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Review

Comparative effects of different types of exercise on health-related quality of life during and after active cancer treatment: A systematic review and network meta-analysis

Vicente Martínez-Vizcaíno [a,b], Iván Cavero-Redondo [b,*], Sara Reina-Gutiérrez [a], Luis Gracia-Marco [c], José J. Gil-Cosano [c], Bruno Bizzozero-Peroni [a,d], Fernando Rodriguez-Artalejo [e,f,g], Esther Ubago-Guisado [g,h,i]

[a] *Universidad de Castilla-La Mancha, Health and Social Research Center, Cuenca 16071, Spain*
[b] *Facultad de Ciencias de la Salud, Universidad Autónoma de Chile, Talca 3460000, Chile*
[c] *PROFITH (PROmoting FITness and Health through physical activity) Research Group, Department of Physical Education and Sports, Faculty of Sport Sciences, Sport and Health University Research Institute (iMUDS), University of Granada, Granada 18012, Spain*
[d] *Higher Institute for Physical Education, Universidad de la República, Rivera 40000, Uruguay*
[e] *Department of Preventive Medicine and Public Health, School of Medicine, Universidad Autónoma de Madrid, Madrid 28029, Spain*
[f] *IdiPaz (Instituto de Investigación Sanitaria Hospital Universitario La Paz), Madrid 28029, Spain*
[g] *Epidemiology and Control of Chronic Diseases, CIBER of Epidemiology and Public Health (CIBERESP), Madrid 28029, Spain*
[h] *Cancer Registry of Granada, Escuela Andaluza de Salud Pública, Granada 18011, Spain*
[i] *Cancer Epidemiology Group, Instituto de Investigación Biosanitaria, Granada 18012, Spain*

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Abstract

Background: The positive influence of most types of exercise has been reported repeatedly, but what the most effective exercise approaches are for improving health-related quality of life (HRQoL) in people with cancer remains unknown. The aim of this systematic review and network meta-analysis was to synthesize the evidence from intervention studies to assess the effects of different types of exercise on HRQoL during and after cancer treatment.

Methods: MEDLINE, SPORTDiscus, the Cochrane Library, Web of Science, and Scopus were searched for randomized controlled trials aimed at testing the effects of exercise interventions meant to improve HRQoL in people with cancer. Separate analyses were conducted for HRQoL as measured by general and cancer-specific questionnaires. We also evaluated whether the effects of exercise were different during and after cancer treatment in both the physical and mental HRQoL domains.

Results: In total, 93 studies involving 7435 people with cancer were included. Network effect size estimates comparing exercise intervention *vs.* usual care were significant for combined exercise (0.35, 95% confidence interval (95%CI): 0.14−0.56) for HRQoL as measured by general questionnaires, and for combined (0.31, 95%CI: 0.13−0.48), mind−body exercise (0.54, 95%CI: 0.18−0.89), and walking (0.39, 95%CI: 0.04−0.74) for HRQoL as measured by cancer-specific questionnaires.

Conclusion: Exercise programs combining aerobic and resistance training can be recommended to improve HRQoL during and after cancer treatment. The scarcity and heterogeneity of these studies prevents us from making recommendations about other exercise modalities due to insufficient evidence.

Keywords: Cancer; Exercise; HRQoL; Physical activity

1. Introduction

Recent estimates predict that more than 28 million new cancer cases will occur in 2040 worldwide, which represents a 47% increase from 19.3 million cases in 2020.[1] In parallel

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* Corresponding author.
E-mail address: Ivan.Cavero@uclm.es (I. Cavero-Redondo).

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with this increasing incidence, the number of people living with cancer is expected to increase due to earlier diagnoses and treatment improvements, the decline in cardiovascular mortality, and the ageing of the population.[2] Maintaining the functional capacity and overall health-related quality of life (HRQoL) of cancer survivors will challenge health and social services.

HRQoL is a construct that reflects the perceptions of patients regarding their well-being, which is mainly determined by their social, physical, and psychological functioning.[3] Cancer negatively impacts all dimensions of the HRQoL of patients not only during treatment and the early years after diagnosis but also over the long term.[4] Moreover, cancer therapies are often associated with direct adverse effects such as cardiotoxicity, which greatly impairs the cardiorespiratory capacity, but there are also some indirect effects, such as deconditioning and weight gain. As a consequence, both the direct and indirect effects of treatments further undermine the HRQoL of cancer patients.[5] Therefore, strategies to mitigate the negative impacts of cancer in each of its dimensions are important from a clinical and public health perspective.

Among such strategies, exercise is the main nonpharmacological intervention suggested for producing improvements in the different dimensions of HRQoL. It has been reported that exercise may attenuate the development of metastases,[6] enhance the immune system by fostering natural killer cells,[7] decrease low-grade inflammation and insulin resistance via the release of myokines triggered by the contraction of skeletal muscle,[8] improve cardiorespiratory fitness,[9] and enhance the effects of systemic therapies by improving tumoral microenvironment perfusion and thereby mitigating the aggressiveness of the cancer phenotype.[10]

There is growing interest in studying the effects of exercise interventions on the physical, psychological, and social dimensions of HRQoL. Several systematic reviews have documented improvements in cardiorespiratory fitness, fatigue, strength, physical function,[10,11] and psychological outcomes (depression, anxiety, and sleep quality).[12] Likewise, a systematic review of systematic reviews concluded that, for all cancer types, exercise before, during, and after treatment elicits benefits with respect to a wide variety of adverse health consequences.[12] Finally, in 2018, an international multidisciplinary consensus roundtable was convened to update available evidence on the benefits of physical activity and exercise for patients with cancer. They recommended exercise prescription during and after treatment as a therapeutic strategy to mitigate the adverse effects of cancer diagnosis and treatment, including decrease in physical function, greater levels of fatigue, anxiety, and depressive symptoms, and lower HRQoL.[13] Still, although a positive influence has been reported for most exercise modalities, it remains unknown what the most effective exercise approaches for improving the HRQoL of people with cancer are.

