

Intervention combinations within multimodal prehabilitation and their effect on health-related quality of life, fatigue, and adherence in the adult cancer population: an umbrella review protocol

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ABSTRACT

Objective: This umbrella review will investigate intervention combinations that are provided as multimodal prehabilitation and their effect on health-related quality of life, fatigue, and adherence in the adult cancer population.

Introduction: Cancer and treatment-related long-term and late effects are a significant source of impairment worldwide. Multimodal prehabilitation has been the subject of intense research in recent years due to its potential to improve cancer treatment and surgical outcomes. Prehabilitation has been provided in different combinations of exercise, nutrition, and psychological support, although evidence of effectiveness varies in the literature.

Inclusion criteria: The review will consider quantitative and mixed methods (segregated approach) systematic reviews investigating the effectiveness of multimodal prehabilitation compared with any other or no intervention for adults with cancer (≥ 18 years). Systematic reviews focusing solely on unimodal prehabilitation or rehabilitation during or after cancer treatment will be excluded.

Methods: This review will follow the JBI methodology for umbrella reviews. The following databases will be searched from 2001 onwards: MEDLINE, Emcare, PsycINFO, and AMED (Ovid); CINAHL (EBSCOhost); PEDro; Cochrane Database of Systematic Reviews; and Epistemonikos. Backchaining and forward citation tracking will also be performed. Organizational websites will be searched for relevant gray literature. Two reviewers will perform title/abstract and full-text screening against the inclusion criteria, and disagreements will be resolved via discussion or a third reviewer. Relevant population, intervention, and outcome data will be extracted from included full-text documents, and the quality of reports will be determined using the JBI checklist for systematic reviews. The results will be presented in tabular and narrative format.

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Introduction

The number of people affected by cancer is growing, with new cases estimated to reach 28.4 million by 2040 globally compared with 19.3 million in 2020.¹ Cancer survival is also increasing, with more accurate early screening and improved treatment modalities resulting in more and more people living with a cancer diagnosis longer.² Regardless of increasing survival, cancer is a significant source of impairment, affecting individuals as well as

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their families, social networks, and society, while also putting pressure on health care systems.³ Cancer-related impairments can originate from the disease itself as well as from treatment-related long-term and late effects.⁴

Long-term effects are defined as health issues that appear during active treatment and can affect people's lives after the end of treatment.⁴ Late effects can be described as treatment-related whole organ system issues that appear 6 months or later after active cancer treatment.⁴ Various long-term and late effects depend on cancer type and the treatment received, and may include mobility problems, pain, breathlessness, malnutrition, depression, cardiovascular toxicities, reduced bone density, or hypothyroidism.⁴ While the exact prevalence of long-term and late effects is not yet fully understood, estimates are available for some health issues.⁴ For example, fatigue, one of the most common long-term effects—typically described as feelings of unusual exhaustion, weakness, and reduced activity levels—has an estimated prevalence of 59% to 100% of people with cancer.⁵ However, regardless of the type of long-term or late effect, a common consequence of cancer-related impairments is that they significantly affect people's health-related quality of life (HrQOL).⁶ HrQOL, a multidimensional concept incorporating aspects of both physical and psychological health, is often used as an indicator of overall health in medical research.⁷

Nutrition, exercise, and psychological interventions have been increasingly found to have a positive impact on cancer outcomes and HrQOL following treatment or surgery.^{8–10} There is growing evidence that these interventions could reduce fatigue,¹¹ increase muscle strength,⁹ and improve psychological health.⁸ The American Society of Clinical Oncology (ASCO) recommends the use of psychological interventions for anxiety and depression, which are common effects in people affected by cancer.¹² Such interventions should be based on symptom severity, and could include cognitive behavioral therapy, mindfulness or interpersonal therapy, relaxation, or problem-solving, and could be delivered by a range of trained mental health professionals.¹² Nutritional support is also recommended by ASCO to manage symptoms and other problems that contribute to the progression of cancer cachexia.¹³ This is a multifactorial syndrome that manifests as reduced appetite, weight, and muscle mass, which can often lead to decreased survival.¹³

