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Somatic acupressure for the management of the fatigue–sleep disturbance–depression symptom cluster in breast cancer survivors: a study protocol for a phase III randomised controlled trial

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ABSTRACT

Introduction The fatigue–sleep disturbance–depression symptom cluster (FSDSC) is commonly experienced by breast cancer (BC) survivors, leading to a deteriorated quality of life (QoL). Somatic acupressure (SA) has been recommended as a promising non-pharmacological intervention for cancer-related fatigue (the core symptom of the FSDSC) in the guidelines, showing its encouraging role in relieving cancer-related sleep disorders, fatigue and depression. This phase III randomised controlled trial (RCT) is designed to evaluate the effects, safety and cost-effectiveness of SA for managing the FSDSC in BC survivors.

Methods This phase III RCT will be a partial-blinded, sham-controlled, three-arm, parallel clinical trial, involving a 7-week SA intervention period and a 12-week follow-up period. 108 BC survivors will be randomly allocated in a ratio of 1:1:1 to either a true SA group (self-administered acupressure plus usual care), a sham SA group (self-administered light acupressure at non-acupoints plus usual care) or a usual care group. The primary outcomes will be the effectiveness of SA on the FSDSC at both the individual symptom level and cluster symptom level. Each individual symptom will be specifically measured by the Brief Fatigue Inventory (fatigue), the Pittsburgh Sleep Quality Index (sleep disturbance) and the Hospital Anxiety and Depression Scale-Depression (depression). The cluster symptom level will be measured by using an FSDSC composite score, an averaging score of three separated 0–10 numeric rating scales for fatigue, depression and sleep disturbance. The secondary outcomes will include QoL (measured by the Functional Assessment of Cancer Therapy-Breast), adverse events and cost-effectiveness. Outcomes will be assessed at baseline (week 0), immediately after intervention (week 7) and follow-up (week 19). All outcomes will be analysed based on the intention-to-treat principle using the Statistical Package for Social Science (SPSS 25) software.

Ethics and dissemination Ethical approvals of this study have been granted by the Human Research Ethics Committee at Charles Darwin University (H22110) and the Clinical Trial Ethics Committee at the Affiliated Hospital of Zunyi Medical University (KLL-2023-594), and the Second Affiliated Hospital of Zunyi Medical University (KYLL-2023-058). Findings from this trial will be published in peer-reviewed journals and presented at professional conferences.

Trial registration number NCT06412107.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study is the first phase III randomised controlled trial (RCT) to determine the effects, safety and cost-effectiveness of an evidence-based acupressure intervention on the fatigue–sleep disturbance–depression symptom cluster among breast cancer survivors.
⇒ The somatic acupressure (SA) intervention in this trial was developed from robust theories and a comprehensive research evidence base, incorporating evidence from clinical practice guidelines, practice standards, systematic reviews, clinical study results, content validation and the phase II RCT findings with qualitative insights.
⇒ A sham control was used to distinguish the specific treatment effects of SA from its non-specific (placebo) effects and identify the size of the non-therapeutic effects of SA.
⇒ This study is unable to achieve a double-blind design due to the visible nature of the acupressure intervention.

INTRODUCTION

Fatigue, sleep disturbance and depression often co-occur as a cluster in breast cancer (BC) survivors throughout the disease trajectory, significantly known as the fatigue–sleep disturbance–depression symptom cluster (FSDSC).[1 2] The occurrence of the FSDSC is likely linked to an inflammatory and/or neuroendocrine response related to cancer or its treatment.[3] Foundational research reveals that proinflammatory cytokines can induce animal behaviour of fatigue, sleep

