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Cognitive functioning and work-related outcomes of non-central nervous system cancer survivors: protocol for a systematic review with meta-analysis

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ABSTRACT

Introduction In recent years, growing attention has been given to the study of the impact of cancer-related cognitive impairment (CRCI) in working non-central nervous system (CNS) cancer survivors. Available literature has shown that working cancer survivors identify cognitive problems at work as very problematic and worrisome. Some reviews have discussed the association between CRCI and work-related outcomes; however, none to date have investigated this association through comprehensive systematic review with meta-analysis. Hence, this work will comprehensively summarise existing evidence from quantitative studies assessing the relationship between CRCI and work-related outcomes of adult non-CNS cancer survivors at working age.

Methods and analysis The systematic review procedures and its report will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. Electronic searches in the databases Web of Science, Scopus, PubMed, ProQuest, PsycINFO and CINAHL, complemented by a manual search of other relevant articles, will be performed from 2000 onwards to identify relevant publications. Two independent reviewers will assess studies for inclusion and extract data from each article using a standardised form. Studies eligible for inclusion must be quantitative, contain adult non-CNS cancer survivors with CRCI, and a measure of cognitive functioning and work-related outcomes. To assess risk of bias, the Joanna Briggs Institute Critical Appraisal Tool Studies checklists will be independently used by the two researchers. Synthesis of the included articles will be conducted using a narrative method and through meta-analysis. Meta-analysis will be reported via correlation for the association between CRCI and work-related outcomes. The cumulative evidence will be assessed using the Grading of Recommendations Assessment, Development and Evaluation system.

Ethics and dissemination Ethics approval is not required since individual patient data will not be collected. The findings will be published in a peer-review indexed journal, presented at scientific meetings and included in a chapter of a Doctoral thesis.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This review will apply the methodology of systematic review and meta-analysis to report the literature regarding the relationship between cancer-related cognitive impairment and work-related outcomes of adult non-central nervous system cancer survivors at working age.
⇒ The protocol of this work was written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols guidelines, to ensure quality of the study in terms of reporting, planning and execution.
⇒ A broad and comprehensive search strategy will be used in multiple databases to maximise the identification of eligible studies, and study selection, data extraction and risk of bias assessment will be performed independently by two reviewers to ensure that the included studies are free from personal bias.
⇒ Unpublished articles/grey literature and publications that consist of abstracts only will not be included, due to lacking important data.
⇒ We anticipate possible heterogeneity across studies to be included, related to the population, type of treatment received, outcome measures and methods/tools, which may increase difficulties in interpreting the meta-analysis.

INTRODUCTION

Increased attention to the care of cancer survivors has led to a growing interest in studying how cancer diagnosis and cancer treatments affect their overall quality of life, their capacity to function and live independently, and their ability to return to work.[1 2] Cancer-related cognitive impairment (CRCI), cognitive problems associated with cancer and cancer treatments experienced by individuals with cancer, is one of the most feared and commonly experienced problems reported by non-central nervous system (CNS) cancer survivors,[2–6] with a significant impact on the functional ability and quality of life of survivors and their families.[4] Although much of the research has focused on breast cancer, it also affects patients with other non-CNS cancers.[7 8] Some of the most frequent

complaints are related to difficulties with short-term memory, concentration, attention, executive functions, multitasking and processing speed.[4 8] Cognitive impairments verified in this population are consistent with the patients' self-report (through self-report questionnaires) and performance-based assessment (with neuropsychological tests).[9 10] However, in some cases, subjective measures of cognitive impairment are poorly associated with objective measures, which indicates the need to include both measures in the assessment of cognitive function.[9 11]

Worldwide, 40%–50% of cancer survivors are of working age,[12] which means that many cancer survivors are at an age at which cancer and its treatments could affect their career and work-related outcomes; this can have an important impact on individual and family lives.[13 14] Work is associated with having a purpose in life, a sense of contributing and a distraction; it can also improve one's self-esteem and sense of well-being, and provide financial security.[15–17] Several studies have shown that survivors with cognitive impairments may experience challenges in their work,[18–20] namely memory problems, reduced efficiency and impaired processing speed,[5 19–21] attention and concentration problems,[5 19] verbal ability, language competences or word finding difficulties,[19 21] and problems with planning and executing their work.[19–21] Therefore, due to CRCI, cancer survivors report less confidence and capability to do their job well,[21] and less prospect of being promoted or assigned to important projects, since they and their employers realise they are no longer able to manage their premorbid level of work.[5] Investigating the potential impact of CRCI on work-related outcomes is further complicated by the association these variables share with multiple factors, such as sociodemographic (eg, age, education), tumour (eg, tumour type, tumour stage), treatment modality (eg, chemotherapy, endocrine therapy), psychological (eg, anxiety, depression) and physiological (eg, fatigue, sleep) factors.[2]

