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# Mediators of physical exercise for improvement in cancer survivors' quality of life

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## Abstract

***Objective*: Mediating mechanisms of a 12-week group-based exercise intervention on cancer survivors' quality of life (QoL) were examined to inform future exercise intervention development.**

***Methods*: Two hundred nine cancer survivors ≥3 months posttreatment (57% breast cancer) aged 49.5 (±10.4) years were assigned to physical exercise ($n = 147$) or wait-list control ($n = 62$). QoL, fatigue, emotional distress, physical activity, general self-efficacy and mastery were assessed at baseline and post-intervention using questionnaires. Path analysis was conducted using Mplus to explore whether improved physical activity, general self-efficacy and mastery mediated the effects of exercise on fatigue and distress and consequently QoL.**

***Results*: The intervention was associated with increased physical activity (β = 0.46, 95% confidence interval (CI) = 0.14;0.59), general self-efficacy (β = 2.41, 95%CI = 0.35;4.73), and mastery (β = 1.75, 95% CI = 0.36;2.78). Further, the intervention had both a direct effect on fatigue (β = −1.09, 95% CI = −2.12;0.01), and an indirect effect (β = −0.54, 95%CI = −1.00;−0.21) via physical activity (β = −0.29, 95%CI = −0.64;−0.07) and general self-efficacy (β = −0.25, 95%CI = −0.61;−0.05). The intervention had a borderline significant direct effect on reduced distress (β = −1.32, 95%CI = −2.68;0.11), and a significant indirect effect via increased general self-efficacy and mastery (β = −1.06, 95%CI = 1.89;−0.38). Reductions in fatigue (β = −1.33, 95%CI = −1.85;−0.83) and distress (β = −0.86, 95%CI = 1.25;−0.52) were associated with improved QoL. Further, increased physical activity was directly associated with improved QoL (β = 3.37, 95%CI = 1.01;5.54).**

***Conclusion*: The beneficial effect of group-based physical exercise on QoL was mediated by increased physical activity, general self-efficacy and mastery, and subsequent reductions in fatigue and distress. In addition to physical activity, future interventions should target self-efficacy and mastery. This may lead to reduced distress and fatigue, and consequently improved QoL of cancer survivors.**



## Introduction

It has been estimated that 12.7 million cancer cases and 7.6 million cancer deaths occurred worldwide in 2008 [1]. Due to advances in early detection and treatment, survival after cancer diagnosis has improved substantially. Currently in the Netherlands, having almost 16.8 million inhabitants, the prevalence of patients living with cancer is estimated to be 450 000 [2]. This number is expected to increase to 670 000 in 2020 [2], and will continue to rise afterwards. Unfortunately, for many patients, cancer survivorship is associated with long-term adverse physical and psychosocial symptoms. These symptoms often include fatigue, pain, increased risk of anxiety and depression, and reduced physical fitness and physical function [3], which negatively affect patients' quality of life (QoL) [4]. Particularly, fatigue has been identified as one of the most common and distressing symptoms affecting QoL in patients with cancer [4,5].

Previous reviews and meta-analyses showed that exercise programs have beneficial effects on QoL in cancer patients during and after cancer treatment [3,6–8]. However, little is known about the mediators of the effect of exercise programs on QoL in patients with cancer. Previous studies in survivors of breast and colon cancer suggest that reduced fatigue and distress mediate the association between exercise and QoL [9–11]. However, these findings were not based on prospective controlled trials. Sherman *et al*. [12] showed that exercise familiarity and self-efficacy may mediate the effect of an 8-week community-based exercise and information support program on QoL in women who completed breast cancer treatment. As the mediated effect disappeared when both variables were entered into the model, a mediational sequence may be present [12]. More insight in mediating pathways is necessary to unravel working mechanisms of the exercise effect on QoL in patients with cancer. This is important for identifying and subsequently targeting critical intervention components to improve effectiveness and efficiency [13–15].

