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Effect of different types of exercise on health-related quality of life during and after cancer treatment: a protocol for a systematic review and network meta-analysis

Esther Ubago-Guisado,[1] Luis Gracia-Marco,[2,3] Iván Cavero-Redondo,[1,4] Vicente Martinez-Vizcaino,[1,5] Blanca Notario-Pacheco,[1] Diana P Pozuelo-Carrascosa ,[1] Esther G Adalia,[1] Celia Álvarez-Bueno [1,4]

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For numbered affiliations see end of article.

Correspondence to
Iván Cavero-Redondo;
Ivan.Cavero@uclm.es

ABSTRACT

Introduction Cancer (and survival) is known to affect the quality of life. Strategies as physical activity and exercise during and after cancer may improve health-related qualify of life (HRQOL) outcomes and are, therefore, of clinical and public health importance. To the best of our knowledge, comparative evidence of the effect of the different types of exercise on improving HRQOL in cancer patients has not been synthesised thus far. We aim to conduct a systematic review and network meta-analysis in order to synthesise all available evidence regarding the effect of different types of exercise interventions on HRQOL during and after cancer treatment.

Methods and analysis MEDLINE (via PubMed), Web of Science, Embase, The Cochrane Library and SPORTDiscus will be searched from inception to December 2018 for relevant randomised controlled trials (RCTs) and non-RCTs. Studies assessing physical activity and exercise interventions in cancer patients (during treatment) and survivors (after treatment) will be selected. Two independent reviewers will identify eligible studies. After quality appraisal and data extraction, we will conduct meta-analyses for outcomes of interest, including data from mental and physical dimensions of cancer-specific and/or generic HRQOL questionnaires. Risk of bias assessments will be completed using the Quality Assessment Tool for Quantitative Studies. Study heterogeneity will be measured by the I^2 statistic. Bayesian (and traditional approach) network meta-analysis will be performed when possible to determine the comparative effect of the different physical activity or exercise interventions.

Ethics and dissemination This systematic review and network meta-analysis will synthesise evidence on the effect of different types of exercise interventions on HRQOL during and after cancer treatment. The results will be disseminated by publication in a peer-reviewed journal and through scientific conferences and symposia. Ethical approval will not be required because the data used for this work will be exclusively extracted from published studies.

PROSPERO registration number CRD42019125028.

Strengths and limitations of this study

- This study presents an explicit and replicable methodology for analysing the effect of different types of physical exercise on health-related quality of life during and after cancer treatment, enhancing transparency of research, reducing publication bias, preventing selective publication and selective reporting of research outcomes.
- The publication of this protocol for a systematic review and network meta-analysis prevents unnecessary duplication of research, helping researchers to know which criteria for inclusion of trials are planned to be considered in the systematic review and network meta-analysis
- The assessment of risk of bias of the selected studies and heterogeneity among studies included, with particular reference to sample characteristics, is a featured point in this evidence review.
- Potential limitations of this research could be publication bias, information bias, poor statistical analysis and inadequate reporting of methods and findings within the included studies.
- This work will follow the existing guidelines included in the Preferred Reporting Items for Systematic Review and Meta-Analysis and the Cochrane Collaboration Handbook, and it will take into account potential risks of bias for each study.

INTRODUCTION

Cancer is a major cause of burden of disease worldwide and is responsible for one out of three deaths globally.[1 2] However, as a consequence of early diagnosis and timely treatment strategies, survival rates are improving in such a way that cancer is now recognised as a chronic disease. Although improvements in the effectiveness of treatment options could improve survival,[3] they also have a negative impact on physical and psychological

functions such as depression, anxiety, fatigue, pain, sleep quality and stress, all of which can affect the quality of life of cancer patients.[4]

Health-related qualify of life (HRQOL) is a multidimensional construct reflecting patients' perceptions regarding the effect of disease and its treatment on their physical, psychological and social functioning, and well-being.[5] Importantly, growing evidence confirms that cancer survivors, especially younger patients, continue experiencing the detrimental effects of the disease not only during the early years after treatment, but also in the long term.[6] Thus, since cancer must be considered a chronic disease with a negative impact on the physical, social and emotional life of cancer survivors,[7] strategies to improve HRQOL outcomes during and after cancer are of clinical and public health importance.

