High intensity or low-to-moderate intensity exercise after chemotherapy:

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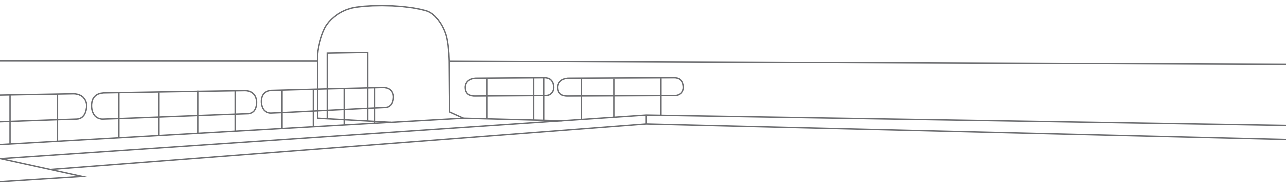
2017

CHAPTER 4

Mediators of exercise effects on health-related quality of life in cancer survivors after chemotherapy



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Medicine & Science in Sports & Exercise, 2016; 48:1859

ABSTRACT

Purpose: We investigated the hypothesis that combined resistance and endurance exercise improves cardiorespiratory fitness and muscle strength, thereby reducing fatigue and improving global quality of life (QoL) and physical function among cancer survivors who completed curative treatment including chemotherapy.

Methods: Cancer survivors were assigned to a 12-week exercise intervention (n=186) or a waiting list control group (WLC, n=91). Data were collected at baseline and after 12 weeks. Path analyses using follow-up values adjusted for baseline values, age, and gender were conducted to test if the exercise effects on global QoL and physical function (European Organization Research and Treatment of Cancer-Quality of Life questionnaire-Core 30) were mediated by changes in cardiorespiratory fitness (peakVO_2), hand-grip strength, lower body muscle function (30-seconds chair-stand test), and fatigue (Multidimensional Fatigue Inventory).

Results: Compared with WLC group, exercise increased cardiorespiratory fitness (β=1.7, 95% confidence interval (CI)=0.9;2.6 mL/kg/min) and reduced general (β=-1.0, 95%CI= -1.8;-0.2) and physical fatigue (β=-1.4, 95%CI=-2.2;-0.6). The exercise effect on physical fatigue was mediated by change in cardiorespiratory fitness (β=-0.1, 95%CI=-0.2;0.0). Higher hand-grip strength was significantly associated with lower physical fatigue, and better lower body muscle function with lower physical and general fatigue. Lower general and physical fatigue were significantly associated with higher global QoL (β=-1.7, 95%CI= -2.2;-1.1 and β=-1.7, 95%CI=-2.3;-1.2, respectively), and physical function (β=-1.0, 95%CI=-1.3;-0.7 and β=-1.1, 95%CI=-1.5;-0.8, respectively). The models explained 44-61% of the variance in global QoL and physical function.

Conclusion: Beneficial effects of exercise on global QoL and physical function in cancer survivors were mediated by increased cardiorespiratory fitness, and subsequent reductions in fatigue.

INTRODUCTION

Recent systematic reviews and meta-analyses showed beneficial effects of exercise interventions on physical fitness, fatigue, and health-related quality of life (HRQoL) in cancer survivors [20,28,35]. However, reported effect sizes were small to moderate. To improve the effectiveness of exercise, it is important to gain more insight into the mechanisms by which an exercise intervention achieves its effect. Mediators may help identify effective intervention components. By keeping effective intervention components and by removing ineffective ones, the cost-effectiveness and participant burden of the interventions can be improved [12]. Furthermore, identification of mediators may support in the building and refining of intervention theory [27]. It is hypothesized that physical inactivity induces muscle catabolism and causes further detraining, which may result in a self-perpetuating detraining state with easily induced fatigue. Physical exercise may break this self-perpetuating cycle by improving physical fitness, and consequently reducing fatigue and improving HRQoL [16,26].

Few previous studies investigated mediators of exercise effects on HRQoL in cancer survivors. They showed that the association between improved cardiorespiratory fitness and improved HRQoL was mediated by fatigue [8,10,11,33]. In a randomized controlled trial (RCT) among 57 prostate cancer survivors, Buffart et al. [8] showed that upper body muscle strength and walking speed mediated the effects of a 12-week combined resistance and endurance exercise intervention on physical health and that fatigue and walking speed mediated the effects on general health. Lower body muscle strength also mediated the effects of resistance and endurance exercise on global QoL and physical function in older long-term prostate cancer survivors. However, no mediating effects were found for cardiorespiratory fitness and fatigue [9].