In the Netherlands, a group-based physical exercise program was developed for cancer survivors [16]. This program is aimed at improving the QoL of cancer survivors by improving general self-efficacy and mastery and encouraging the adoption of a physically active lifestyle, and consequently reducing fatigue and distress [16]. In previous studies, we found that this 12-week group-based physical exercise program reduced fatigue [17], anxiety and depression [18], and improved QoL [19] in cancer survivors as compared to a wait list control (WLC) group. The improvements in QoL persisted at 9-months follow-up [20]. In the current analyses, we aim to examine the mediators of the effects of our physical exercise program on improved QoL in cancer survivors. We hypothesized that exercise leads to increased physical activity, self-efficacy and mastery, which results in lower fatigue and distress, and consequently in higher QoL.

## Methods

### Patient recruitment and allocation

This study is part of a prospective randomized multicenter trial to study the effect of group-based exercise on cancer survivors' QoL. The trial was conducted at four Dutch centers, that is, at the rehabilitation units of two university medical centers, one general hospital, and one rehabilitation center [21]. The study was approved by the medical ethics committee of the University Medical Center Utrecht and the local research ethics committees.

Cancer patients aged ≥18 years who completed curative cancer treatment at least 3 months ago with a minimum estimated life expectancy of 1 year participated in the study. After a written consent, eligible subjects were scheduled for baseline measurements and allocated randomly to physical training (PT) incorporating principles of self-management or to PT plus cognitive-behavioral therapy (PT + CBT). Eligible patients were invited to participate in a WLC group if, because of full rehabilitation groups, they had to wait at least 3 months to start with a 12-week group-based multidisciplinary cancer rehabilitation programs in other Dutch centers than the four centers that had recruited patients for the interventions using the same inclusion criteria. Detailed recruitment and allocation procedures are described elsewhere [17,19].

In total, 209 patients participated in the study; 76 were allocated to PT + CBT, 71 to PT, and 62 to WLC. Measurements were performed at baseline and after 12 weeks. No differences in physical fitness, fatigue, distress, and QoL were found between PT and PT + CBT groups from pre-intervention to post-intervention [17–21]. Therefore, in the present study, we combined the two intervention groups into one group.

### Interventions

To improve exercise adherence and encourage the adoption of a physically active lifestyle, the intervention consisted of a structured exercise program including self-management techniques: that is, goal selection, information collection, information processing and evaluation, decision making, action, and self-reaction [16,21]. The intervention took place in groups of 8–12 cancer survivors. PT was supervised by two physical therapists and CBT by a psychologist and a social worker, all experienced professionals in the field of cancer rehabilitation.

Physical training included personalized physical exercise twice a week to improve exercise capacity, muscle strength, reduce physical limitations and fatigue, and increase physical activity. Each session consisted of individual aerobic stationary cycle training (0.5 h), based on baseline maximal exercise testing, muscle strength training (0.5 h), and group sports and games (1 h). Sports and games were aimed at promoting enjoyment in sports and improving self-efficacy to incorporate sporting activities in daily life and to adopt a physically active lifestyle. Additionally, patients received information on exercise physiology, illness perceptions, and self-management to support them in regulating their physical activity. All patients received information on the benefits of physical exercise, and depending on their individual goals, also information on coping with fatigue and how to restore the balance between demand and capacity during tasks and activities. Self-management principles were incorporated by asking the patients to set their own personal training goals and monitor their own training process using exercise logs, heart rate monitors, and the Borg scale for dyspnoea and fatigue. Four strategies for improving self-efficacy were addressed. First, exercise started at a low intensity to ensure that all patients would be able to complete the training to perceive a mastery experience



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that might increase self-efficacy. Second, improvement in self-efficacy was also expected as a result of improvement in physiological arousal that was supposed to be felt by the patient through the improvement in their exercise capacity. Third, verbal persuasion was used by the therapist to encourage patients to perform training activities, and fourth, the program was delivered in a group format to enhance vicarious learning [22].

Cognitive-behavioral therapy was based on a cognitive-behavioral problem-solving protocol for individual cancer patients [23] and a group problem-solving protocol for low back pain patients [24]. During the intervention, self-management skills [25] were developed to enable participants to solve and present future problems associated with the physical and psychosocial consequences of cancer. CBT was provided once a week during 2 h sessions and supervised by a psychologist and a social worker. Detailed descriptions of PT and CBT are provided elsewhere [17,19,21]. More than 80% of the sessions were completed for both PT and CBT [21].