We conducted this systematic review and network meta-analysis (NMA) to synthesize the evidence provided by intervention studies aimed at assessing the effects of different types of exercise on HRQoL during and after cancer treatment. We distinguish between studies that assess HRQoL with cancer-specific *vs.* general questionnaires as well as between the physical and mental domains of HRQoL. NMA techniques allow us to comparatively evaluate the effects of different types of exercise on HRQoL in people with cancer.

2. Methods

This NMA was reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols statement extension for PRISMA−NMA guidelines[14] (Supplementary Table 1) and conducted following the Cochrane Handbook for Systematic Reviews of Interventions recommendations.[15] This systematic review and NMA have been registered in International Prospective Register of Systematic Reviews (PROSPERO) (registration number: CRD42019125028), and its protocol has been published previously.[16] Approval was not requested from any institutional ethics research committee because this study did not include individual patient data and all studies were published previously.

2.1. Data sources and searches

The systematic search for studies was carried out through 5 databases (MEDLINE (via PubMed), SPORTDiscus, the Cochrane Library, Web of Science, and Scopus) from their inception to September 16, 2022 (Supplementary Tables 2 and 3). In the MEDLINE and Embase databases, the search was conducted using controlled (MeSH and Emtree vocabulary) and not controlled vocabulary. The search strategy was structured according to the Peer Review of Electronic Search Strategies 2015 guidelines.[17]

To perform the search, the following keywords were used: (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 ("quality of life" OR "QoL" OR "health related quality of life" OR "HRQoL" OR "life quality"). Furthermore, we searched for relevant studies in the reference lists of included articles and previous systematic reviews or meta-analyses, as well as using ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform, and the International Standard Randomized Controlled Trial Number Registry for all registered clinical trials and randomized controlled trials (RCTs). The study records were managed using Covidence software (Level 4; Covidence, Melbourne, VIC, Australia).

2.2. Eligibility

RCT studies concerning the effects of physical exercise on the HRQoL of cancer survivors were included in the meta-analysis. The inclusion criteria were as follows: (a) population: cancer patients (during treatment) and/or cancer survivors (after treatment) over 18 years of age; (b) intervention: type of exercise (aerobic, resistance training, combined exercise (aerobic and resistance), anaerobic, walking, stretching, and mind−body exercises (pilates, Tai Chi, and yoga)); (c) outcome: quality of life measured by general or cancer-specific questionnaires; and (d) comparison: inclusion of 2 or more groups (i.e., exercise *vs.* control group).

The exclusion criteria included: (a) quasi-experimental studies not including a comparison group; (b) studies of interventions combining exercise with diet or drug treatments; and (c) studies not written in English or Spanish (authors' languages).

2.3. *Study selection and data extraction*

The selection of studies was independently performed by 2 researchers (VMV and EUG). When agreement was not reached between them, a third reviewer (ICR) was consulted. The agreement rate between reviewers was 0.92 (calculated using κ statistics).

The following data were independently collected from each study that met the inclusion criteria: (a) first author and year of publication, (b) country of the study where data were collected, (c) design, (d) sample characteristics (age and sample size), (e) cancer characteristics (cancer type and stage of treatment), (f) outcome measures (baseline and/or follow-up values), and (g) intervention characteristics (type of exercise, length, frequency). When a lack of information was detected in any of the included studies, we contacted the authors through e-mail.

2.3.1. *Classification as "during" or "after" cancer treatment*

Most studies addressing the effects of exercise on HRQoL in cancer patients distinguish between benefits achieved during and after treatment.[11] Therefore, this study distinguishes between analyses that include patients receiving chemotherapy or radiotherapy as the initial cancer treatment or as treatment in the presence of metastasis or cancer recurrence, classifying these as "during", and those studies that include patients currently not on chemotherapy or radiotherapy, which were categorized as "after". Studies including both types of patients were classified as "both"; studies including patients receiving androgen suppression therapy without chemotherapy or radiotherapy were defined as "after".

2.3.2. *Missing data imputation*

For HRQoL (continuous variable) values, means and standard deviations were extracted when available. When standard deviations were not reported, they were calculated from standard errors, confidence intervals, or other measures. When the sample size was not provided in the analysis table, it was extracted from the descriptive statistics. If HRQoL data were missing, we used the number of individuals who met the response criteria as defined by the study's authors.[18]

2.3.3. *Categorization of available evidence*

Physical exercise refers to the subset of planned and repetitive physical activity aimed at improving physical fitness and, thus, maintaining a good health status.[19] The exercise interventions depicted in this NMA were classified as aerobic exercise (including interventions aimed at increasing heart rate and energy expenditure), resistance training (interventions aimed at increasing muscle strength and muscle power), walking, combined exercise (aerobic exercise and resistance training), stretching, and mind−body exercises (i.e., pilates, Tai Chi, and yoga; modalities of exercise that combine body movement, mental focus, and controlled breathing for improved strength, balance, and flexibility).

2.3.4. *Risk of bias assessment*

Once the information about the authors, dates, and sources of each included manuscript was blinded, 2 researchers (VMV and EUG) independently assessed the risk of bias. Disagreements were resolved by a third reviewer (ICR). The agreement rate between reviewers was 0.90 (calculated using κ statistics).

The risk of bias of the RCTs was assessed using the Cochrane Collaboration's tool for assessing risk of bias (RoB2).[20] This tool evaluates the risk of bias according to 5 domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Overall, there is a "low risk of bias" if all domains are classified as "low risk", there are "some concerns" if at least 1 domain is rated as "some concern", and there is a "high risk of bias" if at least 1 domain is rated as "high risk" or if several domains are rated as "some concerns".