To further build the knowledge of mechanisms underlying the exercise intervention effect on HRQoL, we tested the hypothesis that a combination of resistance and endurance exercises improves cardiorespiratory fitness and muscle strength, thereby reducing fatigue, and improving global QoL and physical function [13]. To test this hypothesis, we used data from the Resistance and Endurance exercise After ChemoTherapy (REACT) study [21,22], that was conducted in a large group of cancer survivors (n=277) who had recently completed treatment with curative intent, including chemotherapy.

METHODS

Patient recruitment and allocation

The REACT study was a multicenter RCT which evaluated the effectiveness of a 12-week high intensity exercise program (HI) and a low-to-moderate intensity (LMI) exercise program compared to a waiting list control (WLC) group on physical fitness, fatigue, and HRQoL [22]. A detailed description of the study procedures has been published previously [22]. The medical ethics committees of the VU University Medical Centre and the local ethical boards of the participating hospitals had approved the study and written informed consent was obtained from all cancer survivors prior to participation [22].

Cancer survivors were eligible for the study if they were aged ≥18 years, were treated for histologically confirmed breast, colon, ovarian, lymphatic, cervical or testicular cancer, had completed primary cancer treatment with curative intent including chemotherapy, and had no indication for recurrent or progressive disease [22]. Cancer survivors were not eligible for the study if they were unable to perform basic activities of daily life, had cognitive disorders or severe emotional instability, had other serious diseases that might hamper the capacity of carrying out high intensity exercise (e.g., severe heart failure), or were unable to understand and read Dutch [22].

Cancer survivors were recruited between 2011 and 2013 from 9 hospitals in the Netherlands. Baseline measurements were performed 4-6 weeks after completion of primary cancer treatment. After baseline measurements, participants were stratified by cancer type and hospital, and were randomly assigned into one of the three study arms. Both HI and LMI exercise groups started with their 12-week exercise program. Participants from the WLC group were offered the intervention, that they were randomly allocated to, after 12 weeks.

In total, 277 cancer survivors (response rate 37%) participated in the study. We previously reported that both HI and LMI exercise were able to increase cardiorespiratory fitness, reduce fatigue, and improve quality of life and physical function compared with WLC group [22]. The current analyses examine the mechanisms underlying the intervention effects on global QOL and physical function. Because we assumed that the intervention effects follow the same path as proposed in the hypothesized model, and to increase statistical power, we combined both intervention groups into one group. Therefore, 186 cancer survivors were allocated to the exercise intervention and 91 to the WLC group. Measurements were performed at baseline and after 12 weeks.

Interventions

A detailed description of the exercise interventions has been published elsewhere [22]. In short, the exercise interventions took place twice a week for 12 weeks and were identical with respect to exercise type, frequencies and durations, and differed only in intensity. Resistance exercises included vertical row, leg press, bench press, pull over, abdominal crunch and lunges, and these were performed at 70 to 85% of 1 repetition maximum (1-RM) in the HI exercise group and at 40 to 55% of 1-RM in the LMI exercise group. Aerobic interval training aimed to improve cardiorespiratory endurance and included two times 8 minutes of cycling in the first four weeks, with an alternating workload of 30% and 65% of the maximal short exercise capacity (estimated by the steep ramp test [15]) in the HI exercise group and 30% and 45% in the LMI exercise group. From the fifth week onwards, an additional aerobic interval session was included in exchange for 8 minutes cycling. This interval session consisted of three times 5 minutes cycling at constant workload, with 1 minute rest between each bout. The constant workload was defined by means of heart rate reserve based on the Karvonen formula [23], and was at least 80% of heart rate reserve for HI exercise and 40-50% for LMI exercise. On average, 70% of the cancer survivors had high adherence rates, defined as attending 80% of the prescribed supervised exercise sessions [22].

Outcome measure

HRQoL was measured with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 [1], with higher scores representing a higher global QoL and better function. We used the global QoL and physical function scales for further analyses.