However, nutritional, exercise, and psychological interventions are not only for the post-operative phase or after treatment. Providing such interventions prior to acute treatment and surgery can further improve cancer outcomes.¹⁰ Nutritional, exercise, and psychological interventions provided prior to active cancer treatment are often referred to as “prehabilitation.”¹⁴ Prehabilitation can be defined as care provided between diagnosis and the start of acute treatment. It includes physical and psychological assessment of the patient to determine baseline health status while identifying already existing impairments.¹⁴ Based on the initial health assessment, prehabilitation also provides interventions that support both physical and psychological health to decrease the chance of new impairments or reduce the severity of expected long-term and late effects.¹⁴ Recently, the concept of multiphasic prehabilitation has arisen, whereby prehabilitation is provided throughout the cancer continuum prior to any new treatment, and is not limited to the initial cancer therapy or surgery.¹⁴

Prehabilitation first emerged as a concept in surgical specialties to prepare people for operation. In the past few years, it has also started to be incorporated into cancer care.¹⁴ Nevertheless, as of 2001, exercise and rehabilitation in the pretreatment phase of the cancer continuum was a fairly under-researched area.¹⁵ Courneya and Friedenreich¹⁵ identified numerous research priorities to investigate the effect of exercise in the pretreatment phase. Since then, multiple studies have emerged investigating the effect of exercise as cancer prehabilitation.¹⁶ The role of nutritional and psychological interventions has also been recognized, particularly as part of Enhanced Recovery After Surgery programs.¹⁷ Some interventions have been provided and researched in isolation, and are often referred to as *unimodal rehabilitation*.¹⁸ However, prehabilitation by definition should contain multiple interventions, depending on the participants' needs.¹⁴ Multi-intervention prehabilitation consisting of exercise, nutritional, and psychological support, or a combination of at least 2 of these, is often referred to as *multimodal prehabilitation*.¹⁹ For example, Waterland *et al.*¹⁹ collated exercise-based cancer prehabilitation programs and found that out of 22 included studies, 13 were multimodal. Of these, 1 paired exercise with psychological support, 2 provided exercise and nutrition, while the rest offered a mixture of exercise, respiratory interventions, nutrition, psychological support, and education.

Numerous primary research studies have been published about the effects of multimodal prehabilitation in recent years, contributing to an increasing amount of systematic reviews available.^{18,19} Evidence from these reviews has identified that, although several prehabilitation intervention combinations exist, their effectiveness may vary.¹⁹ It is important to summarize what intervention combinations are provided as multimodal prehabilitation across the evidence base, and how their effectiveness varies. This umbrella review will investigate the intervention combinations provided as multimodal prehabilitation and their effect on the HrQOL and fatigue of the adult cancer population. These primary outcomes were chosen, as HrQOL could provide an overall assessment of people's health status,⁷ while fatigue is one of the most common long-term effects that can significantly affect people's self-reported quality of life.⁶

While the reported variation in effectiveness could be the result of numerous factors, such as intervention characteristics, dosage, methodological issues, or sample size, adherence is also crucial to the success of prehabilitation.²⁰ However, adherence to prehabilitation, particularly in exercise-based interventions, has been historically low.²⁰ For example, a systematic review on prehabilitation in gastrointestinal cancer surgery found that adherence to different interventions ranged from 16% to 100%, with poor compliance reflecting no change or even deterioration in selected outcome measures (6-minute walk test).²¹ Therefore, it is important to investigate how adherence changes in different intervention combinations. Hence, this umbrella review will also examine the literature regarding adherence to multimodal cancer prehabilitation.