2.3.5. *Grading the quality of evidence*

The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) tool was used to evaluate the quality of the evidence and make recommendations.[21] Each outcome obtained a high, moderate, low, or very low evidence value, depending on the design of the studies, risk of bias, inconsistency, indirect evidence, imprecision, and publication bias. The GRADE tool was used only for the pairwise meta-analysis.

2.4. *Data synthesis and statistical analysis*

The included studies were summarized qualitatively in an *ad hoc* table describing the types of direct and indirect comparisons. Our systematic review and NMA were carried out in accordance with the PRISMA−NMA statement[14] under a frequentist perspective in 5 steps. Separate analyses were conducted for HRQoL as measured by general and cancer-specific questionnaires. To display the relative accumulated available evidence on each modality of exercise, we designed a network geometry graph in which the nodes represent each type of exercise intervention and the edges correspond to direct head-to-head comparisons between interventions. The size of the nodes correlates to the number of participants for each type of exercise, and the thickness of the edges is proportional to the number of studies accumulated in trials that directly compare each pair of physical exercise interventions; the dashed lines represent indirect comparisons between any 2 interventions.[22] Second, to verify that the effects of direct interventions were consistent with those of indirect comparisons, we utilized the Wald test and, because of its low statistical power, used side-splitting as an additional consistency assessment. Third, we conducted pairwise meta-analysis for direct and indirect comparisons between interventions and control/non-interventions using the random effects DerSimonian−Laird method.[23] For this analysis we used the standardized mean difference (as effect size (ES)) between the change in HRQoL of intervention and control/non-intervention groups. We conducted analyses for effects on HRQoL during and after active treatment separately, and when possible, we analyzed physical and mental domains of HRQoL separately as well. For this analysis, we examined statistical heterogeneity by calculating the I^2 statistic, the values of which were considered not important (0%−40%), moderate (30%−60%), substantial (50%−90%), or considerable (75%−100%).[15] In addition, to determine the size and clinical relevance of heterogeneity, we calculated the τ^2 statistic; its degree of clinical relevance of heterogeneity was estimated as low when values were lower than 0.14, moderate when values ranged from 0.14 to 0.40, and substantial when values were higher than 0.40.[24] Fourth, the pooled effect of each intervention was performed using a frequentist approach of the NMA. Fifth, for the transitivity assessment, we used sensitivity to check that all the participants in the studies included in the NMA had the same baseline distribution (on average) of effect. Sensitivity analysis (systematic reanalysis while removing studies one at a time) was conducted to assess the robustness of the summary estimates. Lastly, once the ES estimates of the effects of exercise interventions were calculated, we ranked the interventions to identify superiority and presented them graphically using rankograms. Additionally, we estimated the surface under the cumulative ranking (SUCRA) for each intervention. SUCRA involves the assignment of a numerical value between 0 and 1 to simplify the classification of each intervention in the rankogram. The best intervention obtained a SUCRA value closest to 1, and the worst intervention obtained a value closest to 0.[22,25] We also calculated rank exercise modalities using the p score as the probability of being, comparatively to others, the best treatment option.[26]

Finally, publication bias was assessed through visual inspection of the funnel plots as well as by the method proposed by Egger.[27] Pairwise meta-analysis, frequentist NMA, and production of network graphs and resulting figures were performed using the network and network graph packages in Stata 16.0 (Stata Corp., College Station, TX, USA).

2.5. Data sharing

After the publication of this article, the full dataset will be available online in Mendeley Data, a repository of research data that allows the assignment of a permanent digital object identifier in such a way that the data can be easily referenced (doi: 10.17632/2c4y6k32g5.1).

2.6. Modifications to the initial protocol

Although the protocol initially included The Quality Assessment of Systematic Reviews and Meta-analyses of the National Heart, Lung, and Blood Institute for the assessment of the risk of bias, as the studies included are all clinical trials, this NMA followed the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions and used the RoB2 tool for the assessment of the risk of bias.

3. Results

3.1. Study characteristics

A total of 93 studies[28−120] were included in this NMA (Fig. 1). The characteristics of the included studies are shown in Supplementary Table 4. All included studies were RCTs. The most frequently reported type of exercise was combined exercise ($n = 39$ interventions), followed by resistance training ($n = 22$ interventions), aerobic exercise ($n = 19$ interventions), walking ($n = 10$ interventions), and mind−body exercises ($n = 10$ interventions). Furthermore, 8 studies had 3 arms (2 interventions and 1 control). In total, 3697 participants were randomly allocated to an exercise intervention and 3466 were assigned to a control group. Participants in exercise intervention groups and control groups showed no differences in age or baseline QoL scores.

3.2. Risk of bias and GRADE

The overall risk of bias for RCTs showed some concerns, especially due to the high risk of bias in most included studies. Specifically, for measurement of outcome and missing outcome data, respectively, 92 (98.9%) and 90 (96.8%) studies were scored as low bias; for randomization process and deviations from intentional interventions, respectively, 77 (82.8%) and 70 (75.3%) studies showed a low risk of bias (Supplementary Table 5).