disturbance and depression.[4 5] This aligns with clinical studies indicating that proinflammatory cytokines trigger the same symptoms.[5] Furthermore, disrupted brain connectivity and altered neurochemistry, such as increased excitatory neurotransmitters, have emerged as contributors to cancer-related symptoms.[6 7] Neuroimaging studies in BC survivors have indicated that disturbed default mode network (DMN) connectivity is linked to fatigue and sleep issues.[6] The prevalence of FSDSC in BC survivors has been reported to be up to 84.4%,[8–10] with more than 40% of the BC survivors experiencing persistent fatigue, sleep disturbance and depression for two to three years after diagnosis, significantly leading to the decreased everyday functioning and quality of life (QoL).[9 11] In addition to the accumulation and magnification of negative impacts of individual symptoms within the FSDSC, ineffective management in the long term can further lead to a series of secondary problems, such as increased financial hardship, poorer treatment compliance and even decreased survival rates.[12–14]

Currently, no specific pharmacological interventions are available to alleviate the FSDSC in BC survivors. The medications used are usually prescribed to manage the specific symptom (eg, cancer-related pain, insomnia) individually, rather than the entire symptom clusters and/or other individual symptoms within the same cluster.[15] Even though the tailored pharmaceutical agents provide immediate relief, they are mainly effective for short-term management rather than for a long-term solution.[16 17] Moreover, medications used to alleviate cancer-related symptoms have also caused concerns about the potential interactions with concurrent cancer therapies and adverse events, such as physical dependence, cognitive impairment and daytime drowsiness.[15] Thus, there has been a growing interest in using non-pharmacological interventions to manage cancer-related symptoms, such as physical exercise, cognitive behavioural therapy and yoga. The current symptom management guidelines (eg, National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology) also recommended some non-pharmacological strategies for managing multisymptom or symptom clusters in cancer patients, including exercise, psychoeducation, acupuncture/acupressure and relaxation.[18 19] However, some of these non-pharmacological interventions are not widely used due to intense labour (eg, physical exercise), high cost (eg, cognitive behavioural therapy) and the requirement of professional-supervised and extensive skills (eg, cognitive behavioural therapy, yoga).[20–22] Also, empirical evidence on the effectiveness of these recommended non-pharmacological interventions for FSDSC management in BC survivors remains limited.

Somatic acupressure (SA) is a well-known non-invasive technique based on fundamental theories in traditional Chinese medicine.[23] According to the *Yin-Yang* and *Zang-Fu* organs and meridians theories, cancer-related symptoms, including the FSDSC, likely arise from *Qi* stagnation and insufficient blood circulation to organs.[24 25] SA practice entails applying physical pressure with fingers to acupoints, which is believed to facilitate *Qi* flow in viscera and meridians, and enhance organ blood circulation, potentially alleviating symptoms.[26 27] Evidence suggests that SA may help alleviate cancer-related symptoms through potential biological mechanisms, such as reducing proinflammatory cytokines (eg, IL-1β, TNF-α) or stimulating the release of anti-inflammatory cytokines (eg, IL-4)[28], influencing the connectivity between the DMN of brain and regions that regulate sensations of specific symptoms.[29] Compared with other non-pharmacological methods, SA exhibits several advantages: it is self-administered, requiring less effort and time from patients; it is low-cost, well-tolerated and requires only minor instructions from healthcare professionals.[30] Specifically, SA has been demonstrated encouraging effects in managing the individual symptoms of fatigue,[31] sleep disturbance,[32] depression[33] and some specific symptom clusters, including insomnia–depression–anxiety symptom cluster,[34] fatigue–pain–sleep disturbance–depression–anxiety symptom cluster and pain–fatigue–sleep disturbance symptom cluster in cancer survivors.[35] However, whether SA is also effective in improving the FSDSC in BC survivors is still unclear. Based on our preliminary research work, an evidence-based SA intervention protocol was demonstrated feasible. A well-designed phase II randomised controlled trial (RCT) showed significant group-by-time effects of SA on the FSDSC in BC survivors.[36 37] These encouraging results of the SA intervention suggested that a large-scale RCT is warranted to determine the definite effects of SA on the FSDSC among BC survivors. The current study, therefore, aims to assess the effects, safety and cost-effectiveness of the evidence-based SA for FSDSC management in BC survivors through a phase III RCT.