Physical activity and exercise interventions are powerful tools associated with numerous benefits in terms of the HRQOL of cancer patients[8–13] and survivors,[9 10 14 15] including improvement in cardiorespiratory and muscular fitness, reduction in fatigue and improvement in body composition and well-being (ie, depression, anxiety, sleep quality and quality of life). As such, cancer patients and survivors have been encouraged to undertake regular exercise.[16 17] However, the benefits that different types of exercise have on HRQOL are yet to be extensively studied.

There is a recent systematic review and network meta-analysis by Hilfiker *et al*[18] that evaluated different types of exercise and/or other non-pharmaceutical interventions on cancer-related fatigue in any type of cancer during or after treatment. They found strong evidence that relaxation, yoga or cognitive–behavioural therapy, combined with physical activity or resistance or aerobic training, reduces cancer-related fatigue substantially more than usual care.[18]

To the best of our knowledge, comparative evidence of the effect of the different types of exercise on improving HRQOL in cancer patients has not been synthesised thus far. To achieve this, a network meta-analysis will be performed. Briefly, network meta-analysis is a relatively recent technique which extends the principles of meta-analysis to the evaluation of multiple treatments simultaneously in a single analysis by combining direct and indirect evidence. Therefore, we aim to conduct a systematic review and network meta-analysis in order to synthesise all available evidence regarding the effect of different types of exercise interventions on HRQOL during and after cancer treatment.

METHODS AND ANALYSIS

This protocol has been registered within the PROSPERO database for systematic reviews and meta-analyses (registration number: CRD42019125028). The protocol has been designed and reported following the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) statement[19] and the Cochrane Collaboration Handbook.[20]

Inclusion/exclusion criteria for study selection

Type of studies

Because of the likely scarcity of studies, in addition to the barriers for randomisation of some interventions in cancer patients, the eligible studies will include randomised controlled trials, cluster randomised trials, cross-over trials, non-randomised experimental studies and two-arm prepost studies written in English or Spanish. For the cluster randomised trials, only the studies including the number of participants as unit of analysis will be included. For the cross-over trials, since the wash out period could represent an additional source of variability we will consider the outcomes of the first period. Only peer-reviewed publications will be included.

Type of participants

Studies assessing physical activity and exercise interventions in cancer patients (during treatment) and survivors (after treatment) will be selected, regardless of the age of the participants or cancer site. Cancer patients (during treatment) will refer to those that received surgery and/or undergone chemotherapy, radiotherapy or immunotherapy as an initial cancer treatment or as a treatment for metastasis or cancer recurrence. Cancer survivors (after treatment) will refer to those not receiving chemotherapy, radiotherapy or immunotherapy. Studies including both types of patients will be classified as mixed. When more than one study provides data from the same sample, we will only consider the one presenting the most detailed results or providing the longest follow-up data. However, data regarding sample characteristics could be extracted from multiple reports to obtain the most complete information.

Type of interventions

Eligible studies will report any type of physical exercise (aerobic, resistance, anaerobic, high-interval training, balance, stretching, alternatives (Pilates, yoga, Tai Chi) or a combination (eg, aerobic + resistance)). Physical exercise will be understood as repeated bouts over time involving more than one session/week with a duration of at least 4 weeks. However, studies combining physical activity and/or exercise with other health-related interventions, such as nutritional interventions, will be excluded when data cannot be separately extracted. Other intervention-related characteristics such as intensity or supervision will be retrieved from each included study.

Type of outcome measurements

Overall HRQOL and specific HRQOL domains (eg, mental and physical domains) from cancer-specific and/or generic HRQOL questionnaires will be selected for the meta-analysis. If the data are available and reliable scales were used, the studies will be combined in a meta-analysis.

Table 1 Search strategy

cancer OR tumour OR tumor OR oncology OR chemotherapy OR radiotherapy	AND	exercise OR “physical activity” OR aerobic OR resistance OR anaerobic OR muscular OR strength OR cardiovascular OR flexibility OR balance	AND	well-being OR depression OR anxiety OR fatigue OR “sleep quality” OR “quality of life”

Search strategy

The literature search will be conducted in the following electronic databases from inception to December 2018: MEDLINE (via PubMed), Web of Science, Embase, The Cochrane Library, SPORTDiscus and CINAHL. Searches for unpublished studies will be conducted at OPEN GRAY, ProQuest dissertations & Thesis Global, Theseo, Networked digital library of theses and dissertations and Google Scholar. The search strategy will include the following text free terms (table 1): (cancer OR tumour OR tumor OR oncology OR chemotherapy OR radiotherapy) AND (exercise OR “physical activity” OR aerobic OR resistance OR anaerobic OR muscular OR strength OR cardiovascular OR flexibility OR balance) AND (well-being OR depression OR anxiety OR fatigue OR pain OR stress OR “sleep quality” OR distress OR HRQOL OR QOL OR “physical functioning” OR “mental functioning” OR “quality of life”). In addition, we will explore the reference lists of included articles and retrieve those studies that potentially meet the inclusion criteria.