## Outcomes

Detailed descriptions of the outcome assessments can be found elsewhere [17–21]. Briefly, global QoL was assessed using the subscale of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QOL-C30) [26]. This subscale includes two questions addressing perceptions of general health and overall QoL. The EORTC QLQ-C30 is a reliable and valid cancer-specific QoL instrument that has been used in many studies evaluating intervention effects on cancer-specific QOL [26]. The 30-item questionnaire incorporates a global QoL subscale, five functional scales (physical, role, emotional, cognitive, and social function), and three symptom scales (fatigue, pain, nausea, and vomiting). After applying a linear transformation procedure according to the manual, the scores of the scale range from 0 to 100, with higher scores representing a higher QoL.

Fatigue was assessed using the Multidimensional Fatigue Inventory [27], which consists of 20 statements for which the person indicates the extent to which the particular statement applies to him or her on a 5-point scale. The statements refer to several aspects of fatigue experienced during the previous few days. Higher scores indicate a higher degree of fatigue. The Multidimensional Fatigue Inventory has good internal consistency (average Cronbach's alpha = 0.84) [27]. We used the general fatigue subscale for further analysis.

Emotional distress was assessed with the 14-item Hospital Anxiety and Depression Scale [28], validated for the Dutch population [29] and cancer patients [30]. We used the total score for further analysis, with higher scores indicating higher levels of distress.

Physical activity was assessed with the 12-item Physical Activity Scale for the Elderly (PASE) [31], a 7-day physical activity recall-questionnaire with good reliability and acceptable validity for cancer patients [32]. The PASE consists of questions about frequency (never, seldom (1–2 days/week), sometimes (3–4 days/week), or often (5–7 days/week)), and duration (less than 1 h, between 1 and 2 h, between 2 and 4 h, or more than 4 h) of leisure time, household and work-related activities (for work-related physical activity, duration was categorized as less than 1 h, between 1 and 4 h, between 5 and 8 h, or more than 8 h [32]). The total PASE sum score is computed by multiplying the amount of time spent on each activity (in hours/week) by the empirically derived item weights and summed over all activities.

General self-efficacy was measured with the standardized Dutch version of the General self-efficacy scale [33]. This 16-item questionnaire yields a total score and three subscales: willingness to expend effort in completing a behavior, persistence in the face of adversity, and willingness to initiate behavior. Higher scores represent higher self-efficacy.

Mastery, that is, the extent to which a person perceives himself to be in control of events and ongoing situations, was measured by the 7-item Pearlin Mastery Scale [34]. This questionnaire includes items such as 'I have little control over things that happen to me' and 'I can do almost everything, if I want to'. Items are scored on a scale from 1 ('strongly agree') to 5 ('strongly disagree'), and negatively worded items are scored reversed. The total score ranges from 7 to 35, with higher scores indicating more feelings of mastery.

Sociodemographic and medical data were collected using a self-report questionnaire. Education level was categorized into low (elementary and lower vocational education), medium (secondary and secondary vocational education), or high (higher vocational and university education). Medical data were confirmed by the referring physicians.

## Statistical analysis

We calculated mean and standard deviations (SD) or numbers and percentages of patient characteristics, and pre-intervention and post-intervention values of the outcomes.

We conducted path analysis using maximum likelihood estimation with MPlus. We examined whether the intervention had a direct effect on physical activity, self-efficacy and mastery. Subsequently, we evaluated whether increased physical activity, self-efficacy and mastery were associated with reduced fatigue and distress, and consequently with increased global QoL. Because we used valid and reliable questionnaires, the path analysis was conducted on the sum scores of the instruments. In the analyses, correlations between physical activity, self-efficacy and



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mastery, and correlations between fatigue and distress were taken into account.

