


# BMJ Open Effectiveness of virtual reality-based interventions in rehabilitation management of breast cancer survivors: protocol of a systematic review and meta-analysis

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## ABSTRACT

**Introduction** Breast cancer is the leading cause of global cancer incidence and represents 11.7% of all new cancer cases. However, breast cancer survivors (BCS) suffer from many intense physical and psychological symptoms, functional deficits and adverse effects during and after treatment, significantly affecting their quality of life. Virtual reality (VR) technology uses computer technology to create an interactive three-dimensional world by visual, audio and touch simulation and is being used in breast cancer rehabilitation management. This paper reports on the protocol for a systematic review and meta-analysis exploring the efficacy of VR-based interventions in the rehabilitation management of BCS.

**Methods and analysis** This protocol for conducting a systematic review and meta-analysis was prepared according to the recommendations of the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols 2015 statement. Web of Science, PubMed, Embase, CINAHL, Cochrane Central Register of Controlled Trials, CNKI, Wanfang, VIP and SinoMed will be used in the search. The search will include randomised controlled trials, quasi-experimental studies and case-controlled trials published in English and Chinese. Further, the risk of bias of the studies included in the systematic review and meta-analysis will be assessed using the Cochrane risk-of-bias tool. The statistical program Review Manager V.5.3 will be used in the meta-analysis. The I<sup>2</sup> test will be used to determine statistical heterogeneity among the included studies.

**Ethics and dissemination** Ethics approval will not be needed because the data to be used in this systematic review and meta-analysis will be extracted from published studies. The systematic review and meta-analysis will focus on whether VR-based interventions are effective in the rehabilitation management of BCS. It will be disseminated by publication in a peer-reviewed journal. **PROSPERO registration number** CRD42021250727.

## INTRODUCTION

Female breast cancer has surpassed lung cancer as the leading cause of global cancer incidence in 2020, with an estimated

## Strengths and limitations of this study

- To the best of our knowledge, this is the first systematic review and meta-analysis to synthesise the totality of evidence on virtual reality-based interventions in the rehabilitation management of breast cancer survivors.
- The results of this systematic review and meta-analysis will be helpful for clinicians in defining rehabilitation strategies to improve rehabilitation effectiveness among breast cancer survivors.
- This study will be limited to English and Chinese languages, resulting in the exclusion of potentially relevant studies published in other languages.
- There is a possibility that we will have a small sample size and a limited number of studies, which may influence the validity and reliability of the findings.

2.3 million new cases and 685 000 deaths, representing 11.7% of all new cancer cases and 6.9% of death cases.<sup>1</sup> Due to the impact of screening programmes, early detection and accessible healthcare services, as well as advanced therapeutic strategies, the 5-year relative survival rate of individuals with breast cancer has increased to 82%.<sup>2 3</sup> However, survivors suffer from a large number of intense physical and psychological symptoms, functional deficits and adverse effects during and after treatment, significantly affecting their quality of life.<sup>4 5</sup>

Emotional distress mainly includes fatigue, pain, anxiety and depression, common in cancer populations.<sup>6</sup> It was designated as the sixth vital sign in 2005 in Canada<sup>7</sup> and is associated with a reduction in overall quality of life among patients with cancer.<sup>8</sup> Cancer-related cognitive impairment is characterised by deficits in areas of cognition, including memory, attention, information processing

speed and executive function.<sup>9 10</sup> Between 15% and 50% of individuals with breast cancer receiving chemotherapy experience persisting cognitive impairment,<sup>11</sup> often referred to as ‘chemobrain’.<sup>12</sup> The duration of symptoms may extend years after the completion of treatment.<sup>9</sup> Due to disruption in the lymphatic system after surgery or radiation treatment, the accumulation of lymph fluid leads to breast cancer-related lymphoedema (BCRL).<sup>13</sup> BCRL is a chronic, potentially debilitating condition that involves progressive swelling and limited range of motion and causes feelings of pain and numbness, requiring life-long symptom management.<sup>14</sup> Breast cancer survivors (BCS) are at lifelong risk of development of BCRL.<sup>14</sup> The incidence is 21.4%.<sup>15</sup>

Virtual reality (VR) technology uses computer technology to create an interactive three-dimensional world by visual, audio and touch simulation and is being used in breast cancer rehabilitation management. The development of VR offers new and non-invasive approaches for different healthcare applications. It creates interactive computer-generated worlds through visual, listening and touch simulations, where an individual feels being there. VR as a distraction tool improves the emotional well-being of patients with cancer and decreases cancer-related psychological symptoms, enhancing their quality of life.<sup>16</sup> In addition, VR-based rehabilitation systems (eg, Xbox 360 Kinect games, BrightArm Duo rehabilitation system) have been identified to be effective in patients with weak arms and diminished grasping ability.<sup>17 18</sup> These systems use VR to engage patients in upper body bimanual exercises and simultaneously provide cognitive training and affective relief.

