived stress, depression, anxiety, and biomarkers in breast cancer patients, we selected intervention assignment ("intention-to-treat" treatment) rather than adhering to intervention ("pre-protocol" effect). The assessment results for the risk of bias are shown in Figs. 2 and 3. Two RCTs only described randomization but did not clarify the methodology. Four of the RCTs did not provide hidden allocation methods. Seven of the 24 RCTs had a low risk of bias, and seventeen had a moderate risk. Appendix B displays the details of the risk of bias for enrolled studies.

3.4. Results of the meta-analysis

This study analyzed the effect of interventions on breast cancer patients' perceived stress, depression, anxiety, and inflammatory factor levels.

3.4.1. Perceived stress

Twenty-four trials yielded pertinent data on perceived stress scores, with an estimated effect of 7.11, a sample capacity of 1887, and high heterogeneity ($P < 0.00001$; $I^2 = 77$ %). This study conducted a subgroup analysis based on different interventions. The results showed that compared to the control group, mindfulness and yoga [13–15,20,22,23,27–32], self-regulation [18,21,38], and exercise [16,33–36] could significantly reduce the perceived stress level (SMD, −0.29∼-0.41; $P < 0.05$). In contrast, the CBSM group [17,37] did not have a significantly lower perceived stress level than the control group ($P = 0.31$). In addition, only one study [39] examined the effect of relaxation training on perceived stress. The results showed that the 95%CI was −3.49 (-4.63, −2.34), with a significant difference in the perceived stress level between the two groups ($P < 0.00001$). Another study [19] explored the effect of acupuncture on perceived stress and showed that the 95%CI was −0.28 (-0.82, 0.27), with no significance between the two groups ($P = 0.32$) (Fig. 4).

Two trials [17,37] yielded pertinent data on perceived stress scores, with an estimated effect of 0.43, a sample capacity of 287, and low heterogeneity ($P = 0.67$; $I^2 = 0$ %). As shown in Fig. 5, perceived stress

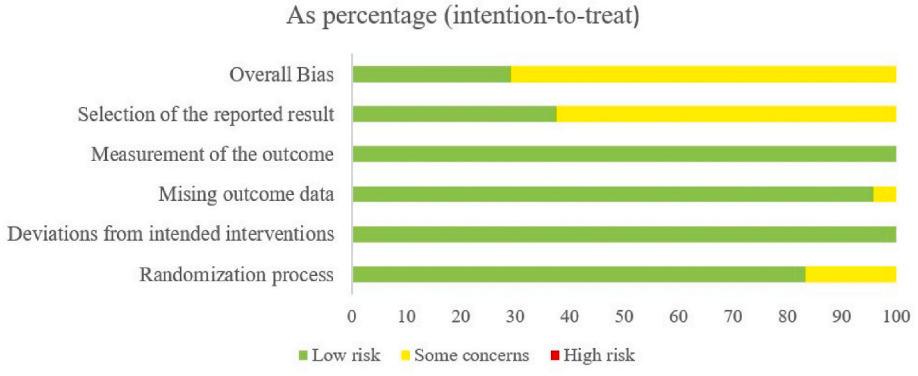

Fig. 2. Cochrane risk of bias in the included studies.