Direct paths from the intervention to other variables in the model reflect intent-to-treat analyses (e.g., comparing patients from the intervention group with the control group). Other paths reflect relationships between variables, and may also reflect indirect effects of the intervention. Bootstrapping techniques were applied to calculate the 95% CI around the estimates of the direct and indirect effects using 10 000 bootstrap samples. For the analyses, we log transformed the physical activity data to obtain a normal distribution. A good rule of thumb for path analysis is to have, at minimum, 10–20 times as many observations as variables [35]. There were seven variables in this study, thus a sample size of 209 can be considered adequate to provide sufficient statistical power.

Model fit was evaluated using the Chi-square test of model fit, the root mean square error of approximation (RMSEA) $\leq$0.06, the Comparative Fit Index (CFI) $\geq$0.95, and the standardized root mean square residual (SRMR) $\leq$0.08 [36]. Analyses started with the full model. Consequently, a backward selection procedure was applied to remove direct associations with $p > 0.10$ step by step, resulting in the final model (Figure 1). The syntax used to generate the final model is presented in Appendix 1.

## Results

The exercise and WLC group were balanced in most sociodemographic and medical variables, except for marital status, educational level, and disease recurrence (Table 1). Therefore, we adjusted for these variables in all analyses.

Descriptive values of all outcomes for the exercise and WLC groups at pre-test and post-test are presented in Table 2.

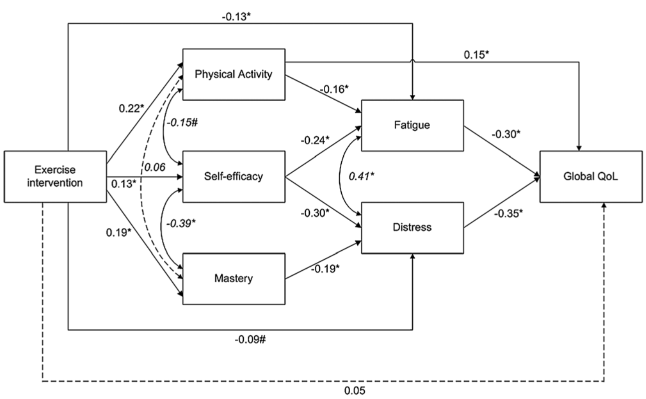


**Figure 1.** Effect of the physical exercise intervention on global quality of life based on path analysis. Coefficients are standardized path coefficients. The straight arrows are paths and the curved ones represent correlations (italic coefficients) among the variables. *$p < 0.05$; # $0.05 \leq p < 0.10$. Path analysis using maximum likelihood estimation with MPlus adjusted for marital status, educational level, and disease recurrence

**Table 1.** Sociodemographic and clinical characteristics of 209 cancer survivors

| | Exercise ($n = 147$) | Wait list comparison ($n = 62$) |
|---|---|---|
| *Sociodemographic* | | |
| Age, mean (SD) years | 48.8 (10.9) | 51.3 (8.8) |
| Sex, *n* (%) female | 123 (83.7) | 56 (90.3) |
| Married/living together, *n* (%)* | 104 (70.7) | 55 (88.7) |
| Education level, *n* (%)* | | |
| Low | 20 (13.6) | 16 (25.8) |
| Medium | 72 (49.0) | 32 (51.6) |
| High | 55 (37.4) | 14 (22.6) |
| Employed at diagnosis, *n* (%) | 107 (72.8) | 46 (74.2) |
| *Clinical* | | |
| Type of cancer, *n* (%) | | |
| Breast | 82 (55.8) | 38 (61.3) |
| Hematological | 23 (15.6) | 10 (16.1) |
| Gynecological | 17 (11.6) | 7 (11.3) |
| Urologic | 9 (6.1) | 0 (0) |
| Lung | 4 (2.7) | 4 (6.5) |
| Colon | 3 (2.0) | 2 (3.2) |
| Other | 9 (6.1) | 1 (1.6) |
| Type of treatment (>3 months ago), *n* (%) | | |
| Surgery | 126 (85.7) | 51 (82.3) |
| Chemotherapy | 100 (68.0) | 39 (62.9) |
| Radiotherapy | 84 (57.1) | 41 (66.1) |
| Recurrence >3 months ago* | | |
| Yes | 14 (9.5) | 15 (24.2) |
| No | 118 (80.3) | 45 (72.6) |
| Unknown | 15 (10.2) | 2 (3.2) |
| Time since treatment, mean (SD) years | 1.3 (1.7) | 1.9 (2.7) |
| Comorbidity at start | | |
| Yes | 68 (46.3) | 27 (43.5) |
| No | 79 (53.7) | 34 (54.8) |
| Unknown | 0 (0) | 1 (1.6) |

*Significant differences between exercise and wait list comparison groups using independent *t*-tests, $p < 0.05$.