To the best of our knowledge, no systematic review or meta-analysis has thus far focused on VR-based interventions in the rehabilitation management of BCS. A single, older, previously published study described the use of VR-based interventions in cancer care, but the review only included reports published in English from 1993 to December 2013.<sup>16</sup> A previously published meta-analysis also described VR-based interventions’ effectiveness in cancer-related fatigue.<sup>19</sup> However, both studies did not retrieve enough databases, which may add to risk of bias. Additionally, they focused on the management of cancer-related symptoms. Different types of cancer show significant differences in population, race, sex, age and complications. Our systematic review and meta-analysis will focus on BCS rehabilitation, which is broader than symptom management. Therefore, we will search for more electronic databases from inception to May 2021. In this systematic review and meta-analysis, we will qualitatively and quantitatively examine the effects of VR-based interventions among BCS.

## Objectives

The overarching objective of this systematic review and meta-analysis is to report on studies using VR-based interventions for the rehabilitation management of BCS and to quantitatively evaluate the effectiveness of VR-based

interventions in breast cancer-related rehabilitation management. This will be achieved with four secondary objectives: (1) to identify the intervention type (immersive and non-immersive) that is most effective in breast cancer-related rehabilitation management; (2) to identify the most effective duration of intervention; (3) to assess any lasting effect of VR-based interventions; and (4) to use a simulation approach to estimate the sample size based on a meta-analysis of existing evidence to recommend an appropriate sample size for a future trial.<sup>20</sup>

## METHODS AND ANALYSIS

### Study design and registration

This systematic review and meta-analysis protocol was prepared based on the recommendations of the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols 2015 statement.<sup>21</sup>

### Eligibility criteria

#### Type of studies

We will include all randomised controlled trials, case-controlled trials and quasi-experimental studies.

#### Type of participants/population

To obtain comprehensive studies and reduce selection bias, we will include all trials that have included patients after first or recurrent breast cancer, regardless of demographic age, race and education status.

#### Type of interventions

To obtain comprehensive studies and reduce selection bias, we will select all trials assessing VR-based interventions, regardless of their aim. In trials, the selection process will not be based on the type or nature of the VR-based intervention (immersive and non-immersive virtual environments).

#### Type of outcome measures

Outcomes are related to rehabilitation management, such as pain, depression, anxiety, fatigue, cognitive function, shoulder range of motion, handgrip strength, lymphoedema, cybersickness symptoms, fear of movement, bleeding, effusion and flap necrosis after surgery.

### Exclusion criteria

The exclusion criteria are as follows: (1) did not specify the type of cancer; (2) described the technologies only; and (3) conference papers, workshop papers, literature reviews, posters, comments, letters, study protocols or proceedings papers.

### Search strategy

We will use a combination of text words and medical subject headings (MeSH) terms depending on the database to capture the following concepts: breast cancer and VR-based interventions. The following electronic databases will be searched from inception to May 2021: Web of Science, PubMed, Embase, CINAHL, Cochrane Central

**Table 1** Search strategy in PubMed

1	“Virtual Reality”[Mesh] OR VR OR “virtual reality” OR “virtual environment” OR “head-mounted display” OR “virtual reality goggle”
2	“Breast Neoplasms”[Mesh] OR “breast neoplasms” OR “breast neoplasm” OR “breast tumors” OR “breast tumor” OR “breast cancer” OR “mammary cancer” OR “mammary cancers” OR “Breast Malignant Neoplasm” OR “Breast Malignant Neoplasms” OR “Malignant Tumor of Breast” OR “Breast Malignant Tumor” OR “Breast Malignant Tumors” OR “Cancer of Breast” OR “Cancer of the Breast” OR “Mammary Carcinoma” OR “Human Mammary Carcinomas” OR “Human Mammary Carcinoma” OR “Mammary Neoplasms” OR “Human Mammary Neoplasm” OR “Human Mammary Neoplasms” OR “Mammary Neoplasm” OR “Breast Carcinoma” OR “Breast Carcinomas”
3	1 AND 2

Register of Controlled Trials, CNKI, Wanfang, VIP and CBM. Further, published studies written in English and Chinese will be included. Details of the search strings in the PubMed database are displayed in [table 1](#). Furthermore, the reference lists and bibliographies from relevant studies will be manually searched for additional primary studies.