Theoretical models suggest a link between cognitive limitations and work-related outcomes in cancer survivors. The latest model was developed by Mehnert *et al*[22] and corresponds to a cancer survivorship and work model adapted from Feuerstein *et al*[16] and Mehnert,[14] considering several work-related outcomes, such as employment/return to work, work ability, work performance, job opportunities, income, work satisfaction, job promotion and training, and sustainability. Nevertheless, since the publication of these theoretical models, a growing body of research has been developed to study the relationship between CRCI and work-related outcomes, including some reviews to systematise studies' findings,[23–26] considering that many occupationally active survivors identify these symptoms as very problematic and bothersome.[18]

Von Ah *et al*[23] were the first to explore the impact of cognitive impairment on work outcomes in 2016. Findings from this integrative review showed that most studies found cognitive impairment to be a common troubling symptom that had a negative impact on work-related outcomes, affecting work ability, job performance and productivity for cancer survivors returning to work after cancer and cancer treatments. Bijker *et al*[24] performed a systematic review in 2018 that explored the association between functional impairments (including cognitive functioning) and work-related outcomes in breast cancer survivors. Findings were inconsistent across studies: studies measuring cognitive functioning with objective neuropsychological tests found no association with work-related outcomes, while results of studies using self-reported measures of cognitive functioning were ambiguous. Lewis and Mackenzie[25] performed a scoping review, aiming to identify what is known about how cognitive changes impact work ability or performance for women with breast cancer. Although discrepancies were found between results from neuropsychological testing and self-report measures, breast cancer survivors can experience challenges in their employment due to cognitive deficits, which may lead to the loss of their employment. In the same year, Tan *et al*[26] performed a systematic review of studies that quantified the impact of cancer-related symptoms (namely cognitive impairment) on work outcomes among cancer survivors. Results indicated that only a small proportion of studies assessing work status (employment status/return to work or early retirement/work disability) and cognitive impairment reported significant findings. The authors indicated that, ideally, estimates from studies should be pooled in meta-analysis for the purpose of quantitative synthesis; however, this approach was not feasible in their work.

To summarise, the collective conclusions of these reviews describe that cognitive functioning can impact work-related outcomes, although inconsistencies are found when cognitive functioning is evaluated by self-report and neuropsychological measures. We note that some reviews had a broader scope, since they explored the association between functional impairments or cancer-related symptoms (including, but not limited to, cognitive functioning) and work-related outcomes[24 26]; therefore, considering that cognitive functioning was not the main focus of the reviews, important studies might have been missed for non-CNS cancer survivors. Furthermore, considering that the reviews focused only on breast cancer[24 25] or included all types of cancer, including CNS cancers,[23 26] the conclusions for non-CNS cancer survivors may not be generalisable or may be confounding. Finally, despite the valuable contribution of these reviews to the current state of knowledge on the association between CRCI and work-related outcomes, this has been done via narrative synthesis; no review has quantitatively synthesised the literature specifically concerning CRCI and work-related outcomes. While narrative synthesis through text and tables is an initial, and in some cases the only, step to summarise and explain the characteristics and findings of the included studies and to provide an analysis of the relationships within and between studies, it is a more subjective process than quantitative synthesis, that is, meta-analysis.[27] The meta-analysis will provide

information on the magnitude of the effect, and will allow to investigate reasons for variations between studies and differences between studies and group of studies, and settle conflicting claims.[28] This is important to clinical practice because, by combining information from all relevant studies, meta-analyses can provide more objective and precise estimates of the effects of healthcare than those derived from the individual studies included within a review, assisting clinicians decisions.[29 30] Consequently, a quantitative investigation of this association is necessary and timely, as suggested by Tan *et al*.[26]

Considering the growing attention that has been given to this area in recent years, the primary aim of the present systematic review with meta-analysis is to comprehensively review the literature and synthesise relevant data to identify the relationship between CRCI and work-related outcomes of adult non-CNS cancer survivors at working age, and to quantify this association, exploring how strong and consistent is the relationship across studies. If possible, a secondary examination of patient and clinical characteristics (eg, age, type of cancer, type of treatment), psychological variables (eg, depression, anxiety) and other influencing factors (eg, fatigue, sleep) and their influence on any association between CRCI and work-related outcomes will also be conducted. Therefore, this work will allow us to further understand the relationship between CRCI and work-related outcomes and help propose recommendations for clinical practice and interventions. Previous CRCI interventional research has been limited and has failed to examine implications on work-related outcomes,[23] although recent efforts have been made to address this gap.[31 32] Therefore, findings from this work can guide the development of patient-centred interventions to address implications of CRCI on work-related outcomes, considering the relationships between these two variables.

METHODS AND ANALYSIS

In accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Protocols (PRISMA-P) 2015 statement[33 34] (see Research Checklist), our systematic review protocol was established and registered with the International Prospective Register of Systematic Reviews (PROSPERO) database.