The quality of evidence of each pairwise comparison was evaluated using the GRADE system. The quality of evidence and recommendations was classified as low in 82 peer

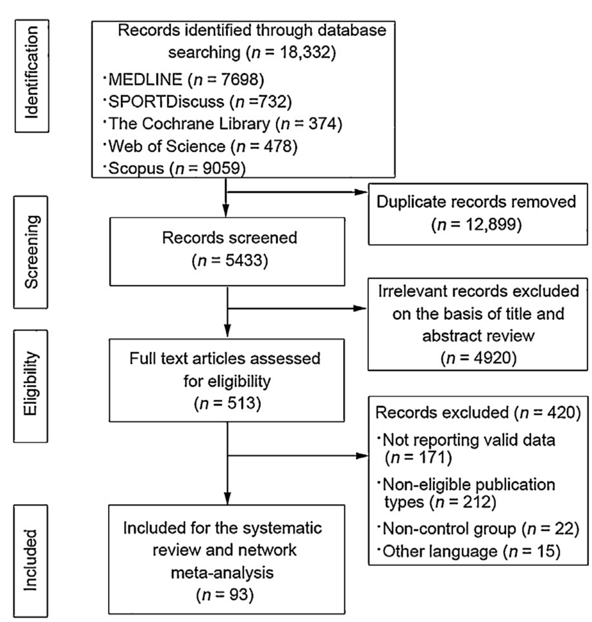

Fig. 1. Preferred Reporting Items for Systematic Reviews flowchart.

comparisons (73.9%) and very low in 29 comparisons (26.1%) (Supplementary Table 6).

3.2.1. *Exercise effects on HRQoL as measured by general and cancer-specific questionnaires*

Network maps of included comparisons testing the effects of different exercise modalities on HRQoL as measured by general and cancer-specific questionnaires are shown in Fig. 2. Table 1 shows the pairwise (upper diagonal) and NMA (lower diagonal) ES estimates. In the pairwise analyses, compared to the control, only the ES for combined exercise was significant (0.45, 95% confidence interval (95%CI): 0.16−0.74) for HRQoL as measured by general questionnaires; also significant were combined exercise (0.20, 95%CI: 0.10−0.29), aerobic exercise (0.14, 95%CI: 0.01−0.27), resistance training (0.17, 95%CI: 0.04−0.29), and walking (0.32, 95%CI: 0.09−0.55) for HRQoL as measured by cancer-specific questionnaires. Network ES estimates were significant for combined exercise (0.45, 95%CI: 0.16−0.74) for HRQoL as measured by general questionnaires and for combined exercise (0.31, 95%CI: 0.13−0.48), mind−body exercise (0.54, 95%CI: 0.18−0.89), and walking (0.39, 95%CI: 0.04−0.74) for HRQoL as measured by cancer-specific questionnaires. Risk of bias and indirectness contributions in the network analyses were assessed with the Confidence in NMA Web application and are presented in Supplementary Figs. 1−4.

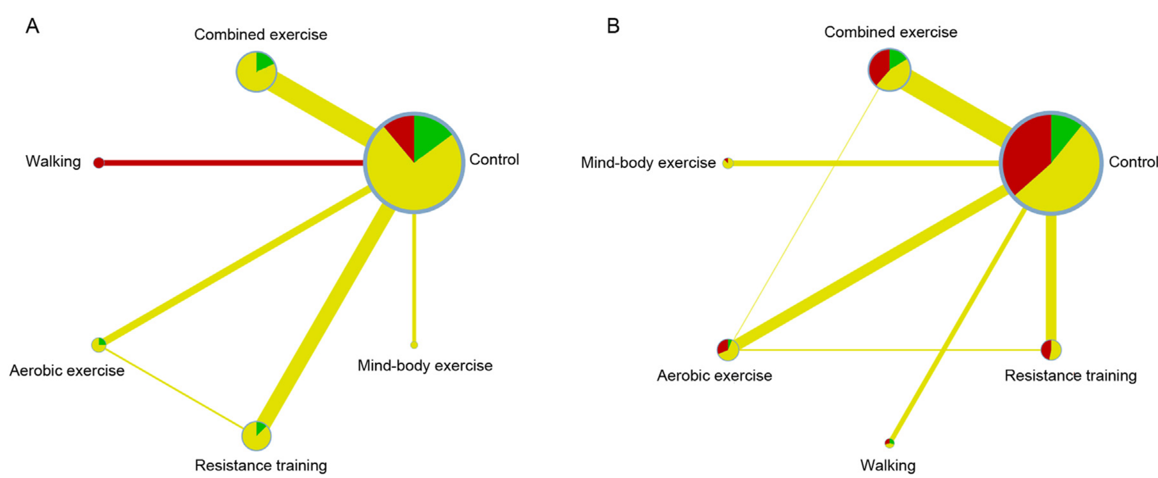

Fig. 2. Network of available comparisons between exercises interventions on quality of life as measured by (A) general questionnaires and (B) cancer-specific questionnaires. The size of the node is proportional to number of trial participants, and thickness of the continuous line connecting nodes is proportional to number of participants randomized in trials directly comparing the 2 treatments. Colored areas correspond with the proportion of studies for each node with respect to risk of bias assessment as follows: green for low risk, yellow for some concerns, and red for high risk of bias. The color of the lines corresponds with the average of the risk of bias assessment of the studies directly comparing the 2 interventions.

Table 1
League table of pooled effect sizes for general and cancer-specific questionnaires on quality of life.