Potential mediators

Cardiorespiratory fitness was measured with a maximal exercise test on an electronically braked cycle ergometer according to a ramp protocol in which the resistance gradually increased every 6 seconds, aiming to achieve the maximum peak oxygen uptake (peakVO_2) within 8-12 minutes [4,19]. PeakVO_2 was defined as the highest VO_2 value averaged over a 15-second interval within the last minute of exercise, and was expressed in mL/kg/min. Hand-grip strength was assessed with a JAMAR hand-grip dynamometer [6], and was expressed in kilograms. The mean score of the three attempts with the dominant hand was used in the statistical analyses. We used the 30-seconds chair-stand test as a measure for lower body muscle function [18]. The total number of times participants raised to a full stand in 30 seconds was used in the statistical analyses.

Self-reported fatigue was measured with the Multidimensional Fatigue Inventory [34]. We used the general and physical fatigue subscales for further analyses, with higher scores indicating higher levels of fatigue.

Covariates

Demographic characteristics were collected at baseline with a self-reported questionnaire and included age, gender, education level, marital status, and smoking. We categorized education level into low (elementary and lower vocational education), medium (secondary and secondary vocational education), and high (higher vocational and university education). Clinical characteristics were collected from medical records and included cancer type, stage of disease, and treatment history (i.e., radiation therapy, immunotherapy, hormone therapy and/or surgery) [22].

Statistical analyses

Baseline characteristics and pre- and post-intervention values of the outcome assessments are presented as means and standard deviations (SD), or as numbers and percentages. To test the hypothesis that exercise improves physical fitness (i.e., cardiorespiratory fitness, hand-grip strength, and lower body muscle function), which is associated with lower general and physical fatigue and higher global QoL and physical function (Figure 1), we conducted path analyses using maximum likelihood estimation with MPlus. Path analysis allows the simultaneous assessment of multiple regression equations [38]. Four separate path models were built using follow-up values of the mediators and outcome variables, adjusting for their baseline values, age and gender: 1) physical fitness and general fatigue as mediators in the intervention effects on global QoL; 2) physical fitness and physical fatigue as mediators in the intervention effect on global QoL; 3) physical fitness and general fatigue as mediators in the intervention effects on physical function; and 4) physical fitness and physical fatigue as mediators in the intervention effect on physical function. Bootstrapping techniques were applied to calculate the 95% confidence interval (CI) around the estimates of the direct and indirect effects using 10,000 bootstrap samples. The model fit was evaluated using the root mean square error of approximation (RMSEA), with values below 0.05 for good fit (acceptable fit: 0.05-0.09), the Comparative Fit Index (CFI), and the Tucker-Lewis (TLI) index with values above 0.95 as good fit (adequate fit:>0.90) [25]. These tests were used because they are least sensitive to sample size, and provide unbiased and consistent model specifications [17]. The path analyses were based on complete cases. Because we pooled data from the HI and LMI exercise groups including a heterogeneous group of cancer survivors, we conducted sensitivity analyses to test whether the mediator effects were similar between the two intervention groups and between survivors of breast cancer (n=181) or other (n=96) cancer types.

RESULTS

The mean age of the participants in the exercise group was 53.6 (SD=11.1) years, 81% was female, and 67% was diagnosed with breast cancer (Table 1). Participants in the WLC group were on average 53.5 (SD=10.9) years old, 78% was female, and 63% was diagnosed with breast cancer. Descriptive values of all outcomes for the exercise and WLC groups at pre-intervention and post- intervention are presented in Table 2.

TABLE 1 Sociodemographic and clinical characteristics of the exercise and waiting list control group (n=277)

	Exercise group n=186	**Waiting list control group n=91**
Sociodemographic		
Age, mean (SD) years	53.6 (11.1)	53.5 (10.9)
Gender, n (%) male	35 (19)	20 (22)
Married/living together, n (%)	160 (86)	72 (79)
Education		
Low	31 (17)	16 (18)
Medium	80 (44)	42 (46)
High	72 (39)	33 (36)
Smoking, n (%)	12 (7)	5 (6)
Clinical		
Type of cancer, n (%)		
Breast	124 (67)	57 (63)
Colon	34 (18)	15 (17)
Ovarian	7 (4)	5 (6)
Lymphatic	18 (10)	8 (9)
Cervical	2 (1)	2 (2)
Testicular	1 (1)	4 (4)
Cancer Stage of cancer, n (%)		
Stage 1-2	125 (67)	62 (68)
Stage 3-4	61 (33)	29 (32)
Type of treatment, n (%)		
Surgery only	170 (91)	80 (88)
Radiotherapy only	87 (47)	48 (53)
Surgery and radiotherapy	80 (43)	46 (51)
Immunotherapy	41 (22)	18 (20)
Hormone therapy	85 (46)	43 (47)

Abbrevation: SD, standard deviation.