To provide a comprehensive picture of how different intervention combinations work, other outcomes, such as adverse events, functional capacity, and cancer treatment/surgery complications also need to be considered. Minor adverse events related to exercise-based cancer prehabilitation, such as musculoskeletal pain and dizziness, have been reported.¹⁹ However, it is unclear whether different intervention combinations could lead to a more diverse range of adverse events or could mitigate their development. Therefore, adverse events will also be investigated in this umbrella review. Understanding the occurrence or absence of adverse events that may or may not be related to prehabilitation is crucial, as the evidence suggests that safety concerns regarding exercising with a cancer diagnosis could influence health care

professionals' decision-making and act as a barrier to exercise counseling for people affected by cancer.²² Information about potential adverse events could ease health care professionals' concerns about exercise safety and aid their decision-making on whether to recommend multimodal prehabilitation that contains an exercise intervention.

Additionally, as multimodal cancer prehabilitation aims to reduce the chance of new impairments, functional capacity and cancer treatment/surgery complications need to be considered. Functional capacity issues are associated with increased risk of severe complications and mortality,²³ hence it is important to investigate whether different intervention combinations are effective in reducing both functional capacity issues and complications.

A preliminary search of PROSPERO, MEDLINE, the Cochrane Database of Systematic Reviews, and *JBI Evidence Synthesis* was conducted to explore whether any umbrella reviews have already been conducted on this topic, to map the available literature, and check the feasibility of conducting an umbrella review. No current or in-progress umbrella reviews focusing only on the effectiveness of multimodal prehabilitation on HrQOL and fatigue were identified. One similar umbrella review is underway, although this focuses on lifestyle-based prehabilitation, which may include combination interventions but is not solely about multimodal prehabilitation.²⁴ Additionally, the proposed umbrella review will investigate adherence to multimodal prehabilitation, highlighting similarities and differences between different intervention combinations, which will help determine which approaches may work best for people affected by cancer. The preliminary search of the literature identified a sufficient number of systematic reviews focusing on multimodal prehabilitation to conduct an umbrella review.^{18,19}

Review questions

What intervention combinations are provided as multimodal prehabilitation and what is their effect on HrQOL, fatigue, and adherence in the adult cancer population?

Inclusion criteria

Participants

This umbrella review will consider systematic reviews focusing on adults 18 years or older who have

a cancer diagnosis. Systematic reviews focusing on participants with any cancer diagnosis will be included. Systematic reviews that contain information about both children and adults 18 years or older will be considered for inclusion if the results for the adult population can be separated.

Interventions

Systematic reviews focusing on multimodal cancer prehabilitation will be included. As described in the introduction, multimodal prehabilitation occurs prior to active treatment or surgery and contains a combination of at least 2 interventions, such as exercise and nutritional/dietary support, exercise and psychological support, all 3 modalities, or other types of care (eg, patient education, physiotherapy, or occupational therapy approaches). Multimodal prehabilitation with any session frequency, duration, timing, mode of delivery, and length will be considered for inclusion. Systematic reviews focusing only on unimodal prehabilitation or on rehabilitation after cancer treatment will be excluded.

Comparator

Systematic reviews with any comparator will be included. This could be standard care, no intervention, unimodal, or other multimodal interventions.

Outcomes

A review will be considered if it reports on any of the following primary outcomes:

- health-related quality of life (HrQOL) recorded via cancer-specific or generic patient reported outcome measures (PROMs), such as the European Organisation for Research and Treatment of Cancer – Core Quality of Life Questionnaire (EORTC-QLQ-C30), Functional Assessment of Cancer Therapy (FACT) questionnaires, Euro-QoL Five Dimensions questionnaire (EQ-5D), or Medical Outcomes Study Short Form 36 (SF-36) health survey
- changes in fatigue levels measured by PROMs, such as Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F)
- adherence to prehabilitation, which can be measured in multiple ways, but for this umbrella review, attendance (percentage or number of prehabilitation sessions attended out of sessions offered), completion or retention (number or percentage of drop-outs, or attendance at follow-

up), and duration (measure of self-reported adherence, such as completion of predefined intervention duration per week that can be measured using physical activity questionnaires).²⁵

Secondary outcomes will include:

- Adverse events related to prehabilitation, defined as an unexpected, potentially harmful outcome that occurred during or after multimodal prehabilitation interventions.²⁶ To investigate these adverse events, an exploratory approach will be taken, meaning that all reported adverse events will be extracted.²⁶ While it may not be possible to infer association between prehabilitation and adverse events from this data, it could provide potential information for future research investigating the safety of prehabilitation interventions.²⁶
- Cancer treatment/surgery complications will be defined as hospital readmission within 30 days, post-operation, emergency department visits, length of hospital stay, and post-operative mortality.
- Changes in functional capacity are measured by tests such as the 6-minute walk test (6MW), VO₂peak (ml/kg) following the steep ramp test or cardiopulmonary exercise test (CPET), timed up and go (TUAG), stair climbing test (SCT), and/or 5 times sit-to-stand (FTSTS).

HrQOL, fatigue, and functional capacity data should preferably be available at baseline, post-intervention (pre-surgery or pre-cancer treatment) and/or follow-up, which could include post-operative or post-treatment period. Adherence and adverse events should be reported at post-intervention and/or follow-up, while cancer treatment and surgery complications should be assessed during the post-operative or post-treatment period.

Context

No restrictions will be made with regards to geographical location or setting of the interventions. Hospital, community, or home-based cancer prehabilitation will be included.

Types of research syntheses

Quantitative systematic reviews with or without meta-analyses will be included. Mixed methods systematic reviews will be included if quantitative findings can be separated, such as in a segregated

approach. We will exclude qualitative systematic or mixed methods reviews with an integrated approach or where the quantitative results cannot be inferred from the reports or supplements. We will also exclude scoping reviews or other review types that do not meet the JBI definition of a systematic review (ie, comprehensive, unbiased syntheses of numerous relevant research studies in a single document using rigorous and transparent methods).

Methods

The proposed review will be conducted in accordance with JBI methodology for umbrella reviews.²⁷ The protocol is registered in PROSPERO (CRD42024511601).

Search strategy

The search strategy will aim to locate both published and unpublished systematic reviews. An initial limited search of MEDLINE (Ovid) and the Cochrane Database of Systematic Reviews was undertaken to identify articles on the topic. The text words contained in the titles and abstracts of relevant articles, and the index terms used to describe the articles, were used to develop a full search strategy for MEDLINE (Ovid; see Appendix I). The full search strategy was designed with the help of an expert information specialist, who assisted with further development of the search terms. The search strategy, including all identified keywords and index terms, will be adapted for each included information source. The databases to be searched will include MEDLINE, Emcare, PsycINFO, and AMED (Ovid); CINAHL (EBSCOhost); PEDro; Cochrane Database of Systematic Reviews; and Epistemonikos. Systematic reviews published since 2001 will be included, as limited research has been conducted on cancer rehabilitation before this date.¹⁵

The reference lists of all included systematic reviews will be screened for additional systematic reviews. Moreover, forward citation tracking will be conducted in Web of Science to maximize the identification of relevant publications. To search for gray literature, relevant organizational websites will be checked (see Appendix II for a list of websites). Moreover, Ethos will be checked for PhD theses that might contain unpublished systematic reviews. Lastly, we will search journals specifically focusing on cancer and systematic reviews (eg, *Cancer, European Journal of Cancer*).

As the reviewers do not have proficiency in languages other than English and there are no resources available for translation, all reviews in languages other than English will be excluded at the full-text screening stage. The excluded studies will be reported in the appendix of the completed umbrella review to provide a more accurate account of the review limitations and inform future work.

Study selection

Following the search, all identified citations will be collated and uploaded into EndNote v.20.1 (Clarivate Analytics, PA, USA). Following the removal of duplicates, all records will be imported into Rayyan (Qatar Computing Research Institute, Doha, Qatar). Two reviewers will pilot study selection on 50 records and discuss any discrepancies. Following the pilot, the 2 reviewers will independently screen titles and abstracts against the inclusion criteria. Any disagreements that arise between the reviewers will be resolved through discussion or with a third reviewer. Once title and abstract screening is completed, the included records will be downloaded for full-text screening.