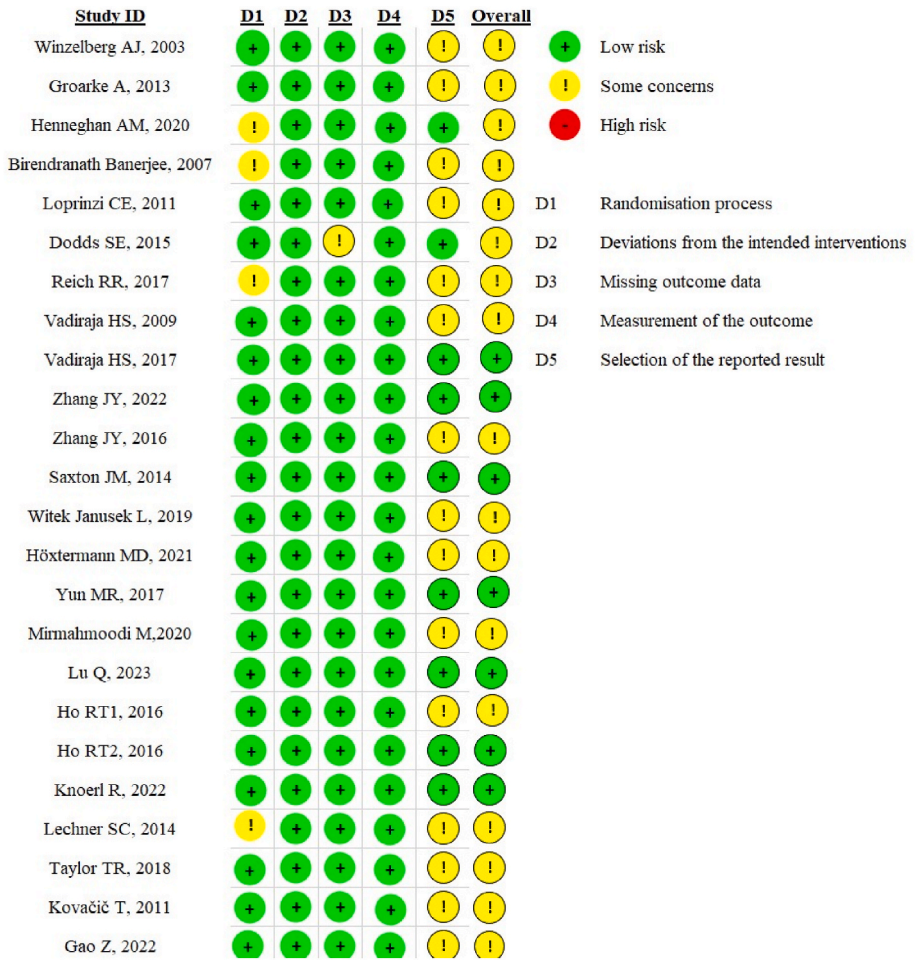

Fig. 3. Details of each dimension of the Cochrane risk of bias tool.

was not significantly reduced in the intervention group compared with the control group during the follow-up (SMD, 0.05; 95 % CI, - 0.18 to 0.28).

As revealed in Figs. 6 and 7, the integrated results of three eligible [15,22,28] studies showed that mindfulness could significantly reduce perceived stress one month after intervention (SMD, −0.39; 95 % CI, −0.71 to −0.07) and six months or more after intervention (MD, −1.98; 95 % CI, −3.44 to −0.52) with low heterogeneity ($P = 0.71$; $I^2 = 0$ %).

3.4.2. Anxiety

As shown in Fig. 8, sixteen trials investigated the impact of interventions on anxiety, with an estimated effect of 5.08, a sample capacity of 1384, and high heterogeneity ($P < 0.00001$; $I^2 = 84.0$ %). Subgroup analysis demonstrated that mindfulness and yoga [14,15,23,27,29–32] could reduce anxiety compared to the control group, with a 95%CI of −0.37 (-0.52~-0.22; $P < 0.00001$). In contrast, CBSM [37], self-regulation [18,21,38], exercise [34–36], and acupuncture [19] did not significantly lower anxiety levels compared with the control group ($P = 0.11$–0.55).

3.4.3. Depression

From Fig. 9, eighteen RCTs explored the interventions on depression, with an estimated effect of 4.58, a sample capacity of 1541, and high heterogeneity ($P < 0.00001$; $I^2 = 84$ %). From the subgroup analysis, compared to the control group, mindfulness and yoga [13–15,22,23,28–31], self-regulation [21,38], and acupuncture [19] reduced the level of depression (SMD, −0.58~-0.27; $P < 0.05$). However, CBSM [17,37] and exercise [33,34,36] did not lower depression levels compared with the control group ($P = 0.12$–0.48).