AIMS AND OBJECTIVES

This phase III RCT aims to evaluate the effects, safety and cost-effectiveness of an evidence-based SA intervention on the FSDSC and QoL among BC survivors. The specific objectives are:

1. To assess the effects of the SA intervention on the FSDSC.
2. To assess the effects of the SA intervention on the individual symptoms of fatigue, sleep disturbance and depression.
3. To assess the effects of the SA intervention on QoL.
4. To assess the safety of the SA intervention for FSDSC management among BC survivors.
5. To assess the cost-effectiveness of the SA intervention in the management of the FSDSC among BC survivors.

METHODS AND MATERIALS

Study design and setting

This study will be a phase III, partially blinded RCT with a true SA group, a sham SA group and a usual care group in a 1:1:1 allocation (figure 1). This trial will be conducted in two hospitals in China, including the Affiliated Hospital of Zunyi Medical University and the Second Affiliated Hospital of Zunyi Medical University.

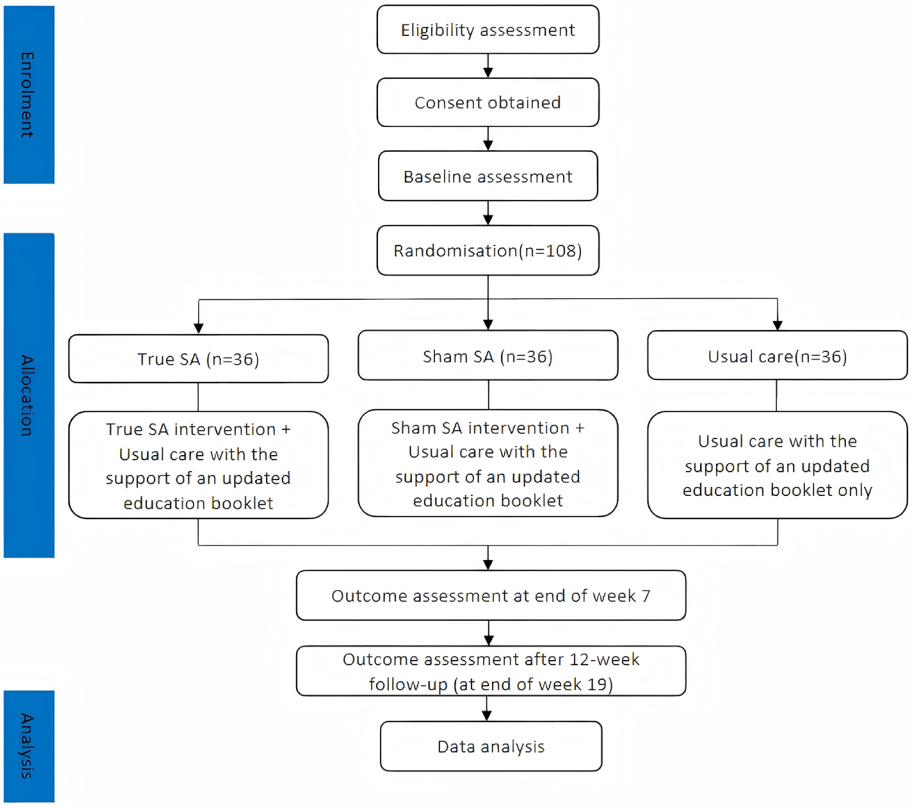

Figure 1 The Consolidated Standards of Reporting Trials flow diagram of the trial. SA, somatic acupressure.