TABLE 2 Pre- and post-intervention values of mediator and outcome variables in the exercise and waiting list control groups.

	Exercise group		**Waiting list control group**	
	Pre-test mean (SD)	Post-test mean (SD)	Pre-test mean (SD)	Post-test mean (SD)
Health-related quality of life				
Global quality of life [a]	73.2 (16.2)	80.9 (14.9)	71.0 (16.5)	75.3 (15.4)
Physical function	82.5 (13.0)	88.8 (9.8)	80.2 (15.4)	84.1 (13.1)
Fatigue [b]				
General fatigue	12.7 (3.9)	10.1 (3.4)	12.7 (4.2)	11.3 (4.1)
Physical fatigue	12.6 (3.9)	9.2 (3.4)	13.2 (4.0)	11.2 (3.9)
Cardiorespiratory fitness [c]				
PeakVO$_2$ (ml/kg/min)	22.1 (6.2)	26.0 (7.1)	21.5 (5.5)	23.8 (5.9)
Hand-grip strength [d]				
Hand-grip strength (kg)	32.7 (9.7)	34.6 (10.1)	33.5 (9.5)	35.5 (10.6)
Lower body muscle function [e]				
Sit to stand (stands)	16.7 (4.0)	19.0 (4.8)	15.6 (3.6)	17.6 (3.9)

Abbreviations: [a] Missing due to incomplete questionnaire (n=1); [b] Missing due to incomplete questionnaire (n=1); [c] Missing due to technical problems (n=5), musculoskeletal problems (n=1), or discomfort (n=6). Eight percent did not achieve the objective end criteria of respiratory exchange ratio ≥ 1.10 at baseline and follow-up; [d] Missing due to technical problems (n=3) or musculoskeletal problems (n=2); [e] Missing due to musculoskeletal problems (n=2); kg, kilograms; ml, milliliters; min, minutes; peakVO$_2$, maximum peak oxygen uptake; SD, standard deviation.

We found a significant beneficial effect of exercise on cardiorespiratory fitness, but not on hand-grip strength or lower body muscle function (Figure 1, Table 3). In addition, higher cardiorespiratory fitness was significantly associated with lower physical fatigue (Figure 1b and 1d), but not with general fatigue (Figure 1a and 1c). Better lower body muscle function test was significantly associated with lower general and physical fatigue. Higher hand-grip strength was significantly associated with lower physical fatigue (Figure 1b and 1d). We also found a direct effect of the exercise on general and physical fatigue.

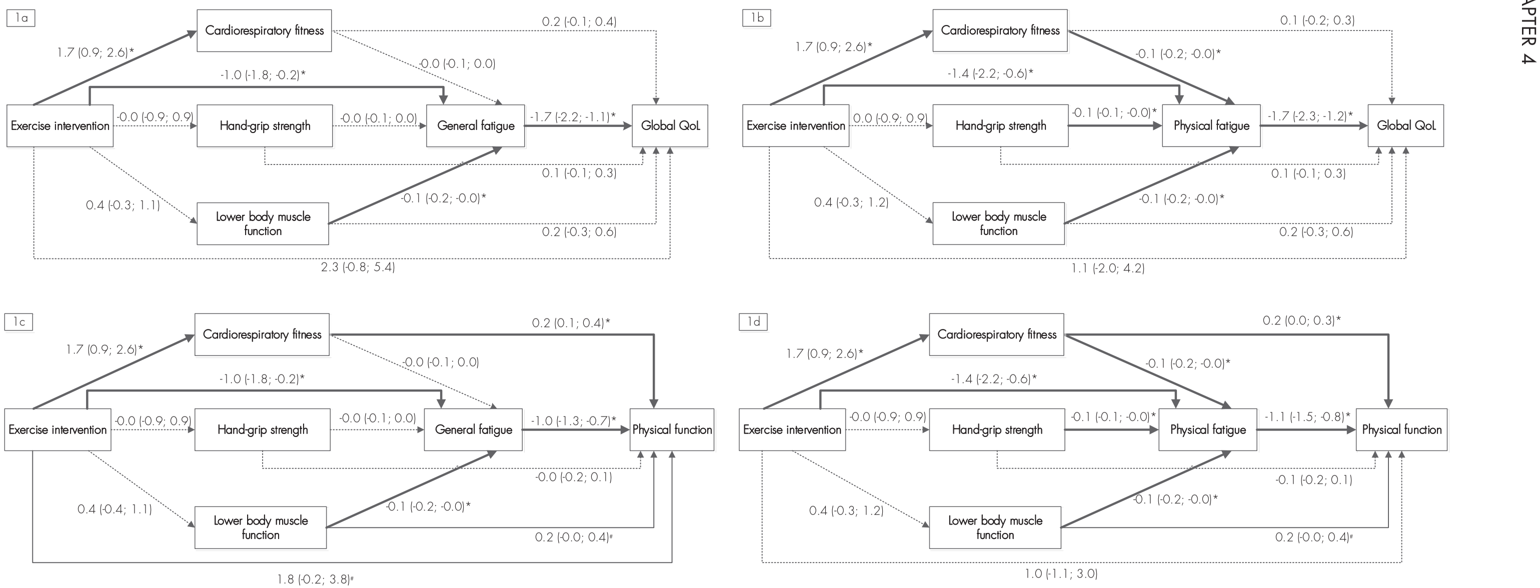
Both lower general and physical fatigue were significantly associated with higher global QoL and physical function. Higher cardiorespiratory fitness was significantly associated with higher physical function (Figure 1c and 1d), but not with global QoL (Figure 1a and 1b). The paths explained 44-61% of the total variance in global QoL or physical function and the models had an adequate fit (RMSEA<0.08; CFI>0.98; TLI>0.95, Figure 1). Sensitivity analyses showed larger effects on global QoL for HI compared to LMI exercise and for survivors of breast cancer compared to survivors of other cancer types. Other paths were comparable across subgroups.