The full text of selected citations will be assessed in detail against the inclusion criteria by 2 independent reviewers. Reasons for exclusion of full-text systematic reviews that do not meet the inclusion criteria will be recorded and reported. Any disagreements that arise between the reviewers will be resolved through discussion or with a third reviewer. The results of the search, review selection, and inclusion process will be reported in full in the final umbrella review and presented in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.²⁸

Assessment of methodological quality

Eligible systematic reviews will be critically appraised by 2 independent reviewers for methodological quality using the standardized critical appraisal instrument from JBI for systematic reviews.²⁹ Any disagreements that arise between the reviewers will be resolved through discussion or with a third reviewer. The results of critical appraisal will be reported in a table with accompanying narrative. All reviews, regardless of the results of their methodological quality, will undergo data extraction and synthesis (where possible).

Data collection

Data will be extracted from included reviews by 2 independent reviewers using a modified JBI data extraction tool.²⁷ Any disagreements that arise between the reviewers will be resolved through discussion or with a third reviewer. The extracted data will include specific details about the populations, study methods, interventions, and outcomes of significance to the review question. Minor additions have been made to the JBI standard data extraction tool to ensure that cancer prehabilitation details are adequately extracted. The minor adjustments include the addition of prehabilitation session frequency, duration, program length, and terms used to refer to the multimodal nature of the interventions. Furthermore, prompts such as hospital, community, and home-based have been added to the setting to code the environment in which the prehabilitation was provided. The data extraction tool will be piloted on 2 selected reviews by all reviewers to ensure consistency in approaches. The modified data extraction tool is provided in Appendix III.

Data summary

The data from the included systematic reviews will be tabulated and accompanied by a narrative synthesis structured around the intervention combinations and their respective outcomes. Regarding the tabular presentation, the traffic light approach will be used to visually represent effectiveness.²⁷ The color green will be used for effective interventions, amber will be used for no difference, and red will be used for interventions that favor the comparison or are detrimental.²⁷ The number of studies that inform the outcome, the number of participants (from included studies), and the heterogeneity of the results will also be reported.

Primary studies from each review will also be charted to determine overlap between the included systematic reviews. The primary study charting will also be a part of a methodological study or study within a review (SWAR) to determine what methods could more efficiently extract primary study details to determine overlap. The compared methods will be manual study extraction and Web of Science reference list download. Further details on the SWAR (Registration number: SWAR27) can be found in the SWAR Store.³⁰ Based on the charted primary studies, corrected covered area

will be calculated.³¹ Moreover, based on the charted primary studies, a map of intervention combinations will be developed.

Assessing certainty in the findings

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach for grading the certainty of evidence will be followed and a Summary of Findings (SoF) will be created.³² The reviewers will check the included systematic reviews for their GRADE assessment, which will be used in the grading of outcomes for this umbrella review. For reviews where a GRADE assessment was not completed, the GRADE assessment checklist developed by Meader *et al.*³³ will be used to determine the certainty of the reviews results. This will be conducted by 2 independent reviewers at the outcome level. Any disagreements that arise between the reviewers will be resolved through discussion or with a third reviewer.

The SoF will present the following information where appropriate: absolute risks for the treatment and control; estimates of relative risk; and a ranking of the quality of the evidence based on the risk of bias, directness, heterogeneity, precision and risk of publication bias of the review results. The outcomes reported in the SoF will include HrQOL, fatigue, adherence, cancer treatment/surgery complications, and functional capacity.

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Author contributions

JC: protocol development; DE: expert methodological guidance; EG: assistance with search strategy development; JH and LS: insights from an oncology perspective. All co-authors checked, edited, and commented on the final manuscript.