The systematic review will be conducted following the PRISMA 2020 updated guidelines.[35]

Eligibility criteria

Eligibility criteria were established according to the Population, Intervention/Exposure, Comparisons, Outcome and Study type (PICOS) framework[25 36 37] and considering the International Cognition and Cancer Task Force (ICCTF) recommendations for the study of CRCI.[38 39] Therefore, studies will be included according to the following criteria: (1) Population—Adults with a non-CNS cancer diagnosis (survivors) at working age (18 years or older) with CRCI; (2) Interventions/Exposure—Non-CNS cancer survivors exposed to any cancer-related treatments, with primary treatment completed at the time of the study; (3) Comparisons—No comparison group will be required; () Outcomes—Association between CRCI and work-related outcomes and, where available, associations between CRCI and work-related outcomes and additional potential moderator variables (eg, measures of anxiety, depression) and (5) Study type/design—Quantitative studies. Further details about the eligibility criteria are outlined in table 1. The primary search question thus formulated is 'What is the relationship between cognitive functioning and work-related outcomes in adult non-CNS cancer survivors at working age provided by quantitative evidence?'.

For the purpose of this article, the following definitions are used to avoid ambiguity in terms of cognitive functioning, work-related outcomes and non-CNS cancer survivors. Cognitive functioning refers to a higher order mental process related to the capacity to process information, regulated by numerous areas of the brain. It consists of a multidimensional concept encompassing multiple inter-related domains, including attention and concentration, executive function, information processing speed, language, psychomotor function, visuospatial ability and learning and memory.[40–42] Therefore, impairments in cognitive functioning correspond to a decline in function in one or more of these cognitive processes.[41 42] Work-related outcomes are conceptualised following the 'Cancer Survivorship and Work Model' by Mehnert *et al*,[22] which is an adaptation from Feuerstein *et al*[16] and Mehnert[14] models, considering several work-related outcomes (detailed information about these outcomes are defined in the aforementioned articles). CNS tumours may either be primary, originating and developing within the CNS (eg, gliomas, meningioma, medulloblastoma and primary CNS lymphoma) or metastatic, originating in non-CNS tissue and migrating to the CNS. Therefore, in the present work, non-CNS tumours refer to diagnosis other than CNS location, including, for example, breast, colorectal, prostate, skin, head and neck, or lymphoma.[42 43] Non-CNS cancer survivors refers to men and women who have been diagnosed with a non-CNS cancer and have completed primary treatment, regardless of stage, time since diagnosis and type of treatment.[24]

Studies will be included if they are written in English, Portuguese, French or Spanish to avoid idiom-related bias; considering the language knowledge and proficiency of the review team in these languages and the lack of resources to include articles written in other languages, only studies written in these languages will be considered. The authors will search for articles from January 2000 onwards, considering that CRCI began to be recognised around this date.[25]

Information sources

The literature search will be performed by the first author by searching title, abstract and keyword fields. The

Table 1 PICOS framework components and description for the eligibility criteria

PICOS framework components	Description
Population	Only survivors of adult-onset cancers (ie, diagnosed with cancer at 18 years or older) will be considered, considering the potential developmental impact on cognitive functioning. Survivors of CNS cancers will be excluded, due to potential differences in cognitive function between non-CNS and CNS cancer survivors. When studies with mixed populations have more than 20% of participants meeting exclusion criteria, they will be excluded[37]; authors of these articles will also be contacted to clarify this issue and confirm if they did not include CNS cancer survivors. No setting restrictions will be considered.
Interventions/exposure	No restrictions will be applied regarding type of cancer treatments. Cancer survivors should not have been engaged in primary treatment (radiotherapy, chemotherapy, immunotherapy) at the time of enrolment, due to the focus of this work being related to late survivorship issues; hormone-related therapies will not be considered primary treatment and therefore studies reporting that will not be excluded.
Comparisons	Although a comparison group will not be required, studies including a comparison/control group (disease specific and/or healthy controls) will be included, whereas the outcomes of interest are evaluated for the population.
Outcomes	Report a measure of cognition (assessed through subjective self-report measures and/or by objective neuropsychological assessment instruments) and have measured a work-related outcome (assessed by subjective self-report measures and/or by patient's perspective; (see[14 16 22] for the models considered for the types of work-related outcomes included)). Associations between the cognitive and work-related outcomes need to be directly reported to be included. Studies that focus on psychological or mental health that do not have a separate measure of cognitive functioning and those in which the cognitive measure is delirium/dementia/geriatric-related will be excluded. Additionally, studies that do not have an identified work-related outcome will also be excluded, considering that the aim of this review is to examine the impact of CRCI on work-related outcomes. Secondary outcomes, such as age, type of cancer and treatment, anxiety, depression, fatigue and sleep, will also be considered if they are reported as potential moderator variables on the association between CRCI and work-related outcomes.
Study design/type	Empirical articles published (or ahead of print) in a peer-reviewed journal that report original quantitative data will be included, both cross-sectional, longitudinal or retrospective (only baseline data will be extracted where multiple timepoint assessments are made). Studies reporting an intervention or only qualitative evidence will be excluded. Unpublished articles/grey literature (eg, thesis, conference proceedings, technical reports) and publications that consist of abstracts only (eg, conference abstracts) will be excluded, due to lacking important data. Literature/systematic reviews or meta-analysis, case studies and studies that do not report original data (eg, commentaries, editorials) will not be included.