### Path analysis

Path analysis was started with the full model, including all hypothesized paths. The direct associations between physical activity and distress, between mastery and fatigue, between mastery and QoL, and between self-efficacy and QoL were not significant, and were therefore removed from the model. This resulted in the final model (Figure 1). The final model explained 53% of the total variance in QoL, and fitted the data, $\chi^2$ (34, $n = 192$ (because of missings on covariates)) = 45.5, $p = 0.090$; RMSEA = 0.042, with 90% confidence interval (CI) = 0.000; 0.071; CFI = 0.985; SRMR = 0.029. Similar results were found when the final model was run in the subgroup of patients with breast cancer ($n = 120$).

The direct and indirect associations of the final model are presented in Tables 3 and 4, respectively. There was no significant direct effect of the intervention on QoL ($\beta = 1.73$; 95% CI = −2.61 to 6.62), but it was mediated by the hypothesized path. We found significant beneficial



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**Table 2.** Pre-intervention and post-intervention values of exercise and wait list comparison groups

| | Exercise ($n$ = 147) | | Wait list comparison ($n$ = 62) | |
|---|---|---|---|---|
| | **Pre-test mean (SD)** | **Post-test, mean (SD)** | **Pre-test mean (SD)** | **Post-test mean (SD)** |
| Quality of life (EORTC QLQ-C30) | | | | |
| Physical functioning | 72.8 (14.7) | 84.9 (11.2) | 73.4 (16.5) | 79.6 (16.6) |
| Role functioning | 57.3 (24.2) | 74.6 (22.1) | 73.4 (16.5) | 68.6 (21.7) |
| Emotional functioning | 62.1 (21.5) | 75.9 (19.1) | 64.9 (23.2) | 72.8 (19.2) |
| Cognitive functioning | 64.5 (25.9) | 74.4 (21.5) | 68.0 (25.5) | 73.6 (22.4) |
| Social functioning | 62.9 (27.4) | 82.5 (20.0) | 67.5 (23.1) | 81.9 (21.1) |
| Global quality of life | 57.1 (17.6) | 72. 7 (15.7) | 60.1 (18.4) | 66.0 (19.1) |
| Fatigue (MFI) | | | | |
| General fatigue | 15.6 (3.4) | 11.5 (3.6) | 15.0 (3.3) | 13.1 (4.1) |
| Physical fatigue | 15.2 (3.4) | 9.7 (3.6) | 14.3 (3.7) | 12.3 (4.3) |
| Mental fatigue | 12.9 (4.1) | 11.0 (3.8) | 12.7 (4.3) | 11.9 (4.4) |
| Reduced activity | 13.0 (3.9) | 9.3 (3.7) | 13.0 (3.9) | 11.1 (4.3) |
| Reduced motivation | 10.8 (3.9) | 8.2 (3.5) | 11.4 (3.7) | 10.0 (3.7) |
| Distress (HADS) | | | | |
| Total score | 13.4 (7.7) | 9.1 (6.5) | 13.9 (7.5) | 12.0 (7.0) |
| Anxiety | 7.8 (4.3) | 5.5 (3.9) | 7.5 (4.3) | 6.8 (4.0) |
| Depression | 5.6 (4.1) | 3.6 (3.3) | 6.5 (3.9) | 5.2 (3.6) |
| Physical activity (PASE) | | | | |
| Total score | 12.9 (9.7) | 19.4 (13.6) | 15.1 (12.7) | 14.5 (13.6) |
| Self-efficacy (ALCOS) | | | | |
| Total score | 44.0 (8.8) | 47.3 (8.5) | 42.6 (8.5) | 44.2 (8.8) |
| Initiative | 10.4 (3.5) | 11.3 (3.0) | 10.0 (3.5) | 10.3 (3.3) |
| Competence | 14.0 (4.2) | 15.3 (3.8) | 13.3 (4.0) | 14.0 (3.7) |
| Persistence | 19.6 (3.5) | 20.8 (3.3) | 19.4 (4.4) | 19.9 (3.9) |
| Mastery | | | | |
| Mastery | 22.7 (4.0) | 24.7 (4.3) | 22.2 (4.4) | 22.5 (4.3) |