Participants and sample size

The participants will be adult BC survivors who meet the inclusion and exclusion criteria (table 1). A power analysis software G*Power was used for sample size calculation.[38] Due to the unsatisfactory participants' adherence to self-administered acupressure at home, the results of effect size in the phase II RCT have been confounded.[37 39] The effect size for sample size estimation in this phase III RCT was therefore inferred from existing clinical trials in the literature. Power and sample size estimation were based on evaluating the primary hypothesis of the SA intervention improving the FSDSC at individual and symptom cluster levels after intervention and follow-up. However, given the very limited studies on the use of self-acupressure for the FSDSC, fatigue (the core symptom of the FSDSC) measured by the Brief Fatigue Inventory (BFI),[2 40] was selected as the basis for sample size calculation. Recent studies on self-acupressure for fatigue after intervention and follow-up have reported moderate-to-large effect sizes, ranging from 0.32 to 0.96.[41–43] To be conservative, the smallest effect size of at least 0.32 was presumed. The attrition rate in the phase II RCT was

Table 1 Inclusion and exclusion criteria of participants

Inclusion criteria	Exclusion criteria
1. Diagnosed with early-stage female BC without distant metastases (from stages I to IIIa). 2. Have experienced at least moderate FSDSC with a score of ≥4 on an 11-point NRS (0='no symptom',10='worst symptom') for fatigue, sleep disturbance and depression during the past month. 3. Had completed chemotherapy for at least 1 month and up to 3 years (to capture persistent symptoms) 4. Have no scheduled chemotherapy or radiotherapy during the study. 5. Being willing to participate in this study and consenting in writing.	1. Currently using pharmaceutical drugs (eg, antidepressant medications or hypnotics) to treat symptoms of fatigue, sleep disturbance, or depression. 2. Inability (or difficulty) in following the study procedures and instructions due to being extremely weak and/or cognitively impaired. 3. Have received any type of somatic acupressure interventions during the past 6 months. 4. Currently involved in any other studies.

BC, breast cancer; FSDSC, fatigue–sleep disturbance–depression symptom cluster; NRS, Numeric Rating Scale.

11.76%. Given that other similar studies reported attrition rates ranging from 15% to 29%,[44–46] a 25% dropout rate would be considered.[47] A power of 80% and an alpha of 0.05 were also adopted as commonly reported values, participants in each group will be 36, 108 in total.

Recruitment and consent

Prior to conducting the trial, a research team consisting of the research investigators (the doctoral investigator and research assistants (RAs)) and senior clinical nurses at each of the study site will be formed. Participant recruitment and data collection will be supported by the RAs. The clinical nurses will be involved in introducing this trial to potential participants and assisting with participant recruitment. The clinical nurses of each study site will approach the participants (outpatient and inpatient) who potentially meet the predefined inclusion criteria (see table 1). The clinical nurses will introduce this project to the potentially eligible participants. If the participants express interests, they will be referred to the investigator (being responsible for recruitment) in person, who will further explain the study information, make the final decision of eligibility and obtain informed written consent before the baseline assessment. If the participant refuses to participate or is ineligible, the relevant reasons will be recorded. After obtaining written informed consent (online supplemental appendix 1), the baseline assessment will be carried out by the same investigator. The recruitment process will continue until the calculated sample size for this study is reached. The feasibility of the recruitment procedure was validated in phase II RCT.[37]

Randomisation, allocation and blinding

Block randomisation will be applied to keep the equal size of each arm. As recruited participants will be allocated into three groups using a 1:1:1 ratio, the block sizes of three, six and nine will be considered.[48] Since 108 is divisible by nine, and to avoid the predictability of group allocation from the researcher, nine will be the size of the block. The randomisation table will be conducted centrally at Sealed Envelope (https://www.sealedenvelope.com/) by an independent statistician. After an eligible participant signs up and completes the baseline assessment, the doctoral investigator will contact the statistician to determine the participant's group allocation using predefined random sequences. Participants in the true and sham SA groups along with their outcome assessor, and data analyst of this trial will be blinded to group allocation, while participants in the usual care group will not be blinded due to the visible nature of SA intervention. Following the 12 week follow-up, participants in both true and sham SA groups will be asked if they know their group allocation in relation to the type of SA treatment to determine the success of the blinding design. Regular meetings will be held among the investigators to monitor the research progress and effectively address any issues in this study. The doctoral supervisor panel oversees the study's implementation for quality assurance.