TABLE 3 Unstandardized regression coefficients of the total and indirect effects and their 95% confidence intervals (CI) of the exercise intervention effect on global quality of life (QoL) and physical function, with cardiorespiratory fitness, hand-grip strength, lower body muscle function, and fatigue (either general or physical) as potential mediators

Model results	**General fatigue**	**Physical fatigue**
	Estimate (95% CI)	Estimate (95% CI)
Global QoL		
Effect from intervention on fatigue		
Total effect	**-1.1* (-1.9; -0.3)**	**-1.6* (-2.4; -0.8)**
Total indirect effect	-0.1 (-0.3; 0.0)	**-0.2* (-0.4; -0.1)**
Specific indirect effect via:		
Cardiorespiratory fitness	-0.1 (-0.2; 0.0)	**-0.2* (-0.4; -0.1)**
Hand-grip strength	0.0 (-0.0; 0.1)	-0.0 (-0.1; 0.1)
Lower body muscle function	-0.0 (-0.2; 0.0)	-0.0 (-0.2; 0.0)
Effect from intervention on global QoL		
Total effect	**4.5* (1.2; 7.8)**	**4.1* (0.8; 7.4)**
Total indirect effect	**2.2* (0.8; 3.8)**	**3.0* (1.5; 4.8)**
Specific indirect effect via:		
Fatigue	**1.6* (0.4; 3.1)**	**2.4* (1.1; 4.2)**
Cardiorespiratory fitness	0.3 (-0.1; 0.9)	0.1 (-0.3; 0.7)
Hand-grip strength	-0.0 (-0.2; 0.1)	0.0 (-0.1; 0.2)
Lower body muscle function	0.1 (-0.1; 0.6)	0.1 (-0.1; 0.6)
Cardiorespiratory fitness and fatigue	0.1 (-0.1; 0.4)	**0.3* (0.1; 0.7)**
Hand-grip strength and fatigue	-0.0 (-0.1; 0.1)	0.0 (-0.2; 0.1)
Lower body muscle function and fatigue	0.1 (-0.0; 0.3)	0.1 (-0.0; 0.3)
Physical function		
Effect from intervention on fatigue		
Total	**-1.1* (-1.9; -0.3)**	**-1.6* (-2.4; -0.8)**
Total indirect	-0.1 (-0.3; 0.0)	**-0.2* (-0.4; -0.1)**
Specific indirect		
Cardiorespiratory fitness	-0.1 (-0.2; 0.0)	**-0.2* (-0.4; -0.1)**
Hand-grip strength	0.0 (-0.0; 0.1)	-0.0 (-0.1; 0.1)
Lower body muscle function	-0.0 (-0.2; 0.0)	-0.0 (-0.2; 0.0)
Effect from intervention on physical function		
Total effect	**3.3* (1.2; 5.5)**	**3.2* (0.9; 5.3)**
Total indirect effect	**1.5* (0.7; 2.6)**	**2.2* (1.2; 3.5)**
Specific indirect effect via:		
Fatigue	**0.9* (0.2; 1.9)**	**1.6* (0.7; 2.7)**
Cardiorespiratory fitness	**0.4* (0.1; 0.9)**	0.3# (0.0; 0.7)
Hand-grip strength	0.0 (-0.1; 0.1)	-0.0 (-0.1; 0.1)
Lower body muscle function	0.1 (-0.0; 0.3)	0.1 (-0.0; 0.4)
Cardiorespiratory fitness and fatigue	0.1 (-0.0; 0.2)	**0.2* (0.1; 0.5)**
Hand-grip strength and fatigue	-0.0 (-0.1; 0.0)	0.0 (-0.1; 0.1)
Lower body muscle function and fatigue	0.0 (-0.0; 0.2)	0.0 (-0.0; 0.2)