CNS, central nervous system; CRCI, cancer-related cognitive impairment.

following six electronic databases will be searched for the relevant publications: Web of Science, Scopus, PubMed, ProQuest, PsycINFO and CINAHL (through EBSCOhost). Searches in these databases will be complemented by a manual search of the reference lists of other relevant and key publications related to CRCI and work-related outcomes in cancer survivors (eg, systematic reviews excluded at title/abstract stage, studies mentioned in screened and/or included articles) to include any additional studies not previously identified and to ensure saturation of data. A snowball procedure will also be used, to manually search the references cited in the included articles to identify additional studies. When these studies are not duplicates already included in the search, they will be added for screening. Attempts will be made to find unavailable articles by contacting authors, as well as to clarify information.

Search strategy

The search strategy will encompass the identification of the main terms/concepts based on the PICOS framework, consisting of three primary topics: "cancer", "cognition", and "work". The authors will also identify associated keywords and/or synonyms; different spellings; singular/plural forms, verbal forms, and adjectives (eg, searching the keywords of key articles and other reviews of the topic), and controlled vocabulary/medical descriptors (eg, Medical Subject Headings (MeSH) terms) to improve the sensitivity of the search and obtain the maximum number of publications (table 2).

The truncation symbol (*), quotation marks (" ") and Boolean terms (OR, AND) will be applied to combine the different search terms/concepts and to narrow the search based on the eligibility criteria; multiple search terms will be used for each main search term/concept combined

Table 2 Main search terms/concepts, free-text terms and medical headings

Main search terms/concepts	Keywords and/or synonyms, different spellings, singular/plural forms	MeSH terms
1) Cancer	cancer* OR oncolog* OR neoplasm* OR tumour* OR tumor* OR carcinoma* OR malignan* OR "non-central nervous system" AND surviv* OR patient*	Neoplasms Carcinoma Cancer Survivors
2) Cognition	cogniti* OR cognition OR cognitive OR "cognitive functioning" OR "cognitive impairment" OR "cognitive concern*" OR "cognition disorder"	Cognition Cognition Disorders Cognitive Dysfunction
3) Work	work OR "work-related outcome*" OR occupation* OR vocational* OR "work function*" OR "work capacity" OR "work activity" OR "work status" OR "work ability" OR "work limitation*" OR "return to work" OR "work performance" OR "work productivity" OR "work* hours" OR "work retention" OR "job retention" OR "work environment" OR "work tolerance schedule" OR employ* OR unemployment OR "job performance" OR "job accommodation" OR absenteeism OR "sick leave"	Work Employment Absenteeism Sick Leave Return to Work Work Performance Unemployment

MeSH, Medical Subject Headings.

with the "OR" operator, and the "AND" operator will be used between terms within each of the main search terms/concepts. Specific filters related to publication date, language, and document type will be used whenever possible, considering the eligibility criteria mentioned above. The search terms will be adjusted to the specificities of the different databases. Detailed information about the draft search strategy is available in table 3 to facilitate its replication.

Data management

All literature results identified during the database search will be imported into Mendeley, and then duplicate studies will be removed based on title and author. Remaining results will be exported into Rayyan QCRI (Qatar Computing Research Institute) online software (https://rayyan.qcri.org/), a support tool for references selection in the framework of systematic reviews that facilitates collaboration among reviewers.

Selection process

The selection process will be conducted by the first and second authors considering the review team's preestablished inclusion and exclusion criteria. The two authors will independently review the titles and abstracts of all identified search results, labelling them as included, excluded or maybe. Articles labelled as included and maybe will then be retrieved for full-text examination, and the full text will be reviewed, in both situations. For articles that will be excluded, reasons for not including them will be documented. The authors will seek additional information from study authors where necessary to resolve questions about eligibility. All documents raising any doubts or disagreements will be discussed and resolved in a consensus meeting; a third author of the review team will be consulted in cases in which consensus is not achieved.

Inter-rater agreement will be assessed and interpreted using Cohen's kappa coefficient to explore the consistency of the study selection performed by the two authors (kappa values: <0—less than chance agreement; 0.01–0.20—slight agreement; 0.21–0.40—fair agreement; 0.41–0.60—moderate agreement; 0.61–0.80—substantial agreement; 0.81–0.99—almost perfect agreement).[44] This analysis will be performed using IBM SPSS V.28.0 (IBM).