## Data collection and analysis

### Data management

Records from the search will be imported into an EndNote library (EndNote V.X9.1) and duplicates will be removed. We will use a piloted data collection form in Excel (Microsoft, 2003) to extract data from the included studies.

### Selection process

The titles and abstracts of retrieved articles will be screened independently against the predefined eligibility criteria by two reviewers (XB and WX). Moreover, we will retrieve and examine the full text of all potentially relevant articles for relevance. Any disagreement between the two reviewers will be resolved by discussion or by other investigators (ASKC and XL).

### Data extraction

Data extraction will be performed independently by two reviewers (XB and WX) using a predesigned standardised form in Word (Microsoft, 2003). Any discrepancies between the two reviewers will have to be resolved by discussion or by other reviewers (ASKC and XL). We will remove duplicate data published in different manuscripts. Additionally, to obtain unclear or missing data, the authors of the included trials will be contacted. Data extraction will consist of study characteristics (first author, publication year, data collection method, study design, sampling strategy, random process, blinding, dropout, reporting, etc), participant characteristics (sample size, age), intervention details (characteristics of interventions, follow-up, duration) and patient-important outcomes (pain, depression, anxiety, fatigue, cognitive function, shoulder range of motion, handgrip strength, lymphoedema, cybersickness symptoms, fear of movement, bleeding, effusion and flap necrosis after surgery).

### Assessment of risk of bias of included studies

Two reviewers will independently assess the methodological quality of all the included trials. Any disagreement between the two reviewers will be resolved by discussion or by other investigators (ASKC and XL). The Cochrane risk-of-bias tool will be used to assess the quality of included randomised controlled trials.<sup>22</sup> It consists of six domains of bias: selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias. ROBINS-I (Risk of Bias in Non-Randomised Studies of Interventions) will be used to assess the quality of included non-randomised controlled trials, covering seven distinct domains: bias due to confounding, selection bias, bias in measurement classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in the measurement of outcomes and bias in the selection of the reported results.<sup>23</sup>

## Data synthesis and statistical analysis

### Data synthesis

Review Manager V.5.3 (Cochrane Collaboration) will be used to conduct the meta-analysis. Mean difference or standardised mean difference with 95% CI will be used to calculate continuous variables. Forest plots will be used to perform these analyses.

### Assessment of heterogeneity

The  $I^2$  test will be used to determine statistical heterogeneity among the included studies. First, we will use a fixed-effect model for data analysis. If  $I^2 > 0.5$ , the random-effects model will be used.<sup>24</sup>

### Assessment of reporting bias

Publication bias will be assessed using the funnel plot method if there are  $\geq 10$  included studies per outcome. Begg's and Egger's tests will be conducted to assess publication bias.  $P < 0.05$  indicates existence of publication bias.

## DISCUSSION

With the high prevalence of intense physical and psychological symptoms, functional deficits and adverse effects in patients with breast cancer during and after treatment,<sup>4,5</sup> there is an urgent need for a high-quality systematic review and meta-analysis to inform evidence-based management of these problems. The proposed systematic

review will report on studies using VR-based interventions for rehabilitation management of BCS and quantitatively evaluate the effectiveness of VR-based interventions in the rehabilitation management of BCS. Our systematic review and meta-analysis findings will offer BCS an alternative therapeutic option and provide directions for future research.

### Patient and public involvement

Patients and the public were not involved in the design, conduct or reporting of this study. Dissemination of findings will occur at relevant conferences or will be published in an appropriate journal.

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**Contributors** All authors contributed to the development of the protocol and writing of the manuscript. XB conceived the initial idea for the study. XB, PHFN, QC, YT, QT and XL wrote the first draft of the manuscript. ASKC and WX critically appraised the protocol and contributed to its development by revising different versions. All authors read and approved the final version of the manuscript.

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