PHYSICAL ACTIVITY, EXERCISE AND CANCER

REVIEW ARTICLE

Effects of physical exercise on cancer-related cognitive impairment: Protocol for an umbrella review

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ABSTRACT

Cancer-related cognitive impairment (CRCI) is a mild but meaningful decline in cognitive function among cancer patients, affecting domains such as memory, attention, and executive functions. Emerging evidence suggests that physical exercise is a promising non-pharmacological strategy to mitigate these symptoms. Although several systematic reviews and meta-analyses have examined this topic, no umbrella review has yet synthesized the full body of evidence. This umbrella review aims to integrate findings on the effects of exercise on different cognitive domains in cancer populations, considering both self-reported and objective outcomes. The review will follow PRIOR guidelines and apply a PRISMA-based search strategy across four databases (MEDLINE/PubMed, Scopus, Web of Science, and SPORTDiscus). Eligibility criteria will follow the PICOS framework, including systematic reviews with or without meta-analyses evaluating exercise interventions and their impact on cognitive outcomes in individuals with cancer. Data on intervention characteristics, cognitive domains, and effect sizes will be extracted, and methodological quality will be assessed using GRADE and AMSTAR-2. This review will offer a comprehensive synthesis of current evidence on exercise and CRCI, helping identify the most responsive cognitive domains, effective exercise modalities, and key methodological gaps to inform future research and evidence-based recommendations for cancer survivors' cognitive health.

Keywords: Cognitive function, Physical activity, Oncology, Umbrella review, Protocol.

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INTRODUCTION

Recent advances in biomedical research and improvements in therapeutic strategies have contributed to higher prevalence and survival rates among individuals diagnosed with cancer. Despite these advances, several treatments are associated with a variety of toxicities and adverse effects, including a potential impairment of cognitive function (Olson and Marks, 2019). Some of the treatments among those reported to have associated cognitive toxicities include chemotherapy, radiotherapy, immunotherapy, hormonal therapies, targeted therapies, or endocrine therapies (Spinetti and Orzelleca, 2025).

This cognitive impairment is known as cancer-related cognitive impairment (CRCI) or, more colloquially, chemofog or chemobrain (Whittaker et al., 2022). CRCI is associated with a series of adverse effects in cognitive domains such as executive function, attention, processing speed (Hamilton et al., 2024), memory, learning ability, word retrieval (Oliva et al., 2024), perception or problem-solving (Williams et al., 2016). Patients report symptoms and subjective cognitive complaints, such as increased distraction, memory lapses, difficulties in finding words and names, decreased concentration, slower comprehension of new information or reduced psychomotor efficiency (Oliva et al., 2024; Bai and Yu., 2021). Janelsins et al. (2014) reported that approximately 30% of patients with cancer exhibit cognitive symptoms prior to initiating treatment, with this proportion rising to about 75% during therapy; moreover, up to 35% continue to experience such symptoms for several months or even years following treatment completion.

Several physiological and psychological mechanisms contribute to cancer-related cognitive impairment (CRCI). One of the most widely proposed mechanisms is systemic and central neuroinflammation, characterized by a sustained increase in proinflammatory cytokines such as INF-α, IL-1β, IL-6, IL-8, IL-10, and MCP-1 (Wang et al., 2015). This inflammatory milieu can disrupt the integrity of the blood-brain barrier and activate glial cells, thereby compromising neuronal homeostasis (Lomeli et al., 2021). Neuroinflammation may also induce the production of reactive oxygen species (ROS), promote mitochondrial dysfunction, and trigger DNA damage, collectively impairing synaptic plasticity and neurogenesis (Kim et al., 2025). Brain-derived neurotrophic factor (BDNF) represents another key element in CRCI due to its sensitivity to inflammation associated with cancer and chemotherapy. Neuroinflammatory processes can suppress BDNF expression, reducing its availability within the central nervous system (Yap et al., 2021). Psychological factors also play a significant role, as multiple studies have reported associations between CRCI and anxiety, depression, post-traumatic stress symptoms, and reduced motivation (Rick et al., 2024).

There is increasing evidence supporting physical exercise as an effective non-pharmacological strategy to mitigate CRCI. Benefits have been reported across multiple exercise modalities, including aerobic training, resistance exercise, balance and coordination work, and Eastern practices such as yoga, qigong, and tai chi, which have been shown to improve CRCI-related symptoms and overall quality of life in cancer patients (Bai and Yu, 2020; Lv et al., 2020). Proposed mechanisms underlying these effects include enhanced neurogenesis in the adult hippocampus, the integration of newly generated neurons into functional networks, and improvements in memory (Sekeres et al., 2021). Exercise may also increase BDNF production, improve cerebral oxygenation through augmented blood flow, and attenuate proinflammatory cytokine activity, thereby supporting neuronal plasticity and modulating inflammatory processes linked to cognitive decline (Mackenzie and Marshall, 2022; Lv et al., 2020). Previous studies have already shown the benefits of an intervention with physical exercise on both objective and subjective cognitive function, although the evidence is stronger for cognitive function measured subjectively (Oldacres et al., 2023). Collectively, this evidence highlights physical exercise as a promising intervention for addressing cognitive impairments associated with cancer and its treatments.