Abbreviations: SE, standard error; Path analyses using maximum likelihood estimation with MPlus adjusted for baseline scores of the mediator, age and gender; * $p<0.05$; # $0.05 \leq p<0.10$.

FIGURE 1 Path models showing cardiorespiratory fitness, hand-grip strength, lower body muscle function, and fatigue as hypothesized mediators of the effect of the exercise intervention on global quality of life (QoL) and physical function



Note: Numbers represent unstandardized regression coefficients and their 95% confidence intervals (CI). Dotted lines represent non-significant associations, solid lines represent significant associations. Abbreviations: CFI, Comparative Fit Index; RMSEA, Root Mean Square Error of Approximation; TLI, Tucker Lewis index; a The model fitted the data: RMSEA=0.067, 90%CI=0.041;0.093, CFI=0.981, TLI=0.958. Explained total variance in global QoL=0.4; b The model fitted the data: RMSEA=0.073, 90%CI=0.048;0.098, CFI=0.977, TLI=0.950. Explained total variance in global QoL=0.4; c The model fitted the data: RMSEA=0.065, 90%CI=0.039;0.091, CFI=0.983, TLI=0.963. Explained total variance in physical function=0.6; d The model fitted the data: RMSEA=0.080, 90%CI=0.056;0.105, CFI=0.975, TLI=0.945. Explained total variance in physical function=0.6; * $p<0.05$; # $0.05 \le p < 0.10$

DISCUSSION

The current study found support for the hypothesis that a combined resistance and endurance exercise intervention improves cardiorespiratory fitness, which is associated with lower physical fatigue, and higher global QoL and physical function. Further, we found that higher hand-grip strength was significantly associated with lower physical fatigue, and better lower body muscle function with lower general and physical fatigue.

We previously reported beneficial effects of the exercise intervention on cardiorespiratory fitness, fatigue, and HRQoL [22], which supports previous reviews and meta-analyses [14,20,28]. The current study further elucidates these findings by providing insight into the mechanisms underlying the beneficial effects of resistance and endurance exercise on HRQoL.

Our finding that improved cardiorespiratory fitness mediated the exercise effects on physical fatigue, but not on general fatigue indicates that improving cardiorespiratory fitness is an important intervention strategy to reduce physical fatigue. The lack of mediating effect of improved cardiorespiratory fitness on general fatigue is in line with previous findings in prostate [8] and breast cancer survivors [30]. This may be explained by the fact that general fatigue does not only include physical aspects, but also mental aspects, which are perhaps more likely influenced by concepts other than or additional to cardiorespiratory fitness. It is possible that psychological factors such as depression and anxiety may mediate exercise effects on general fatigue [30]. Furthermore, exercise effects on fatigue could also be mediated by biological factors (e.g., improved body composition, and increased pro-inflammatory cytokines [31], or other psychosocial factors, such as reduced sleep quality, mastery, and self-efficacy [10,30]. These factors may also explain the direct beneficial effect of exercise on general fatigue in the current study as well as in a previous study [10].