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Appendix I: Search strategy

MEDLINE (Ovid)

Search conducted: March 30, 2023

Search	Query	Records retrieved
1	exp Neoplasms/	3,811,254
2	(cancer* or neoplasm* or tumo?r or oncolog* or malignan*).tw.	3,466,930
3	1 or 2	4,891,128
4	exp Preoperative Exercise/	381
5	exp Exercise/	243,035
6	exp Exercise Therapy/	62,423
7	exp Exercise Movement Techniques/	10,149
8	exp Physical Therapy Modalities/	176,701
9	exp Nutrition Therapy/	112,955
10	exp Diet Therapy/	61,776
11	exp Nutritional Support/	48,916
12	exp Dietary Supplements/	98,691
13	exp Cognitive Behavioral Therapy/	35,939
14	exp Behavior Therapy/	88,205
15	exp Psychotherapy/	216,821
16	exp Relaxation Therapy/	10,105
17	(exercise* or physical activit* or nutrition* or diet*).tw.	1,298,035
18	((psych* or emotion*) adj3 (support* or therap* or intervention*)).tw.	78,990
19	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	1,842,245
20	prehab*.tw.	1265
21	(pre-op* or preop* or peri-op* or periop*).tw.	496,960
22	exp Preoperative Care/	72,736
23	exp Perioperative Period/ or exp Perioperative Care/	254,245
24	20 or 21 or 22 or 23	662,619
25	3 and 19 and 24	7829
26	(multimodal or multi-modal or multidimensional or multi-dimensional or multidisciplinary or multi-disciplinary or multicomponent or multi-component).tw.	249,875
27	3 and 20 and 26	186
28	25 or 27	7863
29	exp Meta-Analysis/	178,259

(Continued)

Search	Query	Records retrieved
30	exp "Systematic Review"/	224,424
31	(review* or meta-analy* or metaanaly* or meta-synthesis or metasyntesis).tw.	2,774,902
32	(synthesis or overview*).ti.	395,337
33	29 or 30 or 31 or 32	3,152,124
34	28 and 33	1497
35	limit 34 to yr = "2001 -Current"	1352

Appendix II: Organizational websites

List of organizational websites for gray literature search

MASCC (Multinational Association of Supportive Care in Cancer) https://mascc.org/
ISNCC (International Society of Nurses in Cancer Care) https://isncc.org/
European Cancer Organisation https://www.europeancancer.org/
EONS (European Oncology Nursing Society) https://cancernurse.eu/
National Cancer Institute https://www.cancer.gov/
ASCO (American Society of Clinical Oncology) https://www.asco.org/
Peter McCallum Centre Australia https://www.petermac.org/research/publications
Chris O'Brien Lifehouse https://www.mylifehouse.org.au/cancer-research/
Macmillan Cancer Support https://www.macmillan.org.uk/about-us/what-we-do/research
Cancer Research UK https://www.cancerresearchuk.org/
Tenovus https://www.tenovuscancercare.org.uk/
Maggie's https://www.maggies.org/
Transformation Partners in Health and Care https://www.transformationpartners.nhs.uk/programmes/cancer/personalised-cancer-care/cancer-rehabilitation/
ACPOPC (Association of Chartered Physiotherapists in Oncology and Palliative Care) https://acpopc.co.uk/
Cancer-site-specific organizational websites will also be searched.

Appendix III: Draft data extraction instrument

Study details	
Author/year	
Objectives	
Participants (characteristics/total number)	Cancer type Planned treatment
Setting/context	Hospital/community/home
Description of interventions/phenomena of interest	Term used to describe the intervention (eg, multimodal, multidisciplinary.) Exercise/physical activity Frequency (eg, twice a week) Duration (eg, 45 min/session) Length (eg, 2 weeks, 12 weeks) Nutritional/dietary Length (eg, 2 weeks, 12 weeks) Psychological Frequency (eg, twice a week) Duration (eg, 45 min/session) Length (eg, 2 weeks, 12 weeks) Other (eg, educational)
Search details	
Sources searched	
Range (years) of included studies	
Number of studies included	
Types of studies included	
Country of origin of included studies	
Appraisal	
Appraisal instrument used	
Appraisal rating	
Analysis	
Method of analysis	
Outcome assessed	
Results/findings	
Significance/direction	
Heterogeneity	
Comments	