There will be no limitations on the date of publication or on the location of the study. A librarian was consulted to draft the search strategy. The literature search will be independently conducted by two reviewers, and disagreements will be solved by consensus or involving a third researcher.

Selection of studies and data extraction

Two independent reviewers will identify eligible studies by screen titles and abstracts, after removing duplicate works using Endnote software (Thomson Reuters). Reviewers will then examine the full texts and those that do not meet the selection criteria will be excluded, verifying the reasons for exclusion. Inconsistencies or disagreements will be solved by consensus or involving a third researcher. The process of identifying, screening and including or excluding studies will be shown using the PRISMA flow chart (figure 1).[19]

The following data will be extracted from the original reports by the reviewers: (1) first author and year of publication, (2) country of the study where data were collected, (3) length of follow-up, (4) sample characteristics (age, sample size, body mass index, stature, weight, type of population) (5) cancer characteristics (cancer type and stage of treatment), (6) intervention characteristics (type of exercise, length, frequency) and (7) outcome measures (baseline and/or follow-up values).

Assessment of risk of bias

The methodological quality of the RCTs will be assessed using the Cochrane Collaboration’s tool for assessing risk of bias (RoB2).[21] This tool includes five domains: (1) bias arising from the randomisation process, (2) bias due to deviations from intended interventions, (3) bias due to missing outcome data, (4) bias in measurement of the outcome and (5) bias in selection of the reported results (online supplementary file 1). To assess the risk of bias in non-RCTs, the Quality Assessment Tool for Quantitative Studies will be used.[22] This tool evaluates seven domains: (1) selection bias, (2) study design, (3) confounders, (4) blinding, (5) data collection methods, (6) withdrawals and (7) dropouts. For both quality assessment tools, each domain will be assessed as ‘strong’, ‘moderate’ or ‘weak’, and studies will be classified as low risk of bias (with no weak ratings), moderate risk of bias (with one weak rating) or high risk of bias (with two or more weak

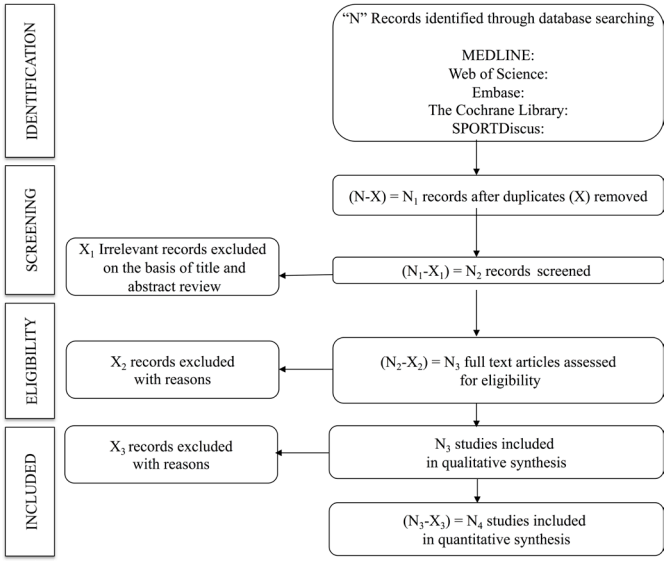

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of identification, screening, eligibility and inclusion of studies.

ratings; online supplementary file 2). The agreement rate between reviewers will be reported by calculating kappa statistics. Any inconsistencies will be resolved by the third researcher.

Grading the quality of evidence

The Grading of Recommendations, Assessment, Development and Evaluation tool will be used to assess the quality of the evidence and make recommendations.[23] Each outcome could obtain a high, moderate, low or very low evidence value, depending on the study design, risk of bias, inconsistency, indirect evidence, imprecision and publication bias. By default, RCTs will receive an initial grade of high and will be downgraded based on the following prespecified criteria: risk of bias (weight of trials showing risk of bias by the RoB2 tool), inconsistency (substantial unexplained inter-study heterogeneity, I^2>50% and p<0.10), indirectness (presence of factors that limit the generalisability of the results), imprecision (the 95% CIs for effect estimates are wide or cross a minimally important difference for benefit or harm) and publication bias (significant evidence of small-study effects).