Although the literature on exercise and its effect on CRCI has grown in recent years, the evidence remains heterogeneous. After an initial search, no umbrella review on the topic was found. This highlights the need for an umbrella review that integrates the current evidence on the effects of physical exercise on CRCI from existing systematic reviews and meta-analyses. The main objective of this umbrella review, therefore, is to synthesize the current evidence on the effects of physical exercise on cognitive impairment in cancer patients, critically evaluate it, understand the current state of the issue, identify strengths, limitations, and research gaps, and guide future research and clinical practice.

MATERIAL AND METHODS

This umbrella review will be conducted following the guidelines of the PRIOR statement (Gates et al., 2022). Additionally, the search strategy will be designed and carried out according to PRISMA recommendations (Page et al., 2021). The protocol for this review was registered with the Open Science Framework (OSF): https://doi.org/10.17605/OSF.IO/DHBR5

Search strategy

A comprehensive search will be conducted in four electronic databases: MEDLINE/PubMed, Scopus, Web of Science, and SPORTDiscus. The research terms to be used in the databases are:

("physical activity" OR "exercise" OR "sports" OR "movement therapy") AND ("cognitive impairment" OR "crci" OR "chemobrain" OR "chemo-fog" OR "cognition" OR "neuropsychology" OR "executive functions" OR "attention" OR "memory") AND ("cancer" OR "tumor" OR "tumour" OR "metastasis" OR "chemotherapy" OR "radiotherapy" OR "hormonetherapy") AND ("Review" OR "Systematic Review" OR "Overview" OR "Meta-Analysis").

Once the resulting articles have been reviewed, a backward citation searching and forward citation searching will be conducted using Google Scholar and the reference lists of the included studies.

Eligibility criteria

This umbrella review will use the definition of a systematic review described by PRISMA: "*A systematic review is a review that uses explicit, systematic methods to collate and synthesize findings of studies that address a clearly formulated question*". Systematic reviews, with or without meta-analysis, that provide evidence on the effects of physical exercise on cognitive function in oncology patients will be included. The inclusion criteria will be based on the Participant-Intervention-Comparison-Outcome-Study (PICOS) framework: 1) Participants: Adult oncology patients with cognitive impairment. 2) Intervention: Systematic reviews examining the effects of physical activity interventions. 3) Comparison group: Control group or a baseline phase without physical activity intervention. 4) Outcome measures: Measures related to cognitive functions.

Studies will be considered eligible if they have been published or accepted for publication in peer-reviewed journals. Additionally, an accessible abstract will be required for the preselection process, and no language restrictions will be applied.

Articles will be excluded from the umbrella review based on the following criteria: 1) narrative reviews without a search algorithm or that do not describe how studies were selected for the review; 2) reviews that include mixed samples, unless specific data are available for the cancer subgroup; 3) reviews that include exclusively observational studies; 4) conference abstracts, books, theses, and dissertations.

Study selection

The selection of the included articles will be carried out by two authors (FGA and CG). The Rayyan software (Rayyan Systems Inc., Cambridge, MA, USA) will be used to initially assess the titles and abstracts of the identified articles. Subsequently, both researchers will review the full texts of the selected studies to confirm their inclusion. Discussions will be held, and mutual agreements will be reached in case of conflicts. In the event of discrepancies, a third author (DGD) will be consulted.

Data extraction

Two independent reviewers (FGA and CG) will extract all relevant information from the included systematic reviews, as well as the corresponding assessments conducted using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach and the A Measurement Tool to Assess Systematic Reviews (AMSTAR-2) instrument. Extracted data will be cross-checked between reviewers to ensure accuracy and to allow for an independent verification process. In the event of overlap among the articles included in the systematic reviews, the total number of primary articles will be identified and recorded.

The following data items will be extracted: authorship, study design, and publication year; databases searched and search periods reported in each systematic review or meta-analysis; total number of included studies and sample characteristics; types of study designs selected; risk of bias assessments; detailed descriptions of the exercise interventions; cognitive outcomes evaluated; and a synthesized summary of the main conclusions of each review. All the information collected will also be reviewed by the other authors of the article (DGD, CN, and OLV).

Assessment of the methodological quality

A methodological quality analysis of the studies will be conducted using two validated tools: AMSTAR 2 and GRADE. This evaluation will be conducted independently by two authors (FGA and CG) and subsequently peer-reviewed by a third author (DGD).

The AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews) is designed to assess the methodological rigor of systematic reviews by examining weaknesses across a set of critical domains—specifically items 2, 4, 7, 9, 11, 13, and 15 (Liberati et al., 2009). Based on the presence and severity of flaws in these domains, AMSTAR 2 assigns an overall confidence rating in the results of the review, categorized into four levels (Shea et al., 2017): high confidence (none critical flaws and at most one non-critical weakness); moderate confidence (more than one non-critical weakness, but no critical flaws); low confidence (one critical flaw, regardless of the presence of non-critical weaknesses); critically low confidence (more than one critical flaw with or without non-critical weaknesses).

Additionally, the GRADE framework (Grading of Recommendations, Assessment, Development, and Evaluation) will be applied to rate the certainty of the evidence for each intervention analysed in the systematic review. This assessment is specific to each study and considers factors such as study design, risk of bias, inconsistency, indirectness, imprecision, and publication bias (Andrews et al., 2013).

DISCUSSION

Several systematic reviews and meta-analyses have addressed the impact of exercise on cognitive outcomes in cancer populations, although often with heterogeneous samples in terms of cancer type, exercise modalities, or individual cognitive outcomes (Campbell et al., 2020; Zimmer et al., 2016). Although these reviews frequently report beneficial effects, their conclusions are difficult to interpret due to heterogeneity in

cognitive constructs, assessment methods, and intervention characteristics. The absence of an umbrella review that integrates these reviews has limited the ability to draw higher-level conclusions and to identify consistent patterns across different cognitive domains and assessment approaches.

This umbrella review is designed to address a research gap in the literature by providing the first comprehensive overview of existing systematic reviews and meta-analyses that examine the effects of physical exercise on CRCI. By adopting an umbrella review methodology, this study aims to consolidate scattered evidence, clarify inconsistencies between reviews, and offer a structured synthesis that goes beyond the scope of individual systematic reviews.

This umbrella review aims to synthesize the available evidence on the effects of physical exercise on both self-reported and objectively measured cognitive outcomes, including domain-specific analyses. In addition, detailed information on exercise interventions, such as exercise modality, intensity, duration, and other characteristics, will be extracted. This approach will facilitate the identification of the exercise parameters most strongly associated with improvements in cognitive function.

Given that the diagnosis of CRCI remains a topic of ongoing debate, this umbrella review seeks to compare the materials and methods of the included reviews and primary studies with the research recommendations of the International Cancer and Cognition Task Force (ICCTF), which has proposed diagnostic criteria and recommended neuropsychological assessments for specific cognitive domains (Demos-Davies et al., 2024).

One of the principal strengths of this protocol is the implementation of a rigorous and transparent methodological framework. The review process is guided by the directives of the PRIOR statement and the recommendations outlined in the PRISMA guidelines. The use of AMSTAR-2 and GRADE will enable a critical appraisal of the internal validity of the included systematic reviews and the certainty of their findings. Furthermore, explicit procedures will be employed to identify and manage overlap among primary studies across reviews, allowing for the calculation of the total number of unique primary articles and thereby enhancing the methodological robustness of the umbrella review.

However, several limitations inherent to the proposed methodological approach are anticipated. The conclusions of this umbrella review will be contingent upon the quality, scope, and heterogeneity of the included systematic reviews and meta-analyses. In particular, the variability in CRCI definitions, cognitive assessment instruments, and the characteristics of the exercise interventions may constrain the comparability of findings across reviews and represent a potential limitation for the synthesis and interpretation of results.

The findings of this umbrella review are expected to have implications for both research and clinical practice. At the research level, the synthesis will help identify key methodological gaps, including the limited examination of moderating factors, the inconsistent use of standardized cognitive assessment batteries, and the underrepresentation of neurobiological and neurophysiological outcomes. At the clinical level, the results may support the incorporation of exercise-based interventions into comprehensive survivorship care and contribute to the development of future evidence-based recommendations targeting CRCI.

CONCLUSIONS

This protocol describes the methodology for the first umbrella review to synthesize evidence from systematic reviews and meta-analyses examining the effects of physical exercise on cancer-related cognitive

impairment. By integrating findings from both self-reported and objectively measured cognitive outcomes, across multiple cognitive domains and exercise modalities, and by applying rigorous methodological appraisal and certainty-of-evidence frameworks with AMSTAR 2 and GRADE, this umbrella review aims to deliver a comprehensive and critical synthesis of the current literature. The findings of this umbrella review are expected to clarify the existing evidence base, identify methodological limitations, and guide future research and the development of evidence-based exercise interventions aimed at improving cognitive health in individuals with cancer.

AUTHOR CONTRIBUTIONS

FGA (first and submitting author): Conceptualization, Methodology, Writing – original draft, Writing – review & editing; DGD: Conceptualization, Methodology, Supervision, Writing – review & editing; CG: Conceptualization, Methodology; CN: Conceptualization, Writing – review & editing; OLV (corresponding author): Conceptualization, Methodology, Supervision, Writing – review & editing.

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No potential conflict of interest was reported by the authors.

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