The PRISMA flow diagram will be displayed to provide details on the selection process of the studies, documenting included and excluded studies with the reasons for exclusion[33 34 36] as presented in figure 1.

Data collection process

The main information from all eligible studies will be independently extracted by the first and second authors to ensure that all relevant information is captured and to minimise risk of bias. When the studies have assessed multiple outcomes, only the information that is relevant to this systematic review research question will be extracted. The same standard data extraction form will be used to charter the descriptive data about each study. Extracted data will be confirmed by the two researchers, and disputes will be resolved through consultation and referring to data in original papers; the data extracted will be reviewed and validated by the third author. The authors will also contact the study author to resolve any uncertainties or if there are missing and incomplete data about study characteristics, methods or measures used, or where clarification on data is needed.

Data items

The following information will be extracted from all studies selected (where available): (1) information about the article; (2) participants' characteristics; (3) characteristics of the study; (4) data collection and (5) main findings/conclusions of the study. Table 4 presents the items that will be collected.

Table 3 Draft of search strategy

Database	Query
Web of Science	**TS**=(cancer* OR oncolog* OR neoplasm* OR tumour* OR tumor* OR carcinoma* OR malignan* OR "non-central nervous system") AND **TS**=(surviv* OR patient*) AND **TS**=(cogniti* OR cognition OR cognitive OR "cognitive functioning" OR "cognitive impairment" OR "cognitive concern*" OR "cognition disorder") AND **TS**=(work OR "work-related outcome*") AND **TS**=(occupation* OR vocational* OR "work function*" OR "work capacity" OR "work activity" OR "work status" OR "work ability" OR "work limitation*" OR "return to work" OR "work performance" OR "work productivity" OR "work* hours" OR "work retention" OR "job retention" OR "work environment" OR "work tolerance schedule" OR employ* OR unemployment OR "job performance" OR "job accommodation" OR absenteeism OR "sick leave")
Scopus	**TITLE-ABS-KEY**(cancer* OR oncolog* OR neoplasm* OR tumour* OR tumor* OR carcinoma* OR malignan* OR "non-central nervous system") AND **TITLE-ABS-KEY**(surviv* OR patient*) AND **TITLE-ABS-KEY**(cogniti* OR cognition OR cognitive OR "cognitive functioning" OR "cognitive impairment" OR "cognitive concern*" OR "cognition disorder") AND **TITLE-ABS-KEY**(work OR "work-related outcome*" OR occupation* OR vocational* OR "work function*" OR "work capacity" OR "work activity" OR "work status" OR "work ability" OR "work limitation*" OR "return to work" OR "work performance" OR "work productivity" OR "work* hours" OR "work retention" OR "job retention" OR "work environment" OR "work tolerance schedule" OR employ* OR unemployment OR "job performance" OR "job accommodation" OR absenteeism OR "sick leave")
PubMed	((cancer*[Title/Abstract] OR oncolog*[Title/Abstract] OR neoplasms[MeSH Terms] OR neoplasm* OR tumour*[Title/Abstract] OR tumor*[Title/Abstract] OR carcinoma[MeSH Terms] OR carcinoma* OR malignan* OR "non-central nervous system") AND (surviv*[Title/Abstract] OR patient*[Title/Abstract] OR cancer survivors[MeSH Terms]) AND (cogniti*[Title/Abstract] OR cognition[MeSH Terms] OR cognition disorders[MeSH Terms] OR cognitive dysfunction[MeSH Terms] OR cognitive[Title/Abstract] OR "cognitive functioning"[Title/Abstract] OR "cognitive impairment"[Title/Abstract] OR "cognitive concern*" OR "cognition disorder") AND (work[Title/Abstract] OR "work-related outcome*"[Title/Abstract] OR occupation* OR vocational* OR "work function*" OR "work capacity" OR "work activity" OR "work status" OR "work ability" OR "work limitation*" OR return to work[MeSH Terms] OR work performance[MeSH Terms] OR "work productivity" OR "work* hours" OR "work retention" OR "job retention" OR "work environment" OR "work tolerance schedule" OR employment[MeSH Terms] OR employ* OR unemployment[MeSH Terms] OR "job performance" OR "job accommodation" OR absenteeism[MeSH Terms] OR sick leave[MeSH Terms]))
ProQuest	**ab**((cancer* OR oncolog* OR neoplasm* OR tumour* OR tumor* OR carcinoma* OR malignan* OR "non-central nervous system") AND (surviv* OR patient*) AND (cogniti* OR cognition OR cognitive OR "cognitive functioning" OR "cognitive impairment" OR "cognitive concern*" OR "cognition disorder") AND (work OR "work-related outcome*" OR occupation* OR vocational* OR "work function*" OR "work capacity" OR "work activity" OR "work status" OR "work ability" OR "work limitation*" OR "return to work" OR "work performance" OR "work productivity" OR "work* hours" OR "work retention" OR "job retention" OR "work environment" OR "work tolerance schedule" OR employ* OR unemployment OR "job performance" OR "job accommodation" OR absenteeism OR "sick leave")) NOT **ab**("review")
PsycInfo	**AB**(cancer* OR oncolog* OR neoplasm* OR tumour* OR tumor* OR carcinoma* OR malignan* OR "non-central nervous system") AND **AB**(surviv* OR patient*) AND **AB**(cogniti* OR cognition OR cognitive OR "cognitive functioning" OR "cognitive impairment" OR "cognitive concern*" OR "cognition disorder") AND **AB**(work OR "work-related outcome*") AND **TX**(occupation* OR vocational* OR "work function*" OR "work capacity" OR "work activity" OR "work status" OR "work ability" OR "work limitation*" OR "return to work" OR "work performance" OR "work productivity" OR "work* hours" OR "work retention" OR "job retention" OR "work environment" OR "work tolerance schedule" OR employ* OR unemployment OR "job performance" OR "job accommodation" OR absenteeism OR "sick leave")
CINAHL	**AB**(cancer* OR oncolog* OR neoplasm* OR tumour* OR tumor* OR carcinoma* OR malignan* OR "non-central nervous system") AND **AB**(surviv* OR patient*) AND **AB**(cogniti* OR cognition OR cognitive OR "cognitive functioning" OR "cognitive impairment" OR "cognitive concern*" OR "cognition disorder") AND **AB**(work OR "work-related outcome*") AND **TX**(occupation* OR vocational* OR "work function*" OR "work capacity" OR "work activity" OR "work status" OR "work ability" OR "work limitation*" OR "return to work" OR "work performance" OR "work productivity" OR "work* hours" OR "work retention" OR "job retention" OR "work environment" OR "work tolerance schedule" OR employ* OR unemployment OR "job performance" OR "job accommodation" OR absenteeism OR "sick leave")