3.4.4. Inflammatory factors

Only one study [31] examined the effect of yoga on salivary cortisol. The results demonstrated that the estimated effect (95 % CI) was −0.68 (-1.22, −0.14), with a significant difference in the salivary cortisol level between the two groups ($P = 0.01$). Another study [14] explored the MBSR effect on blood cortisol and CRP, which showed that the 95 % CI was 0.38 (-0.22, 0.97) and 0.48 (-0.12, 1.08), respectively, with no significance between the two groups ($P = 0.12$–0.21). One RCT [28] explored the effect of MBSR on the levels of TNF-α and IL-6, and the results indicated that compared to the control group, MBSR could improve the TNF-α level with a 95 % CI of −0.36 (-0.70, −0.03) ($P = 0.03$) but could not reduce the level of IL-6 with a 95 % CI of −0.25 (-0.59, 0.08) ($P = 0.14$). Similarly, acupuncture [19] did not improve the level of IL-6, with a 95 % CI of 0.45 (-0.10, 1.00) ($P = 0.11$).

In addition, one study [32] clarified that the effect of yoga could reduce the level of DNA damage, with a 95 % CI of −3.08 (-3.87, −2.30) ($P < 0.00001$). Another RCT [33] explored the effect of exercise could not improve the level of total leukocyte count, neutrophil count, and lymphocyte count ($P = 0.10$–0.35), with 95%CI was −0.32 (-0.76, 0.12), −0.38 (-0.82, 0.07), and −0.21 (-0.65, 0.23), respectively.

3.5. Publication bias

As shown in Fig. 10, the funnel plot was symmetrical, indicating no publication bias in any of the 24 studies.