Study arms and interventions

This trial will follow the phase II study, continuing with a three-arm study design. Participants in all three groups will receive usual care and an updated education booklet with general strategies on the management of the FSDSC. These strategies include, but are not limited to, physical exercise, nutrition consultation and energy-saving recommendations, which were retrieved from the latest evidence.[49–51] Additionally, participants in the true SA group will be asked to perform self-acupressure on 11 specific acupoints. Participants in the sham SA group will be asked to perform light self-acupressure on 11 non-acupoints. Each acupoint will be pressed for 2 min, once a day for 7 weeks. The 11 acupoints and the 7 week protocol were identified based on the existing evidence base, related theories and practice standards,[36] as well as the feasibility study findings.[37] More information about the acupoints formula, intensity and technique, frequency and duration is summarised in table 2. On completion

Table 2 Details of study arms and interventions

Intervention component		True SA group	Sham SA group	Usual care group
Acupressure intervention	Acupoints	11 selected acupoints (7 of the selected acupoints are bilateral)[36]	11 non-acupoints (located 1–3 cm away from the acupoints used in the true SA group but away from the meridians)	–
	Technique	Regular pressing evoking '*Deqi*' sensation	Light pressing without '*Deqi*' sensation	–
	Frequency	Daily, 2 min for each acupoint		–
	Session	36 min		–
	Total duration	Seven weeks		–
	Home learning packages	► Demonstration video for true acupressure ► Chart of 11 selected acupoints	► Demonstration video for sham acupressure ► Chart of 11 non-acupoints	–
Component of usual care		An updated education booklet for FSDSC management based on the current evidence		

FSDSC, fatigue-sleep disturbance-depression symptom cluster; SA, somatic acupressure.

of the study, participants in the sham SA group and the usual group will be given the choice to receive the true SA intervention voluntarily.

Prior to the commencement of participants' training, the investigators (responsible for the acupressure teaching for participants) will be arranged for training sessions. The training sessions will be delivered by a professional acupuncture practitioner (a registered Chinese Medical Practitioner in China) until the investigators fully master the SA techniques. On randomisation, participants allocated to the true SA group, or the sham SA group will receive training on self-administered acupressure techniques, respectively. The self-acupressure training is conducted until participants can perform an entirely correct return demonstration. Participants will also be encouraged to mark the acupoints with adhesive-coloured dots to reinforce the locations of the acupoints.

As described in the findings of the phase II RCT, participants' adherence to the SA intervention was unsatisfactory due to the limited monitoring strategies under the COVID-19 restrictions.[38] The WeChat platform will, therefore, be used to improve participants' adherence to self-acupressure at home in this trial. During the intervention period, participants (the true SA group and the sham SA group) will receive regular reminders via private one-to-one WeChat chats. Home learning packages (demonstration video and written interpretations on 11 acupoints and 11 non-acupoints) will be provided to the participants for easy practice at home. Moreover, weekly follow-ups via private WeChat messages or telephone calls will be conducted. These follow-ups aim to document participants' daily practising of SA, such as the duration, frequency and any challenges (eg, acupoint locating) or adverse events encountered during the self-acupressure process. To minimise 'fluctuating' in participants' self-acupressure skills and improve their compliance with the SA intervention at home, additional acupressure training (eg, demonstration of acupoint locating and press techniques through private WeChat video) will be provided when necessary. Participants in the usual care arm will also receive weekly contact via telephone of neutral conversation to equalise their attention and expectations.