Outcomes and prioritisation

The primary outcome of this work is the relationship between cognitive functioning (subjective or objective, assessed through self-report questionnaires and by neuropsychological tests, respectively) and work-related outcomes (assessed through self-report questionnaires or

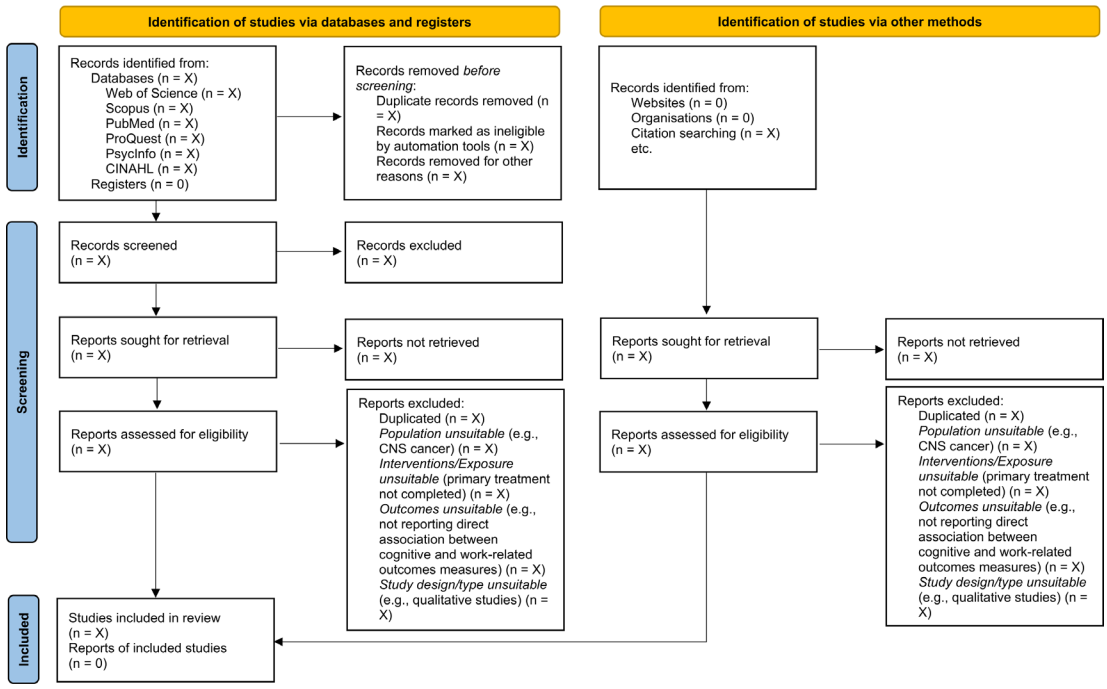

Figure 1 PRISMA flow diagram presenting the selection process for the studies. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