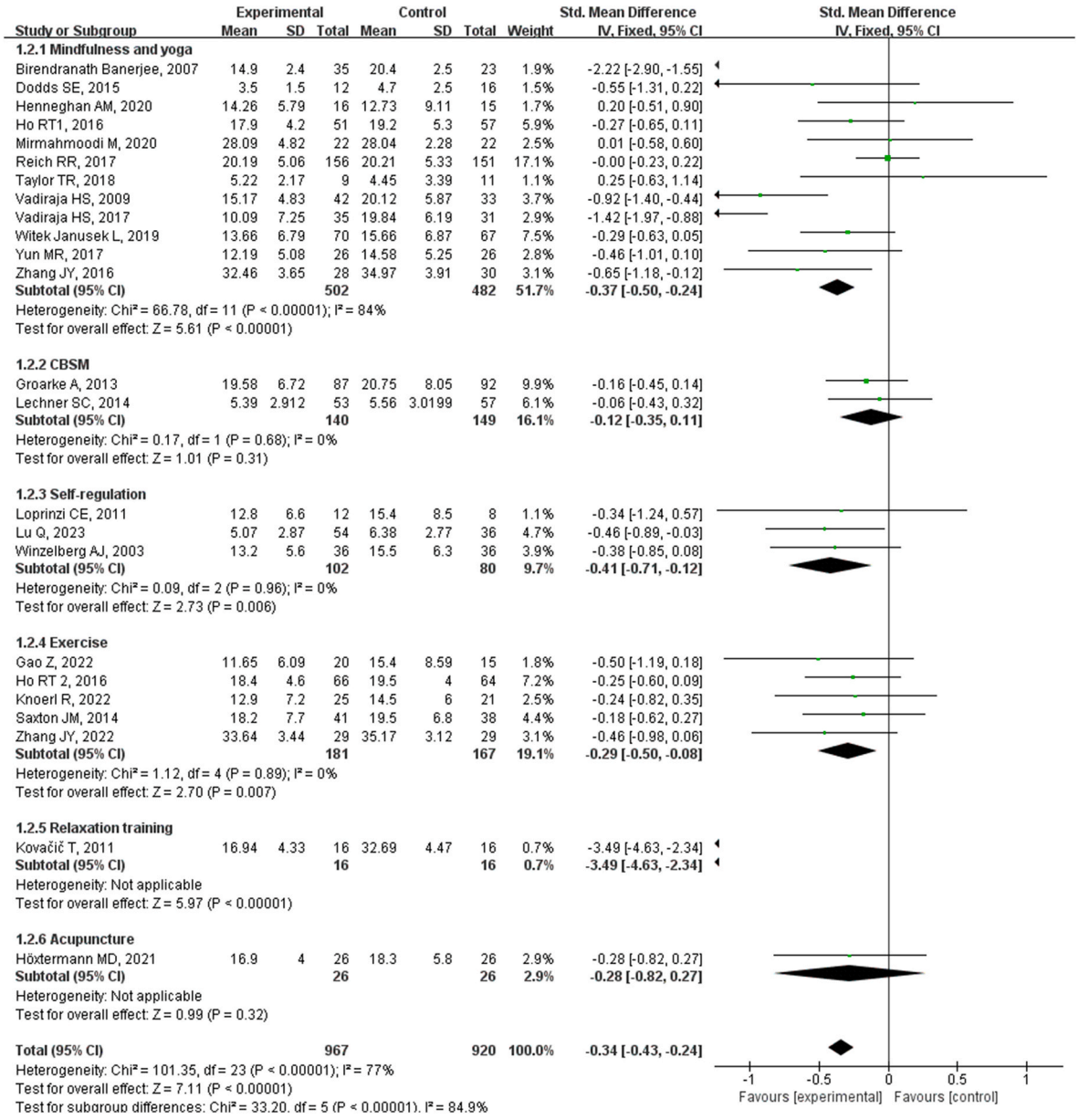

Fig. 4. Forest plot of different interventions on perceived stress.

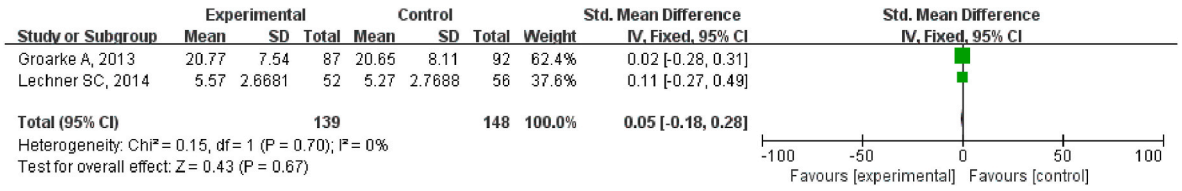

Fig. 5. Forest plot of CBSM on perceived stress during the follow-up.

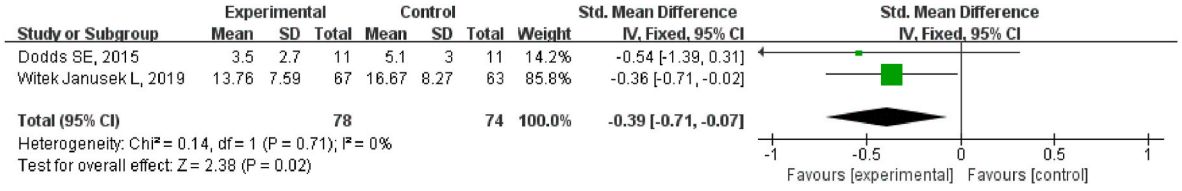

Fig. 6. Forest plot of mindfulness on perceived stress 1 month after intervention.

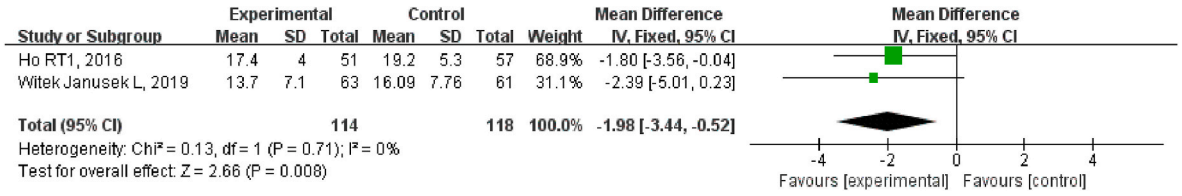

Fig. 7. Forest plot of mindfulness on perceived stress 6 months or more after intervention.