A. Quality of life as measured by general questionnaires					
Control	0.12 (−0.12 to 0.35)	0.12 (−0.01 to 0.25)	0.35 (−0.17 to 0.88)	0.09 (−0.16 to 0.35)	**0.45 (0.16 to 0.74)**
0.15 (−0.22 to 0.52)	Walking	na	na	na	na
0.24 (0.00 to 0.49)	0.09 (−0.35 to 0.54)	Resistance training	na	−0.10 (−0.43 to 0.23)	na
0.58 (−0.39 to 1.55)	0.43 (−0.61 to 1.47)	0.34 (−0.66 to 1.34)	Mind−body exercise	na	na
0.20 (−0.18 to 0.58)	0.05 (−0.48 to 0.58)	−0.05 (−0.49 to 0.40)	−0.38 (−1.42 to 0.66)	Aerobic exercise	na
0.35 (0.14 to 0.56)	0.20 (−0.22 to 0.62)	0.11 (−0.21 to 0.42)	−0.23 (−1.22 to 0.76)	0.15 (−0.28 to 0.59)	Combined exercise
B. Quality of life as measured by cancer-specific questionnaires					
Control	**0.32 (0.09 to 0.55)**	**0.17 (0.04 to 0.29)**	0.40 (−0.17 to 0.97)	**0.14 (0.01 to 0.27)**	**0.20 (0.10 to 0.29)**
0.39 (0.04 to 0.74)	Walking	na	na	na	na
0.25 (−0.01 to 0.50)	−0.14 (−0.58 to 0.29)	Resistance training	na	0.06 (−0.30 to 0.42)	na
0.54 (0.18 to 0.89)	0.15 (−0.36 to 0.65)	0.29 (−0.15 to 0.73)	Mind−body exercise	na	na
0.20 (−0.05, 0.45)	−0.19 (−0.62 to 0.25)	−0.05 (−0.38 to 0.29)	−0.34 (−0.77 to 0.10)	Aerobic exercise	0.05 (−0.57 to 0.67)
0.31 (0.13 to 0.48)	−0.08 (−0.48 to 0.31)	0.06 (−0.25 to 0.37)	−0.23 (−0.63 to 0.17)	0.11 (−0.20 to 0.41)	Combined exercise

Notes: Data are effect sizes (95% confidence intervals). Effect sizes in bold are statistically significant. Positive effect sizes mean that the first intervention improves quality of life compared to the second intervention. Upper right triangle gives pooled effect sizes from pairwise comparisons (column intervention relative to row); lower left triangle gives pooled effect sizes from the network meta-analysis (row intervention relative to column).
Abbreviation: na = not available.

3.2.2. Exercise during and after treatment

Table 2 shows ES estimates for HRQoL during and after treatment as measured by general and specific questionnaires. During treatment, in the pairwise analyses (upper diagonal), compared to the control, combined exercise and aerobic exercise showed significant ES (0.56, 95%CI: 0.20−0.92 and 0.40, 95%CI: 0.02−0.78, respectively) for HRQoL as measured by general questionnaires; combined exercise, aerobic exercise, and resistance training also showed significant ESs (0.15, 95%CI: 0.03−0.27; 0.22, 95%CI: 0.05−0.40; and 0.15, 95%CI: 0.01−0.29, respectively) for HRQoL as measured by cancer-specific questionnaires. Network ES estimates were significant for combined exercise (0.44, 95%CI: 0.27−0.61) for HRQoL as measured by general questionnaires and for combined exercise (0.32, 95%CI: 0.03−0.61) and mind−body exercise (0.92, 95%CI: 0.34−1.51) for HRQoL as measured by cancer-specific questionnaires.

After treatment, no intervention showed a significant ES when general HRQoL questionnaires were used. When cancer-specific questionnaires were used, combined exercise and walking resulted in a significant effect in both pairwise (0.28, 95%CI: 0.12−0.44 and 0.26, 95%CI: 0.03−0.49, respectively) and network analyses (0.41, 95%CI: 0.22−0.60 and 0.35, 95%CI: 0.01−0.68, respectively).

3.2.3. Exercise effects on physical and mental domains

When the analyses were performed separately for the physical and mental domains, only combined exercise showed a statistically significant ES in both pairwise and network analyses (0.52, 95%CI: 0.23−0.82 for the physical domain and 0.59, 95%CI: 0.24−0.95 for the mental domain) (Table 3).

3.3. Probabilities

Mind−body exercise showed a higher probability of being the best treatment (62.8% for HRQoL measured by general questionnaires and 65.1% for HRQoL measured by cancer-specific questionnaire). The SUCRA value was higher for mind−body exercise for HRQoL measured by general questionnaires (77.0%) and for mind−body exercise for HRQoL measured by cancer-specific questionnaires (88.4%) (Fig. 3).

Table 2
League table of pooled effect sizes for general and cancer-specific questionnaires on quality of life by time period.