from the patient's perspective; see the Eligibility criteria section for a description of the work-related outcomes). Among the most common self-report measures of subjective cognitive functioning are the Functional Assessment of Cancer Therapy-Cognitive Function version 3 and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30)-Cognitive Functioning Scale.[4] Objective cognitive functioning is usually assessed with neuropsychological tests; several tests have been used across studies, but the ICCTF recommends prioritising the use of the Hopkins Verbal Learning Test-Revised, the Trail Making Tests parts A and B and the Controlled Oral Word Association of the Multilingual Aphasia Examination to harmonise CRCI research studies.[4 38 39] The Work Limitations Questionnaire and the Work Ability Index are two examples of the most commonly used self-report validated measures to assess work-related outcomes; other outcomes are more frequently reported from the patient's perspective (eg, absenteeism, return to work, working hours).[23–26]

Secondary outcomes, such as anxiety and depression, fatigue and sleep (measured with self-reported instruments, for instance, the Hospital Anxiety and Depression Scale and the EORTC QLQ-C30, respectively[26]), age, type of cancer and type of treatment (as presented in demographic and clinical characterisation of the sample), will also be considered.

Methodological quality (risk of bias) in individual studies

Each study will be rated by two reviewers (first and second authors) independently using two types of procedures. The methodology quality of the retrieved articles will be

Table 4 Data items to be collected from the selected articles

Information about the article	Participant's characteristics	Characteristics of the study	Data collection	Main findings/ conclusion of the study
First author	Sample size	Study design	Outcome measures of cognitive functioning	Variables in association
Year of publication	Age(mean, SD)	Study setting	Outcome measures of work-related outcomes	Data extraction for correlation (with p values)
Country of origin	Gender	Methodology	Outcome measures of other relevant variables	Interpretation
Study main aims	Cancer type			
	Inclusion/exclusion criteria			

critically appraised following the PRISMA 2020 recommendations.[36] The authors will use an appropriate tool for the study design to assess risk of bias in the included studies. To keep the appraisals consistent, the Joanna Briggs Institute (JBI) Critical Appraisal Tool Studies will be used. The goal of assessment of risk of bias (critical appraisal) by using these checklists is to assess the methodological quality of a study and to determine the possibility of bias in its design, conduct and analysis.[45] The checklists consist of several items with the response options 'yes', 'no', 'unclear' and 'not applicable', and cover sample details, the validity and the reliability of the applied measures, identification of confounders, follow-up time and losses, and the adequacy of the statistical analysis applied. The critical appraisal checklists used will be the JBI Critical Appraisal Checklist for Analytical Cross-Sectional Studies (8-item checklist) for cross sectional studies and the JBI Critical Appraisal Checklist for Cohort Studies (12-item checklist) to appraise cohort studies. Each study receives a total score consisting of how many items on the appropriate appraisal tool are satisfactorily met: out of 8 and out of 12, respectively. These checklists can be consulted online at https://jbi.global/critical-appraisal-tools.

The level of evidence, strengths and limitations of each manuscript included in the systematic review will also be evaluated. Level of evidence will be assigned based on the criteria of the Rating System for the Hierarchy of Evidence for Intervention/Treatment Questions developed by Melnyk and Fineout-Overholt[46]: level I (Evidence from a systematic review or meta-analysis of all relevant RCTs), level II (Evidence obtained from well-designed RCTs), level III (Evidence obtained from well-designed controlled trials without randomisation), level IV (Evidence from well-designed case–control and cohort studies), level V (Evidence from systematic reviews of descriptive and qualitative studies), level VI (Evidence from single descriptive or qualitative studies) and level VII (Evidence from the opinion of authorities and/or reports of expert committees).

Study methodology and level of evidence ratings will be used to assess the robustness and confidence in study findings. Ratings of each reviewer will be compared using inter-rater agreement (Cohen's kappa),[44] and any disagreements will be resolved by discussion during a consensus meeting; a third member of the review team will be consulted if a consensus is not reached.

Data synthesis

A systematic narrative synthesis[47 48] will be conducted with information presented in text and tables to summarise and explain the methodological characteristics, strengths and limitations, and findings of the included studies. Tables and narrative summaries will compile and explore the relationship and findings both within and between included studies, in line with the guidance from the PRISMA 2020 recommendations[36] and the Centre for Reviews and Dissemination.[27] Synthesis will be conducted by the first and second authors, and reviewed by the third author, with discussion and final agreement involving all review authors.