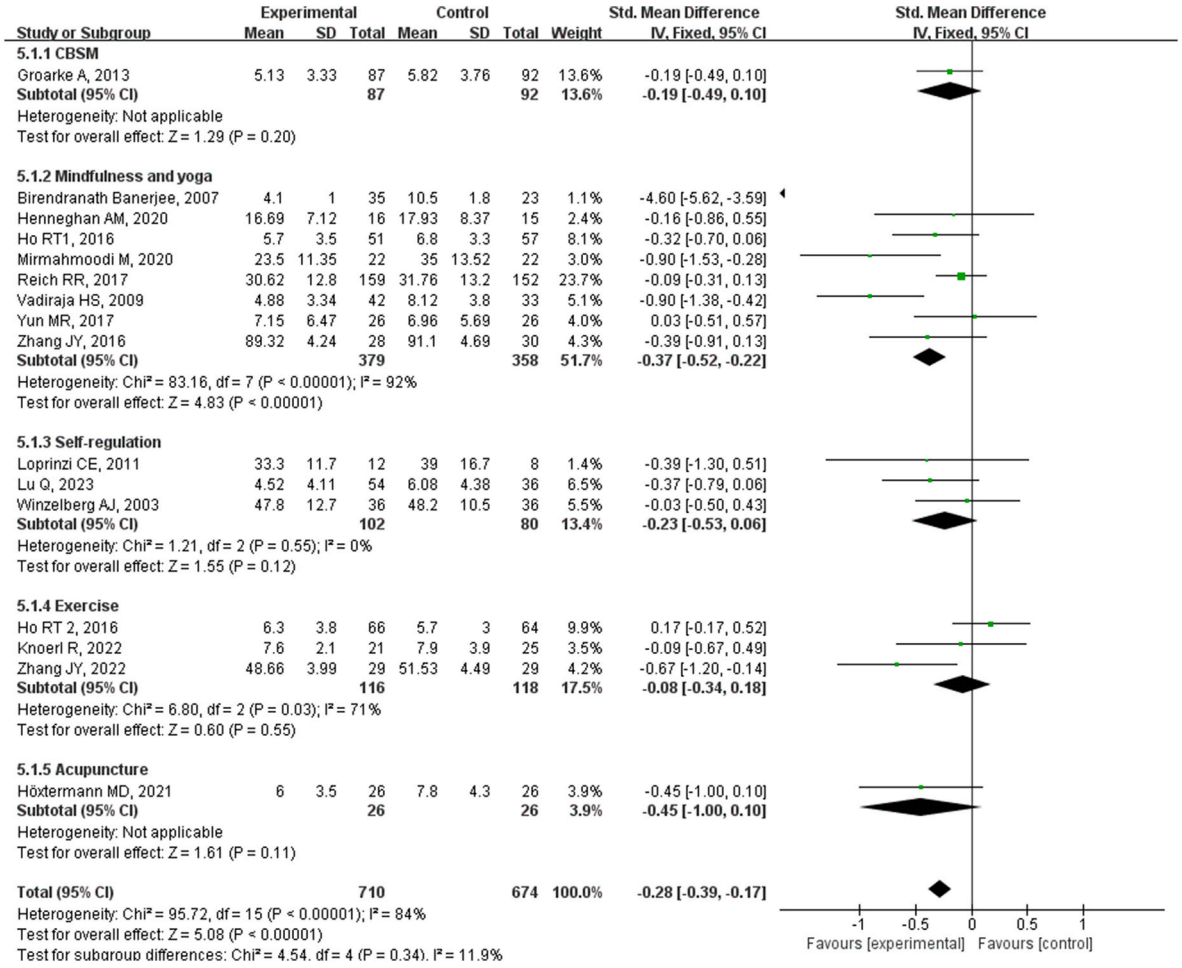

Fig. 8. Forest plot of different interventions on anxiety.

4. Discussion

The meta-analysis validated the efficacy of various interventions on breast cancer patients' perceived stress, anxiety, depression, and inflammatory factors. All eligible RCTs assessed perceived stress, most included studies assessed anxiety and depression, and only a few evaluated the patients' inflammatory factors. Seventeen RCTs could be considered moderate quality based on RoB 2.0, and seven were rated high quality.

This meta-analysis discovered that mindfulness and yoga could reduce perceived stress, anxiety, and depression in breast cancer patients. Self-regulation could reduce perceived stress and depression but cannot alleviate anxiety. Acupuncture could reduce depression but not significantly change perceived stress and anxiety. Nevertheless, it was not found that CBSM could lower the levels of perceived stress, anxiety, and depression. Only one RCT verified that MBSR could improve the TNF-α levels, and another RCT showed that yoga could reduce DNA damage and salivary cortisol. However, those stress relief interventions could not improve blood cortisol, CRP, IL-6, total leukocyte count, neutrophil count, or lymphocyte count.