A. Quality of life as measured by general questionnaires (during treatment)					
Control	0.41 (−0.03 to 0.84)	0.11 (−0.18 to 0.39)	0.35 (−0.17 to 0.88)	**0.40 (0.02 to 0.78)**	**0.56 (0.20 to 0.92)**
0.60 (−0.08 to1.28)	Walking	na	na	na	na
0.21 (−0.21 to 0.62)	−0.39 (−1.19 to 0.40)	Resistance training	na	na	na
0.58 (−0.34 to 1.50)	−0.02 (−1.16 to 1.13)	0.38 (−0.63 to 1.39)	Mind−body exercise	na	na
0.55 (0.02 to 1.08)	−0.05 (−0.91 to 0.82)	0.35 (−0.33 to 1.02)	−0.03 (−1.10 to 1.03)	Aerobic exercise	na
0.44 (0.27 to 0.61)	−0.16 (−0.87 to 0.54)	0.23 (−0.21 to 0.68)	−0.15 (−1.08 to 0.79)	−0.11 (−0.67 to 0.45)	Combined exercise
B. Quality of life as measured by general questionnaires (after treatment)					
Control	0.01 (−0.23 to 0.26)	0.13 (−0.01 to 0.27)	na	−0.05 (−0.25 to 0.15)	0.03 (−0.16 to 0.22)
0.01 (−0.36 to 0.37)	Walking	na	na	na	na
0.21 (0.00 to 0.42)	0.21 (−0.21 to 0.63)	Resistance training	na	−0.10 (−0.43 to 0.23)	na
na	na	na	Mind−body exercise	na	na
−0.07 (−0.53 to 0.39)	−0.08 (−0.66 to 0.51)	−0.29 (−0.78 to 0.21)	na	Aerobic exercise	na
−0.06 (−0.33 to 0.21)	−0.06 (−0.52 to 0.39)	−0.27 (−0.62 to 0.07)	na	0.01 (−0.52 to 0.55)	Combined exercise
C. Quality of life as measured by cancer-specific questionnaires (during treatment)					
Control	0.35 (−0.03 to 0.72)	**0.15 (0.01 to 0.29)**	0.69 (−0.44 to 1.82)	**0.22 (0.05 to 0.40)**	**0.15 (0.03 to 0.27)**
0.43 (−0.11 to 0.96)	Walking	na	na	na	na
0.23 (−0.13 to 0.59)	−0.20 (−0.84 to 0.45)	Resistance training	na	0.06 (−0.30 to 0.42)	na
0.92 (0.34 to 1.51)	0.50 (−0.29 to 1.29)	**0.70 (0.01 to 1.38)**	Mind−body exercise	na	na
0.26 (−0.12 to 0.65)	−0.16 (−0.82 to 0.50)	0.03 (−0.44 to 0.50)	−0.66 (−1.36 to 0.04)	Aerobic exercise	0.05 (−0.57 to 0.67)
0.32 (0.03 to 0.61)	−0.10 (−0.71 to 0.51)	0.10 (−0.37 to 0.56)	−0.60 (−1.25 to 0.05)	0.06 (−0.41 to 0.53)	Combined exercise
D. Quality of life as measured by cancer-specific questionnaires (after treatment)					
Control	**0.26 (0.03 to 0.49)**	0.25 (−0.06 to 0.55)	0.06 (−0.19 to 0.31)	0.05 (−0.15 to 0.24)	**0.28 (0.12 to 0.44)**
0.35 (0.01 to 0.68)	Walking	na	na	na	na
0.35 (−0.09 to 0.80)	0.01 (−0.55 to 0.56)	Resistance training	na	na	na
0.10 (−0.31 to 0.51)	−0.25 (−0.77 to 0.28)	−0.25 (−0.86 to 0.35)	Mind−body exercise	na	na
0.09 (−0.21 to 0.38)	−0.26 (−0.71 to 0.19)	−0.27 (−0.80 to 0.27)	0.02 (−0.49 to 0.52)	Aerobic exercise	na
0.41 (0.22 to 0.60)	0.06 (−0.32 to 0.45)	0.06 (−0.43 to 0.54)	0.31 (−0.14 to 0.76)	0.32 (−0.03 to 0.68)	Combined exercise

Notes: Data are effect sizes (95% confidence intervals). Effect sizes in bold are statistically significant. Positive effect sizes mean that the first intervention improves quality of life compared to the second intervention. Upper right triangle gives pooled effect sizes from pairwise comparisons (column intervention relative to row); lower left triangle gives pooled effect sizes from the network meta-analysis (row intervention relative to column).
Abbreviation: na = not available.

Table 3
League table of pooled effect sizes for physical and mental domains of quality of life.

A. Physical domain					
Control	0.21 (−0.34 to 0.76)	0.13 (−0.26 to 0.52)	0.40 (−0.30 to 1.10)	0.12 (−0.38 to 0.61)	**0.56 (0.25** to **0.87)**
0.21 (−0.32 to 0.75)	Walking	na	na	na	na
0.12 (−0.24 to 0.47)	−0.10 (−0.74 to 0.55)	Resistance training	na	na	na
0.40 (−0.29 to 1.08)	0.18 (−0.69 to 1.05)	0.28 (−0.49 to 1.05)	Mind−body exercise	na	na
0.13 (−0.29 to 0.56)	−0.08 (−0.76 to 0.61)	0.02 (−0.48 to 0.51)	−0.26 (−1.07 to 0.54)	Aerobic exercise	na
0.52 (0.23 to 0.82)	0.31 (−0.30 to 0.92)	0.41 (−0.05 to 0.87)	0.13 (−0.62 to 0.87)	0.39 (−0.12 to 0.90)	Combined exercise

B. Mental domain					
Control	0.21 (−0.40 to 0.82)	0.35 (−0.09 to 0.78)	0.40 (−0.37 to 1.17)	0.01 (−0.60 to 0.62)	**0.63 (0.26** to **1.00)**
0.21 (−0.39 to 0.82)	Walking	na	na	na	na
0.39 (−0.02 to 0.79)	0.18 (−0.55 to 0.91)	Resistance training	na	na	na
0.40 (−0.37 to 1.17)	0.19 (−0.79 to 1.17)	0.01 (−0.86 to 0.88)	Mind−body exercise	na	na
−0.07 (−0.60 to 0.46)	−0.28 (−1.08 to 0.53)	−0.46 (−1.05 to 0.14)	−0.47 (−1.41 to 0.46)	Aerobic exercise	na
0.59 (0.24 to 0.95)	0.38 (−0.32 to 1.08)	0.20 (−0.33 to 0.74)	0.19 (−0.65 to 1.04)	**0.66 (0.03 to 1.30)**	Combined exercise

Notes: Data are effect sizes (95% confidence intervals). Effect sizes in bold are statistically significant. Positive effect sizes mean that the first intervention improves quality of life compared to the second intervention. Upper right triangle gives the pooled effect sizes from pairwise comparisons (column intervention relative to row); lower left triangle gives pooled effect sizes from the network meta-analysis (row intervention relative to column).
Abbreviation: na = not available.