This systematic review will include a quantitative meta-analysis. These statistical analyses will be performed using the meta-package[49] in statistical software R based on the random effects model. Meta-analysis will be performed by the third and fourth authors. The p values will be two sided and values <0.05 will be considered statistically significant. The effect of interest is the association between CRCI and work-related outcomes expressed as a correlation. We will calculate the pooled z values using a Pearson correlation coefficient transformed by the Fisher z-transformation. If study values for the Pearson correlation coefficient (r) are not available, the Pearson correlation coefficient (r) will be calculated from the existing Spearman correlation coefficient (r_s), standardised regression coefficient (β), or OR. Using this transformation, it will be possible to convert the data for correlation to z-scores (normal distribution) to obtain approximate normality and then calculate the mean and standard errors of the transformed correlation. The transformation will be performed taking into account Lipsey and Wilson[50] recommendations, using the Campbell Collaboration online calculator (https://www.campbellcollaboration.org/escalc/html/EffectSizeCalculator-R3.php).[51–53]

Statistical consistency and heterogeneity of the studies will be tested by the $\chi 2$ test and quantified by the Higgins I^2 statistic. Studies with an I^2 value of <25%, ~50% and ~75% will be considered to have low, moderate and high heterogeneities, respectively.[54]

Subgroup analysis

Subgroup analyses will be conducted to investigate the possible source(s) of heterogeneity. To access the stability of the meta-analysis results, a sensitivity analysis will be conducted by omitting individual studies in turn and transforming the random effect model into the fixed-effects model. Furthermore, as the existence of subgroups and heterogeneity is expected, we will undertake random-effects meta-regression analyses if at least 10 studies were collected regarding the primary outcome; this analysis will allow us to examine the impact of important factors and effect modifiers on our results. We will conduct meta-regression analyses to examine, for instance, the association between variables known to adversely impact CRCI and work-related outcomes, including, among others, age, type of cancer and treatment, and presence of anxiety or depression. Meta-regression analyses will serve to investigate unexplained heterogeneity between studies. Each study will be weighted in the regression models using the inverse of its variance; studies with the lowest amount of variance will be given a bigger weight in the regression model than those with the largest amount of variance. The association between each variable of interest and the primary outcome will be illustrated in table format where, for each variable, we will report its regression coefficient (B), SE, 95% CI, and statistical significance. To perform

the meta-regressions, we will use the r2jags package[55] in statistical software R.

Meta-bias(es)

Visual inspection of funnel plots for overall survival and a complemental Egger's test to quantify the plot's asymmetry will be used to determine the potential publication bias.

Confidence in cumulative evidence

The strength of the body of evidence will be assessed using the Grading of Recommendations Assessment, Development and Evaluation system.[56]

Patient and public involvement

This article reports a protocol of a systematic review with meta-analysis that will be based on previously published data. Therefore, patients and/or public were not involved.

DISCUSSION

Understanding the impact of CRCI on work-related outcomes is important, considering the implications for quality of life and other areas of the cancer survivor life.[23] To the best of our knowledge, this study will be the first to present a systematic review with meta-analysis of quantitative studies published in peer-reviewed journals regarding the relationship between CRCI and work-related outcomes. Following the PRISMA-P guidelines, the protocol was previously registered in PROSPERO, to help avoid duplication. Multiple bibliographic databases will be systematically searched to ensure saturation of data, and two independent reviewers will perform study selection, data extraction and risk of bias assessment to reduce personal bias. This review will advance the field of CRCI research by investigating how CRCI influences work-related outcomes and examining how strong this relationship is, and, consequently, this will allow to identify potential targets of intervention, proposing clinical implications of the findings.

It should be noted that there might be limitations in this review. There may be some clinical heterogeneities due to differences in the type of cancer, type of treatment received, outcome measures and methods/tools, as well as due to definitions of work-related outcomes among the included studies. This may have a certain impact on the results of the meta-analysis. There may also be a risk of publication bias as we will only include published articles. Finally, this review will not include qualitative studies, considering that the primary goal is to determine the strength of the relationship between CRCI and work-related outcomes, given that the existence of a relationship has already been documented previously;[23] however, this may limit the contextualisation of our findings by not having a complete understanding of the cancer survivors' experiences.

ETHICS AND DISSEMINATION

Ethics approval is not required for this review, because it relies on secondary data. Any modification/amendment to the systematic review protocol will be submitted to review and approval on the PROSPERO registry and described in the final report of the systematic review. The work is planned to be completed by February 2023. The systematic review findings will be published in a peer-review indexed journal, presented at scientific meetings and included in a chapter of a Doctoral thesis (first author).

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Contributors AFO is the guarantor of the review. AFO conceived the study idea, and together with SF, AT, IMS and DVA developed the design of the protocol, including development of the search strategy, selection criteria, risk of bias assessment strategy and data extraction criteria. JDR and AT designed the meta-analysis protocol. DVA provided expertise on CRCI and work-related outcomes. AFO and SF wrote the first draft of the manuscript. All authors critically read, provided feedback and approved the final manuscript.

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