Intervention fidelity

To ensure the intervention can be implemented as planned, strategies for maintaining fidelity of the intervention design, intervention training, and receipt of intervention are presented as follows.[52] For the fidelity of intervention design, the true and sham SA protocols have been developed and validated.[36] The feasibility and preliminary effects of the acupressure protocol have also been tested in a phase II RCT.[37] Prior to the commencement of the trial, the interventionists (delivering the intervention to participants) will be trained and assessed on acupressure teaching skills by a professional acupuncture practitioner. Thus, a structured training session on the acupoint locations and stimulation techniques will be implemented to ensure the interventionist's mastery of acupressure skills. Furthermore, standardised training on verbal communication with participants will be conducted for the interventionists. For the receipt of the intervention, participants will be provided training on how to perform the self-acupressure based on their group assignment. A required return demonstration on location and stimulation techniques, along with adhesive-coloured dots on the acupoints, will enhance the participants' self-administered intervention. A chart-illustrating acupressure protocol and demonstration video will be provided for participants to reference at home.

OUTCOMES MEASURES

Baseline assessment

A self-designed questionnaire consisting of sections on sociodemographic data (eg, occupational status, age, family income and residential status), BC progression and medical history data (eg, family history of disease, allergy history) will be used.

Primary outcomes

1. Fatigue: the BFI (9 items; item score range 0–10) will be used to measure the participants' fatigue. The BFI in Chinese has been demonstrated to be reliable and valid (Cronbach's α was 0.92 for the severity section and 0.90 for the interference section) for fatigue assessment among cancer survivors.[53]
2. Sleep disturbance: the Pittsburgh Sleep Quality Index (PSQI; 19 items; total score range 0–21) will be used to assess sleep disturbance. The Chinese version of the PSQI was validated in BC survivors (Cronbach's α=0.79) with satisfactory psychometric properties.[54]
3. Depression: the Hospital Anxiety and Depression Scale-Depression (HADS-D; 7 items; total score range 0–21) will be used for evaluating depression. The Chinese version of HADS, a widely used tool among cancer survivors, demonstrated good psychometric properties with Cronbach's α=0.930.[55]
4. The FSDSC composite score: three separated numeric rating scales (NRS) will be used to assess fatigue, depression and sleep disturbance on an 11-point scale, with '0=no present' and '10=as bad as you can imagine'. Then, the three separate symptoms on the 0–10 NRS will be averaged to form 'the FSDSC composite score'.[34 56]

Secondary outcomes

1. QoL: the Functional Assessment of Cancer Therapy-Breast (FACT-B; 37 items; total score range 0–148) will be used for assessing the participants' QoL. The FACT-B's Chinese version showed acceptable psychometric properties among BC survivors (Cronbach's α ranging from 0.59 to 0.85), with test–retest reliability for each domain ranging from 0.82 to 0.91.[57]
2. Adverse events: SA-related adverse events will be assessed through the regular contact between the participant and the RA across the intervention period.

Any discomfort or incidents will be assessed and managed by a professional acupuncture practitioner. The severity of adverse events will be graded by the professional acupuncture practitioner according to the Common Terminology Criteria for Adverse Events V.5.0 and reported and managed accordingly.[58] The causality between the reported adverse events and SA will also be assessed according to the Use of the WHO-UMC System for Standardized Case Causality Assessment by professional acupuncture practitioner.[59]

Economic evaluation

A within-trial economic evaluation will be conducted whereby clinical outcomes and cost data will be compared between the true SA group and the usual care group over 19 weeks.[60] The costs for healthcare care use and intervention-related expenses will be collected. Data on resource use will be captured using a self-designed questionnaire over 19 weeks from randomisation.