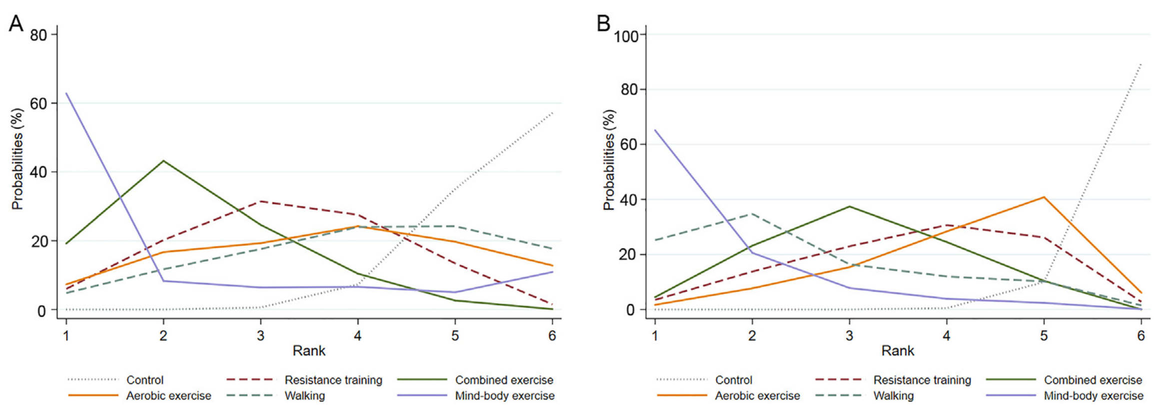

Fig. 3. Relative rankings for type of exercises on general and cancer-specific questionnaires of quality of life. (A) Quality of life measured by general questionnaires and (B) Quality of life as measured by cancer-specific questionnaires.

Comparisons with the control group for combined exercise and mind−body exercise showed considerable heterogeneity for HRQoL as measured by general and cancer-specific questionnaires ($I^2 = 87.8\%$, $\tau^2 = 0.198$; and $I^2 = 90.8\%$, $\tau^2 = 0.609$, respectively) (Supplementary Table 7).

3.4. Sensitivity analysis and publication bias

The pooled ES estimate was not significantly modified (by magnitude or direction) when individual study data were removed from the analysis one at a time.

Publication bias was found only for the comparison of the combined exercise *vs.* control group (Egger test $p = 0.067$) and aerobic exercise *vs.* control group (Egger test $p = 0.065$) for HRQoL as measured by cancer-specific questionnaire (Supplementary Fig. 5).

4. Discussion

In people with cancer, physical activity and exercise have a positive influence on physical fitness, fatigue, and physical and psychological well-being, all of which are components of the HRQoL construct. However, it is not entirely clear which exercise modality produces the best results.

Our systematic review and NMA, which included 93 RCTs involving nearly 7500 people with cancer, separated analyses by type of questionnaire used (general or cancer-specific), by timing of the exercise intervention (during or after treatment), and by physical and mental domains. The analyses showed that all types of exercise appear to have a positive effect on the HRQoL of people with cancer. None of the NMA estimates showed negative results; however, in most cases these estimates were not statistically significant, either due to the scarcity of studies and small sample sizes or because the ES was weak. In addition, our data suggest interventions combining aerobic activities with resistance training were the only exercise modality to result in a significant effect.

4.1. Exercise effects on HRQoL as measured by general and cancer-specific questionnaires

Both general and disease-specific questionnaires are widely used as outcome measures in clinical trials evaluating the effects of interventions in people with cancer, either during or after treatment. It is accepted that the use of cancer-specific questionnaires can be complemented by general questionnaires because while the formers are more sensitive to the psycho-emotional dimensions of HRQoL, generic scales, such as the Short Form 12 Health Survey, are more sensitive to the functional aspects of HRQoL.[121]

Our analyses independently examined the effects of exercise on HRQoL as measured by each of the questionnaire types. The NMA effect estimates (Table 2) showed that all exercise modalities had a positive effect on HRQoL when this construct was measured by general questionnaires, but that the effect was only significant for aerobic and combined exercise. When the outcome measure was a cancer-specific tool, all exercise modalities had a positive effect once again, but it was only significant for walking, mind−body exercise, and combined exercise.

The relative ranking (Fig. 3) shows aerobic and mind−body exercise to be the most effective exercise interventions when HRQoL was measured by general questionnaires, but it shows mind−body exercise and walking to be most effective when the outcome was measured by cancer-specific ones. However, these probabilities should be regarded with caution because both SUCRA values and *p* scores have important limitations. They are based only on relative effects against competing interventions, for example, and treatments that are poorly connected to the network of comparisons (e.g., mind−body exercise) often appear at the top of the ranking, even when these treatments are supported by less consistent or biased evidence.[122] Finally, some exercise modalities (aerobic and combined) are more frequently included in clinical trials in cancer patients likely because they are the same interventions recommended by influential scientific societies.[123]

4.2. Exercise during and after treatment

A decade ago, Mishra et al.[124] conducted a pair of pivotal systematic reviews looking at cancer patients during active treatment as well as at cancer survivors.[125] They concluded that exercise could benefit HRQoL and that supervised exercise was more effective than non-supervised exercise in this regard. However, they suggested more research was needed because of the heterogeneity of the exercise programs tested, the variety of HRQoL instruments used, and the risk of bias of the included trials. Following their lead, our own analyses distinguished between people undergoing active treatment for cancer and cancer survivors. Unfortunately, 10 years later, the evidence for the benefits of specific exercise modalities on HRQoL remains inconsistent.