Interventions, including mindfulness and yoga, self-regulation, and exercise, were suitable for breast cancer patients and can be practiced without being limited by location or time at lower costs. Moreover, most eligibility researchers applied group intervention face-to-face due to its feasibility and cost-effectiveness, and another reason was peer support, which can play a supervisory and motivating role among breast cancer patients. Hu et al. [40] supported this viewpoint. In addition, most intervention durations lasted eight weeks. Furthermore, most interventionists were qualified and experienced professionals. As described above, the various interventions, formats, durations, and guidelines can provide clues for future studies.

Stress affects breast cancer patients' physical and psychological health [9,10]. Reducing patients' perceived stress is crucial. This review integrates 24 RCTs regarding reducing breast cancer patients' perceived stress to provide evidence and references for future research. Mindfulness and yoga significantly reduced adverse psychological outcomes,

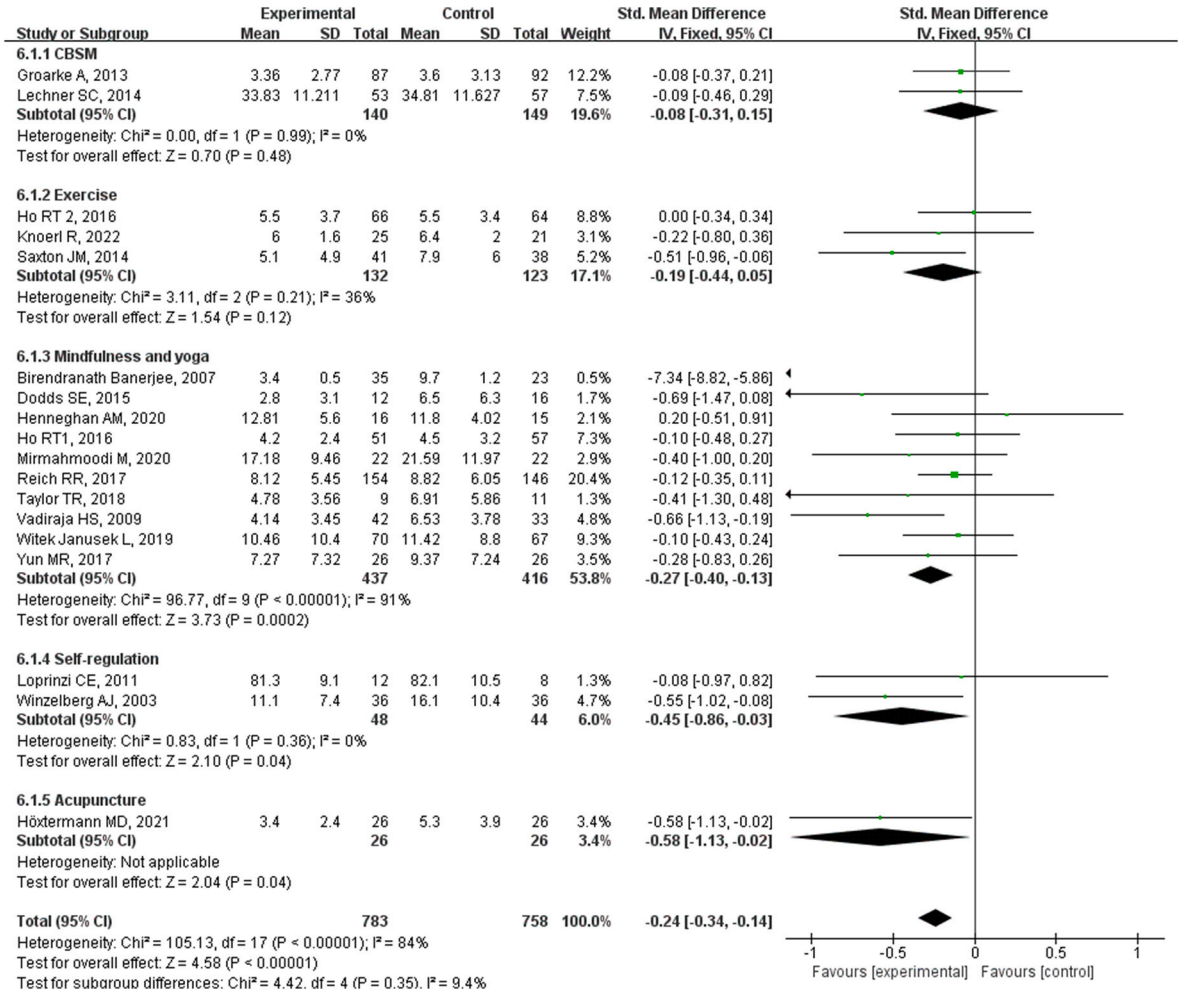

Fig. 9. Forest plot of different interventions on depression.