Statistical analysis

The reviewers will design qualitative ad hoc tables to summarise the main characteristics of the selected studies (table 2), describing the types of direct and indirect comparisons. The feasibility of doing a meta-analysis will be assessed after data extraction is completed. If a meta-analysis is not feasible, a narrative synthesis will be done. If a meta-analysis is possible, the random effects models based on the DerSimonian-Laird method will be used to perform a standard meta-analysis for each direct comparison between two interventions.[24] Study heterogeneity will be measured by the I^2 statistic and evaluated according to the following criteria: no relevant heterogeneity (0%–40%), moderate heterogeneity (30%–60%), substantial heterogeneity (50%–90%) and considerable heterogeneity (75%–100%).[25] The corresponding p values will also be considered.

To compare the effect of the different types of physical activity or exercise interventions, a pairwise meta-analysis for direct and indirect comparisons between interventions and control/non-intervention will be carried out. Additionally, the effects of each intervention will be combined using Bayesian methods of the Markov-Monte Carlo chain using STATA V.15 software. The model developed by Dias *et al*[26] for the UK National Institute for Health and Care Excellence Decision Support Unit will be used.

As the indirect comparisons are not protected by randomisation and maybe confounded by differences between the studies, we will check that all the participants in the studies included in the network meta-analysis have the same baseline characteristics (on average) that might modify the treatment effect.[27]

A graphic representation of the network will be used to assess the strength of the evidence, which will show the number of articles from which the information presented

Table 2 Characteristics of studies included in the meta-synthesis of evidence

Study characteristics			Population characteristics at baseline			Outcome			Intervention			
First author and year of publication	Country	Design	Age (years (mean±SD))	Sample size (n (% male))	Cancer-type/time period	Stature (cm)	Weight (kg)	Method	Baseline values	Follow-up values	Type	Duration of exercise (weeks)	Volume of exercise (hours per week)

comes from (treatment nodes), the comparisons that have direct comparisons and those that present indirect or mixed comparisons and the number of patients with different comparisons, in such a way that confidence in the results will be increased.[28]

The loop-specific approach will be used to evaluate the presence of inconsistency in network meta-analysis models locally.[29] Difference (inconsistency factor) with 95% CI between direct and indirect estimations for a specific comparison will be calculated to assess the presence of inconsistency in each loop. Inconsistency will be defined as disagreement between direct and indirect evidence with a 95% CI excluding 0.

To rank the physical activity and/or exercise interventions, the probability of each intervention being the most effective will be presented graphically by rankograms. In addition, the surface under the cumulative ranking (SUCRA) will be calculated for each intervention. SUCRA represents an inversely scaled average rank of the intervention, with a numerical value between 0 and 1, the highest value meaning that the intervention always ranks first and the lowest value that it ranks last. The best intervention would obtain a value close to 1 and the worst intervention a value close to 0.[30]

Subgroup analyses

Subgroup analyses will be performed based on the type of participants, type of cancer, type of exercise performed and duration of the intervention, because these may be major factors causing heterogeneity.

Sensitivity analysis

Sensitivity analyses will be performed by excluding the included studies from the analysis one by one and comparing the results.

Patient and public involvement

Cancer patient organisations will be involved in both the discussion of the study results and the dissemination of the findings among stakeholders.

ETHICS AND DISSEMINATION

The resulting findings of this systematic review and network meta-analysis could help us develop high-quality recommendations about the type of physical activity and/or exercise during and after cancer treatment in order to improve the HRQOL. Findings will be disseminated to academic audiences through peer-reviewed publications, as well as to clinical audiences, patients' associations and policy-makers through conferences and symposia.

DISCUSSION

The health benefits of an active lifestyle during and after cancer treatment in the adult population have been described in the scientific literature. During cancer treatment, a systematic review of 14 RCTs in patients undergoing chemotherapy reported a positive effect of resistance and aerobic training in cardiorespiratory and muscular fitness.[8] Likewise, a systematic review of 16 RCTs concluded that the practice of aerobic and/or resistance exercise during therapy (chemotherapy or radiotherapy) improved muscular strength.[31] Another meta-analysis including 25 RCTs demonstrated the beneficial effects of aerobic, strength and flexibility exercises during treatment in reducing the levels of cancer-related fatigue.[9] Similarly, two meta-analyses of 6 and 9 RCTs, respectively, found that patients enrolled in aerobic exercise programme during cancer treatment had better sleep quality[12] and depression outcomes,[10] although the latter also included a strength training component.