Our network estimates suggest that during cancer treatment, combined exercise was the only modality to result in a significant effect on HRQoL as measured by general questionnaires; when HRQoL was measured by cancer-specific questionnaires, both mind−body and combined exercise showed significant effects. However, after cancer treatment, combined exercise and walking were the only exercise modalities to suggest significant effects, and only when HRQoL was measured by cancer-specific questionnaires. These results are partially in line with those reported by Gerritsen and Vincent[126] which suggested that exercise leads to benefits in a variety of socio-emotional areas, including improvements in physical and mental domains, but only during cancer treatment; our data additionally suggest benefits from walking and combined exercise after cancer treatment. Moreover, our data confirm those reported in a systematic review and meta-analysis by Ramírez-Vélez et al.[127] showing that combined exercise at moderate-to-vigorous intensity has significantly improved HRQoL levels in women with breast cancer; but our data also suggest that cancer patients may elicit benefits to their HRQoL from most modalities of exercise. Our findings are in line with data from a review of 69 guidelines developed under the auspices of the World Health Organization,[128] which include low intensity exercise, such as walking or mind−body exercises, as effective strategies that result in benefits to the physical and psychological domains of HRQoL.

The scarcity (or even absence, in some modalities) of studies examining the effects of exercise on the HRQoL of cancer survivors makes us very cautious about interpreting our results. Perhaps the only solid conclusion we can draw from these analyses is that, as Mishra et al.[125] recommended a decade ago, well-designed research initiatives with sufficient sample sizes are strongly needed to progress research on the effects of exercise on the HRQoL of people with cancer, especially over the long term.

4.3. Exercise effects on physical and mental domains

HRQoL is a multidimensional construct that is generally agreed to include physical well-being along with social and psychological functioning. However, given that social functioning is strongly determined by socio-economic variables related to family and social determinants that are more difficult to influence (e.g., socio-economic status or access to care), it is very common for many HRQoL assessment scales to synthesize their scores into two domains: physical and mental well-being; but it must be recognized that each of these has a two-way relationship with social functioning. Therefore, to provide an overview of potential differences in the effects of exercise on the physical and mental dimensions of HRQoL, we conducted separate analyses for these 2 domains.

As with previous analyses, our NMA pooled estimates suggest that all exercise modalities have a beneficial effect on the physical and mental domains of HRQoL, but this effect was only significant for combined exercise. Furthermore, our results suggest that the magnitude of the effect is very similar in both domains. These results are not surprising if we consider that physical health is closely related to mental health, and that both are influenced by socio-economic determinants.[129]

4.4. Limitations

Our systematic review and NMA have some limitations to be acknowledged. The primary limitation of this NMA is related to the scarcity of studies, the disparity of their designs, and their lack of statistical power. However, based on the existing research, it would be redundant to conduct a multiple-exercise intervention meta-analysis without making any effort to present comparisons between the different types of exercise. For this reason, we comprehensively synthesized the existing data into an NMA to present indirect pooled estimates. We have pointed repeatedly above to the limitations of this methodology when direct treatment comparison studies are scarce.[122] Second, and closely related, although we present ranking probabilities of treatments as estimates of the average certainty that one treatment is better than another for a given outcome, we are conscious of the limitations of these approaches to ranking treatments (e.g., they are based only on the relative effect and disregard that treatments with scarcity of comparisons tend to rank higher in spite of the weakness of the evidence in favor of such treatments[130]). Third, exercise interventions cannot be blinded; thus, intervention-group patients may be prone to the Hawthorne effect[131] (e.g., patients in an exercise group may behave in what they perceive to be an improved way because they know their outcomes are being compared to those of a control group). Furthermore, in studies comparing 2 types of exercise, it is not possible to know whether patients dropped out of follow-up because the randomization process did not assign them to the type of exercise they preferred. Fourth, most studies did not control for the type or stage of cancer, the treatment that patients underwent, or for the patient's lifestyle before and after the diagnosis, all of which are characteristics of cancer and treatment that influence HRQoL levels. Fifth, studies did not present results adjusting for HRQoL levels at baseline; thus, floor and ceiling effects[132] could bias estimates such that people who have poorer HRQoL levels at baseline have more room for increase than those with high baseline HRQoL levels. Finally, there were great heterogeneities in the frequency, intensity, duration, and supervision of interventions, suggesting the need to further the reproducibility of interventions by better describing their characteristics and justifying why the relevant exercise modality is being tested in each clinical trial.

5. Conclusion

Our systematic review and NMA suggest that all exercise modalities may exert a positive effect on HRQoL, as none of the NMA estimates showed negative results. Our estimates suggested that programs combining aerobic and resistance training were the only ones to result in a statistically significant positive effect on HRQoL levels as measured by both general and cancer-specific tools. Furthermore, our data show that combined exercise is the only exercise modality to show a significant effect on patients during treatment regardless of the type of questionnaire with which HRQoL is assessed. Last, our NMA estimates also suggest that combined exercise is the only modality effective at improving both the physical and mental domains of HRQoL. Therefore, in line with international consensus and guidelines, exercise should be recommended for improving HRQoL in patients with cancer, but only with the understanding that the evidence behind this recommendation is weak. In summary, based on the available evidence, exercise programs combining aerobic and resistance training can be recommended as an adjunct to disease therapy in people with cancer during and following medical intervention. Furthermore, we encourage the launch of well-designed RCTs to determine what kinds of exercise are most advisable depending on tumor type, stage of progression, and other personal characteristics of patients, including age and type of treatment.

Data availability

After the publication of this article, the full dataset will be available in online Mendeley Data, a repository of research data that allows the assignment of a permanent digital object identifier, in such a way that the data of this study can be easily referenced (doi: 10.17632/2c4y6k32g5.1).

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Authors' contributions

VMV (Principal investigator), ICR, and EUG were the core team leading this systematic review and NMA; SRG, LGM, JJGC, BBP, and FRA have made substantial contributions to acquisition, analysis and interpretation of data, drafting the article, or revising it critically for important intellectual content. All authors have read and approved the final version of the manuscript, and agree with the order of presentation of the authors.

Competing interests

The authors declare that they have no competing interests.

Supplementary materials

Supplementary materials associated with this article can be found in the online version at doi:10.1016/j.jshs.2023.01.002.

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