A cost-utility analysis will be conducted to calculate an incremental cost per quality-adjusted life year (QALY) gained in the true SA group compared with the usual care group over 19 weeks. QoL will be evaluated using the FACT-B Scale. Responses from participants to the FACT-B Scale will be converted into utility values through a specific algorithm that translates these into the EuroQoL 5-Dimension.[61] Incremental cost-effectiveness ratios will be computed by dividing the cost difference between the true SA group and the usual care group and the differences in QALYs.[60]

A cost-effectiveness analysis will be conducted, with the primary outcome being the change in the FSDSC composite score as measured by the NRS. Reduction in the NRS will be calculated at week 7 and week 19 (with respect to baseline) for the FSDSC severity. Cost-effectiveness analysis represents the effects of alternative interventions in units and the costs of these interventions in monetary units.[60]

Data collection, management and analysis

Data collection

Data will be collected at baseline (week 0), end of 7-week SA intervention (week 7) and end of 12-week follow-up (week 19) (table 3). After obtaining the written consent from the eligible participants, the baseline data (eg, demographic, clinical characteristics, BFI, PSQI, etc) will be collected face to face at the study site using a self-designed assessment booklet prior to group allocation (week 0). During the 7-week intervention, the acupressure log will be completed by the RA via daily WeChat contact with participants in the true SA and sham SA groups. After completion of the intervention (week 7) and the follow-up (week 19), participants will complete relevant questionnaires (eg, BFI, PSQI, HADS-D, FACT-B) for clinical outcomes. If they are unable to come to the study site for an in-person assessment, the outcome assessments will be conducted by the RAs via private telephone/WeChat voice chat. Since the questionnaires are self-reported, the RAs will only assist with neutral interpretation of the questionnaires as needed.

Table 3 Time schedule for trial enrolment, interventions and assessments

Study period	Enrolment	Allocation	Intervention period		Follow-up period	
	Week -1	Week 0	Week 1–7	End of week 7	Week 8–19	End of week 19
Enrolment						
Eligibility screen	×					
Informed consent	×					
Participants' characteristics	×					
Group allocation		×				
Interventions						
True SA			×			
Sham SA			×			
Assessments						
Three separate NRS	×			×		×
BFI	×			×		×
PSQI	×			×		×
HADS-D	×			×		×
FACT-B	×			×		×
Adverse events			×			
Costs		×	×	×	×	×

NRS: Numerical Rating Scale. BFI, Brief Fatigue Inventory; FACT-B, Functional Assessment of Cancer Therapy-Breast; HADS-D, Hospital Anxiety and Depression Scale-Depression; PSQI, Pittsburgh Sleep Quality Index; SA, somatic acupressure.

Data management

Assigning a serial number in place of all participants' information will make all data anonymous. All raw data of participants will be kept in a locked cabinet at the study sites. Electronic copies will be stored in the instiutional OneDrive on a password-protected computer and only accessed by the primary researchers. The storage, retention and disposal of all research data will strictly follow the policies and instructions of the institutional research data management procedure and Australian Code for the Responsible Conduct of Research.

Data analysis

Statistical data analysis will be performed by an independent statistician using the IBM SPSS Statistics software for Windows. Data analysis will follow the intention-to-treat principle. The appropriate proposed methods (eg, complete-case analysis, imputation methods) will be taken based on the missing data patterns. Cross tabulations of categorical variables at baseline will be built with frequencies and within-group percentages. Between-group differences in categorical data of demographic and clinical characteristics at baseline will be tested using the χ^2 or Fisher's exact test. The mean (SD) and median (IQR) of each continuous data by group categories will be used for the description of normally and non-normally distributed ones, respectively. To identify the potential confounders, the between-category differences in outcome variables by categorical demographic and clinical characteristics at baseline will be examined by a one-way (or Welch) analysis of variance (ANOVA) or Kruskal–Wallis test. Also, correlations between outcome variables and continuous data at baseline will be examined by running Spearman correlation tests (two tailed). Repeated measures ANOVA will be used to test the effect of the group on outcome variables (the FSDSC composite score, BFI, PSQI, HADS-D and FACT-B) by each time point. The generalised estimating equations (GEE) model will be implemented to identify the effects of group, time, group by time and the covariates on clinical outcomes. The effect size for the between-group comparisons of SA on clinical outcomes will be computed using Cohen's *d*, with interpretations made for small, medium and large effects.[62] P values<0.05 (two tailed) will be indicated as statistically significant.