Post-treatment exercise has also been associated with benefits to physical fitness, fatigue, mental health and well-being. Thus, cancer survivors practicing aerobic and resistance exercise improved cardiorespiratory (evidence from seven RCTs) and muscular (evidence from three RCTs) fitness.[14] In addition, exercise programme including aerobic, strength and flexibility training have shown benefits towards levels of fatigue (15 RCTs),[9] quality of life (11 RCTs),[15] anxiety (4 RCTs)[15] and depression (9 RCTs).[10] Finally, evidence from a meta-analysis showed improvements in body weight (16 RCTs) and body fat (10 RCTs) following aerobic and resistance exercise programme.[14]

In our opinion, the scientific literature lacks a meta-synthesis of evidence comparing the benefits of different exercise interventions on HRQOL during and after cancer treatment. A recent systematic review that included a network meta-analysis assessed the effects of different types of exercise and other non-pharmaceutical interventions on cancer-related fatigue during and after cancer treatment.[18] Although cancer-related fatigue is one of the most common and distressing symptoms of cancer,[18] it is only one of the many components that define the multidimensional concept of HRQOL.[5] Recent works from Buffart *et al*[32] and Sweegers *et al*[4] evaluated the effect of exercise on quality of life and physical function in cancer patients. Our systematic review and network meta-analysis will synthesise all the available evidence on the effects that different types of exercise have on the different domains (including both physical and mental domains) of HRQOL during and after cancer treatment, using, apart from the traditional meta-analysis methodology, a comprehensive network meta-analysis approach that allow us to provide both direct and indirect intervention's comparisons.

Potential limitations of this research could be publication bias, information bias, poor statistical analysis and inadequate reporting of methods and findings within the included studies.[33] In addition, it is likely that we find studies in which the treatment lasted longer than the exercise interventions performed, and therefore, we might not be able to firmly conclude about the optimal exercise dose/duration. This work will follow the existing guidelines included in the PRISMA[19] and the Cochrane Collaboration Handbook.[20] In addition, it will take into account potential risks of bias for each study.

Given the importance of health outcomes in terms of a good quality of life in cancer patients and survivors, a more detailed and comprehensive review on the effects of different types of exercise on health parameters in cancer survivors is necessary. This protocol provides a clear and structured procedure for maximising the extraction of relevant information, and provides summarised information. The findings of this systematic review and network meta-analysis could be of interest to patients, practitioners, researchers and policy-makers since they will provide evidence that will assist in the development of effective exercise and/or physical activity programme in these populations.

Author affiliations
[1]Universidad de Castilla-La Mancha, Health and Social Research Center, Cuenca, Spain
[2]PROFITH 'PROmoting FITness and Health Through Physical Activity' Research Group, Sport and Health University Research Institute (iMUDS), Department of Physical and Sports Education, Faculty of Sport Sciences, University of Granada, Granada, Spain
[3]Growth, Exercise, Nutrition and Development Research Group, Universidad de Zaragoza, Zaragoza, Spain
[4]Universidad Politecnica y artística del Paraguay, Asunción, Paraguay
[5]Universidad Autónoma de Chile, Facultad de Ciencias de la Salud, Talca, Chile

Contributors EU-G, LG-M, IC-R and CA-B conceived and designed the protocol. BN-P, DPP-C and EGA participated in the development of the search strategy. BN-P, DPP-C and EGA planned the data extraction and statistical analysis. EU-G, VM-V, IC-R and CA-B tested the feasibility of the study. EU-G drafted the manuscript. VM-V, LG-M, IC-R and CA-B revised the manuscript. All authors have approved and contributed to the final written manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval Ethical approval and informed consent of patients will not be required because the data used for this work will be exclusively extracted from published studies. All the included trials will comply with the current ethical standards and the Declaration of Helsinki.

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ORCID iDs
Diana P Pozuelo-Carrascosa http://orcid.org/0000-0002-0527-5498
Celia Álvarez-Bueno http://orcid.org/0000-0003-4250-5309

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