ALCOS, General self-efficacy scale; HADS, Hospital Anxiety and Depression Scale; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30; MFI, Multidimensional Fatigue Inventory; PASE, Physical Activity Scale for the Elderly; SD, standard deviation.

effects of the intervention on physical activity (β = 0.46; 95% CI = 0.14 to 0.59), self-efficacy (β = 2.41; 95% CI = 0.35 to 4.73), and mastery (β = 1.75; 95% CI = 0.36 to 2.78). Further, the intervention had a direct effect on fatigue (β = −1.09; 95% CI = −2.12 to 0.01; $p = 0.04$, Table 4 and Figure 1.), but also a significant indirect effect (β = −0.54; 95% CI = −1.00 to −0.21, Table 4) via physical activity (β = −0.29; 95% CI = −0.64 to −0.07) and self-efficacy (β = −0.25; 95% CI = −0.61 to −0.05). The direct intervention effect on distress was borderline significant (β = −1.32; 95% CI = −2.68 to 0.11, see Table 3 and Figure 1), and the indirect effect, via improved self-efficacy and mastery was significant (β = −1.06; 95% CI = −1.89 to −0.38, see Table 4). Reductions in fatigue (β = −1.33; 95% CI = −1.85 to −0.83) and distress (β = −0.86; 95% CI = −1.25 to −0.52) were associated with improved global QoL. In addition, there was a direct association between physical activity on QoL (β = 3.37; 95% CI = 1.01 to 5.54).

## Discussion

This study provides insight into the working mechanisms of a group-based physical exercise intervention to improve QoL in cancer patients who completed primary cancer treatment. We showed that the exercise program resulted in increased physical activity, general self-efficacy and mastery, which led to reduced fatigue and distress and consequently improved QoL. The intervention effects on fatigue were partly mediated by improved physical activity and general self-efficacy. Further, we found a direct positive association between physical activity and QoL.

We previously reported beneficial effects of the exercise intervention on fatigue, anxiety, depression, and QoL [17–20], which is in line with previous reviews and meta-analyses [6,37,38]. The current study further elucidates these findings by providing insight into the mechanisms underlying the beneficial effects of physical exercise on QoL. Our finding that fatigue and distress mediate the association between exercise and QoL is in line with previous results from uncontrolled trials [9,11] and a cross sectional study [10]. In this study, we further showed that the physical exercise intervention had both a direct effect on fatigue, as well as an indirect effect via increased physical activity and general self-efficacy. Further, the intervention had a borderline significant direct effect on distress, but the effect was mainly caused by improvements in general self-efficacy and