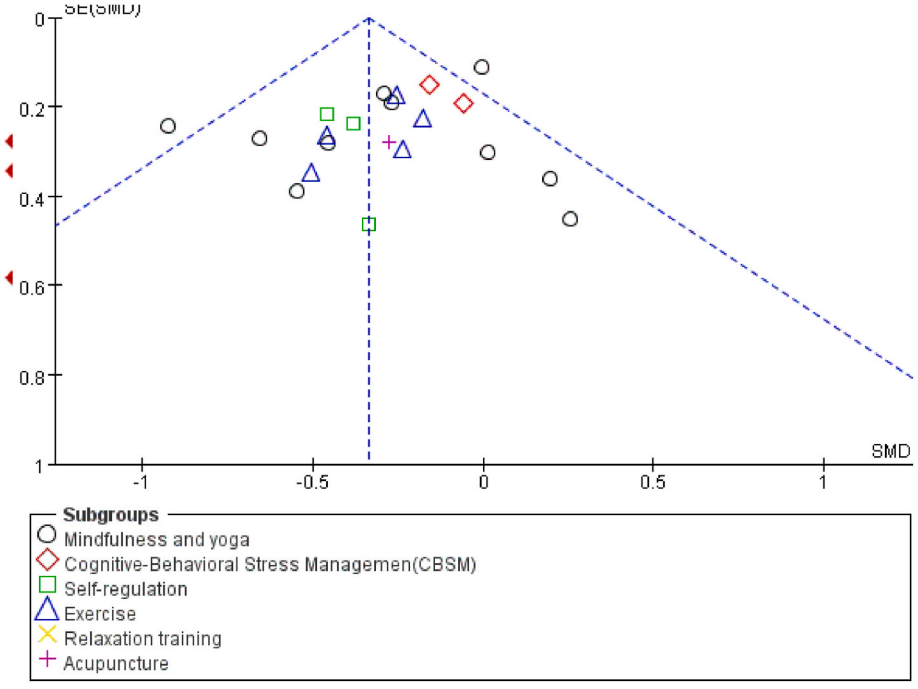

Fig. 10. Funnel plot of all included studies.

consistent with previous studies [41]. MBSR, meditation, and yoga are complementary therapies, and as their concepts, connotations, and methods overlap, this study categorizes these three types of methods as mindfulness and yoga. Mindfulness and yoga, including asanas, meditation, breathing exercises, awareness, and body scans, can help breast cancer patients regulate their meta-cognitive ability, eliminate emotional disturbance by changing their cognition deviation, and transfer their negative emotions to an inner peaceful mood state [27,42]. In addition, these interventions can develop cancer patients' gratitude and equanimity [27], stimulating their post-traumatic growth and resilience.

Additionally, two studies [22,28] verified that mindfulness could reduce breast cancer patients' perceived stress one month after the intervention, while another two RCTs [15,28] indicated that mindfulness could lower patients' perceived stress six months or more after the intervention. Only one RCT [28] found that mindfulness could improve TNF-α levels, and another two studies confirmed that yoga could reduce the levels of salivary cortisol [31] and DNA damage [32]. The evidence implied that mindfulness has particular benefits in relieving short-term and long-term perceived stress in patients with breast cancer. Yoga can alleviate patients' perceived stress in the short term, but the long-term effect and objective effects are unknown. More rigorous RCTs with larger samples should be conducted to address these limitations.

In our review, attention and interpretation therapy [21], supportive-expressive [38], and expressive writing [18] were sorted as the types of self-regulation because these interventions mainly focus on internal adjustment through interpretation and expression. The evidence demonstrated that self-regulation significantly decreased perceived stress and depression. The possible reason was that these interventions could promote patients' suppressive emotional expression, evoking their reflection on cancer and treatment and rethinking the meaning of life, which further reduces the negative emotions of breast cancer patients. However, only a few studies with small sample sizes confirmed the effect on negative emotions. High-quality studies with larger sample sizes are still needed.