DISCUSSION

This study is designed following the Medical Research Council (MRC) Framework for Developing and Evaluating Complex Interventions.[63] An evidence-based SA intervention for FSDSC management in BC survivors was validated,[36] followed by a rigorously designed sham-controlled, partially blinded phase II RCT.[37] A comprehensive assessment of the feasibility and preliminary effectiveness of SA intervention was examined in the phase II RCT.[37] Based on the encouraging results of the phase II RCT, a large-scale RCT was subsequently designed. In the transition from one phase to another in complex intervention research, as outlined in the MRC Framework, the intervention may need refinement based on data collected or the development of a targeted theory.[63] Particularly, the feasibility and acceptability of interventions can be improved by engaging participants to inform necessary refinements. According to the qualitative results and feasibility data from the phase II RCT, the unsatisfactory adherence of participants to the intervention was primarily attributed to (1) personal reasons, such as busy work, burdensome housework, poor memory and emotional distress; (2) insufficient support for long-term maintenance of self-acupressure skills; and (3) lack of strategies for monitoring participants' self-practice at home. Therefore, the application of social media-WeChat (WeChat—free messaging and calling app) was considered a strategy to address these barriers, as it was most frequently recommended by participants in the qualitative interviews. WeChat is the most popular social media and is widely used in cancer management in China.[64] Previous studies have demonstrated that a follow-up strategy combining telephone and WeChat is highly effective in enhancing participants' adherence and satisfaction.[65 66] As such, progressively refining the SA intervention protocol based on feasibility data and participants' feedback from the phase II RCT is desirable and a key focus before proceeding with a full-scale evaluation.[63]

This study is rigorously designed as a partial-blind, sham-controlled RCT. The use of appropriate control groups (both the sham SA group and the usual care group) will ensure that the placebo effects of SA and the specific effects of SA are detectable.[67] The selection of acupoints in the sham group was identified as being 1 to 3 cm from the acupoints in the true group but away from meridians.[67 68] The identification of sham acupoints is the most commonly used sham control method and will ensure the successful blinding of participants in the true SA group and sham SA group.[67 68] Moreover, all the clinical outcomes will be self-assessed by participants. This approach avoids involving independent assessors, minimising the risks of performance bias, as the blinding of the assessors is less likely to bring biases to subjective outcomes.[69] The within-trial economic evaluation will also assess whether the expected benefits of SA intervention justify its associated costs. The results of economic evaluation could help decision-makers translate evidence into practice and generalise the SA intervention to different contexts. Additionally, a 3-month follow-up in a full-scale RCT could provide significant scientific value by monitoring the safety of the intervention, potentially identifying delayed hazards and sustaining beneficial effects.[70]

However, this study is limited by the fact that acupressure trainers cannot be blinded due to the visible nature of the SA intervention. Also, minor deviations in self-acupressure manipulation and acupoint locations are inevitable; however, standardised training provided by study investigators can help reduce performance bias. Home learning materials (eg, demonstration video for acupressure), timely assessment and additional training

(eg, correction of locating and pressing) via social media (WeChat) will also be provided during the intervention period. The results of this study may limit the generalisability of its conclusions since the selected study sites are tertiary hospitals in mainland China. Furthermore, the objective experience of the '*Deqi*' sensation is used as an indicator of the self-administered acupressure technique in this study, which has been widely applied in clinical research and practice.[71] However, it is essential to acknowledge that identifying definitive biomarkers for '*Deqi*' is an ongoing research area, and no conclusive evidence currently exists.

This study protocol offers a standard regimen to guide the conduct of a phase III RCT. By implementing this well-designed RCT, the research project can contribute to the existing body of evidence on the effectiveness of self-acupressure in managing cancer-related symptoms. It could pave the way for self-acupressure to be adopted as a safe, non-invasive, complementary and alternative intervention for the FSDSC, potentially assisting individuals in self-managing their symptoms with minimal risk.

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