**Table 3.** Direct effects of the physical exercise intervention

| Model results | Estimate | SE | 95% CI | Standardized estimate | $R^2$ |
|---|---|---|---|---|---|
| Intervention effects on | | | | | |
| Physical activity | 0.463* | 0.114 | 0.143; 0.589 | 0.219 | 0.329 |
| Self-efficacy | 2.411* | 1.105 | 0.346; 4.729 | 0.132 | 0.472 |
| Mastery | 1.753* | 0.526 | 0.364; 2.772 | 0.187 | 0.401 |
| Fatigue | −1.092* | 0.533 | −2.117; 0.005 | −0.134 | 0.325 |
| Distress | −1.320# | 0.711 | −2.675; 0.110 | −0.092 | 0.574 |
| QoL | 1.729 | 2.343 | −2.613; 6.615 | 0.048 | 0.531 |
| Effects on fatigue: | | | | | |
| Physical activity | −0.795* | 0.290 | −1.340; −0.209 | −0.163 | |
| Self-efficacy | −0.105* | 0.030 | −0.166; −0.048 | −0.236 | |
| Effects on distress | | | | | |
| Self-efficacy | −0.234* | 0.043 | −0.320; −0.151 | −0.299 | |
| Mastery | −0.281* | 0.096 | −0.466; −0.091 | −0.185 | |
| Effects on QoL | | | | | |
| Physical activity | 3.307* | 1.157 | 1.011; 5.535 | 0.153 | |
| Fatigue | −1.333* | 0.259 | −1.850; −0.825 | −0.301 | |
| Distress | −0.885* | 0.184 | −1.246; −0.523 | −0.352 | |
| Correlation between physical activity and | | | | | |
| Self-efficacy | 0.588# | 0.322 | −0.019; 1.235 | 0.152 | |
| Mastery | 0.135 | 0.174 | −0.219; 0.467 | 0.064 | |
| Correlation between mastery and self-efficacy | 8.059* | 1.847 | 4.816; 12.134 | 0.392 | |
| Correlation between fatigue and distress | 5.368* | 0.894 | 3.820; 7.361 | 0.405 | |

CI, confidence interval; $R^2$, explained variance; SE, standard error; QoL, global quality of life.
Path analysis using maximum likelihood estimation with MPlus adjusted for marital status, education level, and disease recurrence.
*$p < 0.05$;
#$0.05 \leq p < 0.10$.

**Table 4.** Total and indirect effects of the physical exercise intervention and confidence limits around the total and indirect effects

| Model results | Estimate | SE | 95% CI | Standardized estimate |
|---|---|---|---|---|
| Effects from intervention on fatigue | | | | |
| Total | −1.634* | 0.545 | −2.661; −0.504 | −0.201 |
| Total indirect | −0.543* | 0.198 | −1.001; −0.212 | −0.067 |
| Specific indirect | | | | |
| Fatigue self-efficacy intervention | −0.253** | 0.134 | −0.606; −0.051 | −0.031 |
| Fatigue activity intervention | −0.289* | 0.141 | −0.640; −0.073 | −0.036 |
| Effects from intervention on distress | | | | |
| Total | −2.377* | 0.767 | −3.858; −0.849 | −0.166 |
| Total indirect | −1.057* | 0.381 | −1.886; −0.381 | −0.074 |
| Specific indirect | | | | |
| Distress self-efficacy intervention | −0.564* | 0.261 | −1.169; −0.123 | −0.039 |
| Distress mastery intervention | −0.493* | 0.226 | −1.062; −0.153 | −0.034 |
| Effects from intervention on QoL | | | | |
| Total | 7.215* | 2.674 | 1.972; 12.452 | 0.200 |
| Total indirect | 5.486* | 1.400 | 2.845; 8.356 | 0.152 |
| Specific indirect | | | | |
| QoL fatigue intervention | 1.455** | 0.787 | 0.051; 3.201 | 0.040 |
| QoL distress intervention | 1.169** | 0.638 | 0.004; 2.553 | 0.032 |
| QoL activity intervention | 1.204* | 0.618 | 0.287; 2.814 | 0.033 |
| QoL fatigue self-efficacy intervention | 0.338** | 0.191 | 0.076; 0.903 | 0.009 |
| QoL fatigue activity intervention | 0.386** | 0.210 | 0.091; 0.957 | 0.011 |
| QoL distress self-efficacy intervention | 0.500** | 0.260 | 0.111; 1.198 | 0.014 |
| QoL distress mastery intervention | 0.436** | 0.239 | 0.125; 1.122 | 0.012 |

CI, confidence interval; SE, standard error; QoL, global quality of life.
Path analysis using maximum likelihood estimation with MPlus adjusted for marital status, education level, and disease recurrence.
*$p < 0.05$;
**$0.05 \leq p < 0.10$.

mastery. These findings are in line with those from a cross sectional study in breast cancer patients showing that physical activity improved general self-efficacy, and general self-efficacy was associated with reduced fatigue and distress [39].