In line with findings from previous studies [8,29], we found that higher hand-grip strength and better lower body muscle function was significantly associated with lower fatigue. We further found that better lower body muscle function tended to be associated with higher physical function. This indicates that muscle strength and function might be important intervention targets when aiming to reduce fatigue and improving physical function. However, due to the lack of a significant intervention effect on hand-grip strength and 30-seconds chair-stand test, we could not confirm that muscle strength and function mediated the exercise effects on fatigue and physical function. The lack of significant effects of exercise on muscle strength is in contrast with a previous meta-analysis [36] and a systematic review [24] summarizing the effects of exercise on muscle strength, and may be related to our choice of instruments used to assess the outcomes. Despite being valid and reliable measures of hand-grip strength [25] and lower body muscle function [5], they may have been less sensitive to detect exercise-induced changes. Future studies are needed to clarify the mediating role of muscle strength in the exercise-intervention effect on fatigue and physical function.

We further found that the effects of exercise on global QoL can be explained by reduced fatigue, which supports findings from previous studies [8,10,11,33]. In older long term prostate cancer survivors, lower general fatigue was associated with higher global QoL [9]. However, in this study lower general fatigue was not a mediator of the exercise effect [9]. Furthermore, our results demonstrate that the effects of exercise on physical function can be explained by reduced general and physical fatigue. This is in contrast to a study in prostate cancer survivors [8], which reported that general fatigue mediated the effects of exercise on global QoL but not on physical function. This lack of mediating effects of general fatigue on global QoL or physical function in these studies may be related to the lower baseline values of fatigue, leaving less room for improvement. In contrast, our study clearly suggests that reducing fatigue can be important to improve global QoL and physical function, and that exercise is an effective strategy to do so.

In addition to its effect via fatigue, we also found a direct association between improved cardiorespiratory fitness and improved physical function. The mediating role of cardiorespiratory fitness in the intervention effect on physical function was not found in studies among prostate cancer survivors [8,9]. Differences in mediating effects may be related to differences in study population, or to the type of instrument used to measure cardiorespiratory fitness [22]. Instead of the submaximal exercise test, the current study used a gold standard maximum exercise test to assess cardiorespiratory fitness, which may be more sensitive to detect changes and less prone to measurement error [2]. Baseline peakVO_2 values of our population were low compared to normative values [32], which may interfere with daily life functioning [37]. Our study showed that this can be (partially) counteracted by a training program of 12 weeks that improves cardiorespiratory fitness.

The strengths of the present study are the examination of mediators in a well-designed RCT with a relatively large sample size, the use of valid and reliable instruments to assess outcome measures, and the use of path analyses enabling the simultaneous evaluation of multiple mediators [7]. However, despite the use of an RCT design, one should still be cautious when making inferences about causality, because the mediator and outcome variables were measured at the same time [39]. Consequently, we studied associations rather than temporal relationships between these variables, and the reverse – that higher global QoL and physical function were associated with lower levels of fatigue – may also be true. However, fatigue was found to be the strongest predictor of HRQoL and physical function [3], supporting the direction of the association studied. Another limitation is the use of indirect measures to assess muscle strength. Both hand-grip strength and 30-seconds chair-stand test are valid and reliable measures to assess hand-grip strength (25) and lower body muscle function [5]. In addition, the use of (indirect) 1-RM tests would introduce learning bias in the intervention group because these tests were included as part of the intervention. However, hand-grip strength and 30-seconds chair-stand test may not have been sensitive enough to detect exercise-induced changes. Finally, to increase statistical power, and because we hypothesized that the intervention effects had similar mechanisms underlying beneficial effects on global QoL and physical function, we pooled the data from both intervention groups. Our sensitivity analyses indicated that paths were comparable across subgroups, except for the intervention effect on global QoL, which was larger for HI than LMI exercise and for survivors of breast cancer compared to other cancer types [22]. As a result of pooling, we were unable to distinguish differences in strengths of mediator effects between HI and LMI exercise.

Current results contribute to the understanding of the mechanisms by which a resistance and endurance exercise intervention achieves its effect on global QoL and physical function in cancer survivors. These results will help to further tailor interventions to the desired outcome. Supported by previous studies showing beneficial effects of exercise on cardiorespiratory fitness [20], it is recommended to improve cardiorespiratory fitness in order to reduce fatigue. Furthermore, reducing fatigue helps to improve the cancer survivors' global QoL and physical function.

In conclusion, this study found support for the hypothesis that exercise increases cardiorespiratory fitness, and consequently reduces physical fatigue and improves global QoL and physical function in cancer survivors shortly after completion of primary cancer treatment. Improving cardiorespiratory fitness could therefore be an important intervention target to reduce fatigue and to improve cancer survivors' global QoL and physical function.

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