Five studies [16,33–36] reported that exercise resulted in a significant decrease in perceived stress, possibly because exercise can divert breast cancer patient's attention from the fear of recurrence and morbidity, reduce negative intrusive thinking, increase self-efficacy for overcoming disease and cancer-related stress, and enhance cognitive evaluation ability. Moreover, exercise can attenuate the reaction to stress by activating the HPA axis and releasing endorphins, reducing patients' stress levels [43]. The evidence clarifies that exercise could effectively lower perceived stress levels in breast cancer patients. However, a large sample of multi-center research is needed to verify the long-term effect. Regarding acupuncture, only one study [19] with 52 breast cancer patients showed that acupuncture could reduce the level of depression, and only one study [39] examining the effect of relaxation training could lower perceived stress, which limited clinical efficacy and still needs further validation through rigors large-scale studies.

According to RoB 2.0, seven studies were rated as low-risk bias, and the remaining studies could be considered moderate risk bias, indicating that the study design was of high quality. However, there were also some deficiencies, such as two RCTs needing more detailed randomization methods and four not considering concealment. Notably, only eight RCT participants received all outcome data, and most were aware of their assigned intervention during the trial due to the psychological interventions being hard to blind. Therefore, future studies should consider these aspects when designing similar RCTs to provide strong evidence for clinical practice.

This review has implications for future studies and clinical practice. First, the study systematically and comprehensively searched nine Chinese and English databases, with 24 studies finally included. The substantial sample size and rigorous literature screening and evaluation methods make our review advantageous and persuasive. Second, the study identified different interventions to improve perceived stress, depression, and anxiety, which can provide a reference basis for clinical practice. In addition, our study focuses on breast cancer patients' perceived stress other than stress, which can provide a new perspective for alleviating patients' stress by centering on an individual's cognitive appraisal, which is perceived stress. Finally, future stress research should focus on how interventions change perceived stress, namely, why interventions can improve perceived stress and why some interventions do not. In addition, future studies should carefully design the trials, comprehensively consider randomization and blinding, and analyze the reasons for the data lost to follow-up.

However, our study also had some limitations. First, interventions aimed at reducing perceived stress were challenging using blind methods for patients, which may influence the validity of the results. Second, most studies focused on the effectiveness indicators of the intervention without paying attention to the implementation outcomes, such as interventions' fidelity, sustainability, and adaptation. Finally, only a few studies focus on the changes in perceived stress and negative emotions during the intervention process, limiting the exploration of interventions' effects at different stages.

5. Conclusion

Breast cancer patients' perceived stress deserves attention since it is common and can impact their physical and psychological health. Mindfulness and yoga could reduce patients' perceived stress, depression, and anxiety; self-regulation could reduce perceived stress and depression; and exercise and relaxation training are also effective interventions for reducing perceived stress. In addition, mindfulness improved TNF-α levels, and yoga reduced salivary cortisol and DNA damage. For breast cancer patients, mindfulness and yoga are the most highly efficient interventions to address negative emotions, which are easy to learn and cost-effective. Health clinicians can select a suitable intervention based on evidence, the clinical situation, and patients' willingness. More rigorous RCTs with large sample sizes are needed to address the limitations of small sample sizes and shortcomings in methodology. Also, it is necessary to conduct network meta-analysis. Future research can identify the most effective intervention through a network meta-analysis of perceived stress in breast cancer patients.

Data availability

All data are available in the manuscript and tables.

Authors' contributions

XTD contributed to the conception and design, searched, screened, evaluated the literature, extracted data, and wrote and edited the original manuscript. FZ made substantial contributions to the conception and design, reviewed and revised manuscript. MYZ contributed conception, searched, screened, evaluated the literature, and reviewed the draft. QW contributed conception and revised the manuscript. SFW extraction data and revised original manuscript. JJX reviewed and revised the manuscript. ZL contributed substantially to the conception, design, review, and editing manuscript.

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Availability of data and materials

The data of original data was available in the manuscript and tables.

Ethical approval

Not applicable.

Declaration of competing interest

The authors did not declare any conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctcp.2023.101803.

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