Increased self-reported physical activity in the intervention group could be because of the exercise sessions as part of the intervention itself. It also suggests that participants did not reduce their daily physical activity to compensate for the exercise sessions. In addition to increasing physical activity, this physical exercise intervention was specifically developed to improve general self-efficacy and mastery by including components of mastery experiences, vicarious experiences, verbal persuasion, physiological feedback, goal setting and monitoring [16]. Also, the group format that was used provided opportunities for contact with fellow patients to enhance social comparison, social support, and modeling, thereby improving self-efficacy [16]. Indeed, results showed that the intervention improved general self-efficacy and mastery, which mediated the intervention effect on fatigue and distress. Therefore, improving self-efficacy is an important component that should be included in future cancer rehabilitation programs. The importance of improving self-efficacy for cancer survivors was previously acknowledged by Mosher *et al.* [40], who showed that change in self-efficacy for eating more fruit and vegetables and lower fat intake partly mediated the effects of Fresh Start, a diet and exercise intervention, on cancer survivors' dietary outcomes. Further, Rottmann *et al.* [41] showed that general self-efficacy was associated with an active adjustment style (i.e., more fighting spirit and less anxious preoccupation and helplessness-hopelessness) and emotional well-being in a large group of breast cancer patients. In the current study, general self-efficacy was positively associated with physical activity and mastery, indicating that these three intervention components may strengthen each other.

The hypothesized model explained 53% of the total variance in QoL. Although this proportion is substantial, additional mechanisms may further explain exercise-induced improvements in QoL in cancer patients and survivors. Potential additional mediators include biological factors such as proinflammatory cytokines (e.g., interleukin 6, tumor necrosis factor alpha) and inflammatory proteins (e.g., C-reactive protein) [42–44], which may mediate the exercise effects on fatigue [42,45]. Further, social factors, such as group cohesion [46] and social support [47,48] may mediate the exercise effects on QoL, and should be examined in future studies.

Strengths of the present study are the supervised, standardized and theory-based intervention, the large sample size, the high attendance, and low dropout rates [17]. Another strength is the use of path analysis to test our hypothesized mechanisms underlying the intervention effects on QoL. Path analysis allows the evaluation of multiple mediators and the effects of individual components within an intervention program [36]. Our hypothesized model fitted the data in a mixed group of cancer patients, as well as in patients with breast cancer. Future studies should confirm whether similar mechanisms can explain exercise-induced improvements in QoL in subgroups of patients with other types of cancer. A limitation of the study was that participants were not randomly assigned to a WLC. Nevertheless, the groups were well balanced in baseline physical and psychosocial outcomes, and we adjusted for sociodemographic and clinical variables in all analyses. Second, in the current analyses, we combined both intervention groups. Because of similar intervention strategies and similar results in outcome, it is unlikely that the general mediating pathways differ between the groups. Nevertheless, some differences in the strengths of underlying mediating associations may be present. Third, despite the strength of an experimental design instead of using cross sectional or longitudinal observational data, one should still be cautious with making inferences about causality, because all mediators and outcome variables were measured at the same time points. Preferably, assessment of the mediator should have preceded assessment of the outcome. Finally, we were unable to measure physical fitness, that is, peak oxygen uptake, peak power output, and muscle strength in the WLC group, and therefore, we could not examine its role as mediator in the intervention effects on QoL. Improvement of physical fitness is an important goal for exercise interventions, and it is known to have beneficial effects on many QoL outcomes [3,6]. Even though physical activity and physical fitness are related, they are different concepts, with physical activity being a behavior and physical fitness a set of attributes that are a combination of motor skills and physiological capacities, such as the capacity of cardiorespiratory and musculoskeletal systems [49].

In conclusion, this study showed that the effect of an exercise intervention on QoL was mediated by increases in physical activity, self-efficacy and mastery, and the subsequent reductions in fatigue and distress. Future interventions should target physical activity, self-efficacy and mastery, because this may lead to reduced fatigue and distress and consequently improved QoL of cancer survivors.

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## Supporting information

Additional supporting information may be found in the online version of this article at the publisher's web site.

**Appendix 1**. Mplus syntax of final model.




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