



## Prostate Cancer

# Effects of Different Exercise Modalities on Fatigue in Prostate Cancer Patients Undergoing Androgen Deprivation Therapy: A Year-long Randomised Controlled Trial

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## Abstract

**Background:** Physical exercise mitigates fatigue during androgen deprivation therapy (ADT); however, the effects of different exercise prescriptions are unknown.

**Objectives:** To determine the long-term effects of different exercise modes on fatigue in prostate cancer patients undergoing ADT.

**Design, setting, and participants:** Between 2009 and 2012, 163 prostate cancer patients aged 43–90 y on ADT were randomised to exercise targeting the musculoskeletal system (impact loading + resistance training; ILRT;  $n = 58$ ), the cardiovascular and muscular systems (aerobic + resistance training; ART;  $n = 54$ ), or to usual care/delayed exercise (DEL;  $n = 51$ ) for 12 mo across university-affiliated exercise clinics in Australia.

**Intervention:** Supervised ILRT for 12 mo, supervised ART for 6 mo followed by a 6-mo home program, and DEL received a printed booklet on exercise information for 6 mo followed by 6-mo stationary cycling exercise.

**Outcome measurements and statistical analysis:** Fatigue was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 36 and vitality using the Short Form-36. Analysis of variance was used to compare outcomes for groups at 6 mo and 12 mo.

**Results and limitations:** Fatigue was reduced ( $p = 0.005$ ) in ILRT at 6 mo and 12 mo ( $\sim 5$  points), and in ART ( $p = 0.005$ ) and DEL ( $p = 0.022$ ) at 12 mo. Similarly, vitality increased for all groups ( $p \leq 0.001$ ) at 12 mo ( $\sim 4$  points). Those with the highest levels of fatigue and lowest vitality improved the most with exercise ( $p_{\text{trend}} < 0.001$ ). A limitation was inclusion of mostly well-functioning individuals.

**Conclusions:** Different exercise modes have comparable effects on reducing fatigue and enhancing vitality during ADT. Patients with the highest levels of fatigue and lowest vitality had the greatest benefits.

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**Patient summary:** We compared the effects of different exercise modes on fatigue in men on androgen deprivation therapy. All exercise programs reduced fatigue and enhanced vitality. We conclude that undertaking some form of exercise will help reduce fatigue, especially in those who are the most fatigued.

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## 1. Introduction

Androgen deprivation therapy (ADT) is extensively used in the management of prostate cancer (PCa) but is associated with an array of adverse effects [1]. One adverse effect which has a considerable impact on quality of life is fatigue and a substantial proportion of men with PCa suffer from fatigue, with ~40% or more of those on long-term ADT reporting chronic fatigue or clinically-relevant fatigue which interferes with daily functioning [2].

Exercise interventions have shown positive effects on reducing or mitigating fatigue [3]. As a result, recent expert reviews in urology/oncology have incorporated aerobic and resistance exercise interventions as evidence-based strategies to mitigate toxicities from ADT including fatigue [1,4]. We [5,6] and others [7,8] have reported in relatively short-term trials (< 6 mo) of progressive resistance (strength) training and/or aerobic exercise consisting of walking/jogging or cycling at moderate to high intensity can reduce or prevent the worsening of fatigue, as can the same exercise modes when combined with dietary advice/behavioural components in a lifestyle intervention [9,10]. However, these studies have examined only the effects of short-term interventions with longer-term outcomes rarely reported. Importantly, advancements to exercise protocols/prescription are required to understand the potential of different exercise modalities on fatigue. Accordingly, we report for the first time the efficacy of a 1-y long randomised controlled trial (RCT) of varying exercise interventions in PCa patients undergoing ADT with changes in fatigue and vitality assessed over 6 mo and 12 mo.

## 2. Patients and methods

### 2.1. Patients

Two-hundred and ninety-three patients with PCa were screened for participation from 2009 to September 2012 at Perth, Western Australia and Brisbane, Queensland and their progress through the study is detailed in Fig. 1. Inclusion criteria included histologically documented PCa, minimum exposure to ADT of 2 mo, without prostate-specific antigen (PSA) evidence of disease activity, and anticipated to receive ADT for the subsequent 12 mo. Exclusion criteria included bone metastatic disease, musculoskeletal, cardiovascular, or neurological conditions that could inhibit them from exercising, inability to walk 400 m or undertake exercise, and structured resistance and aerobic training in the previous 3 mo. All participants obtained medical clearance from their physician. The study was approved by the University Human Research Ethics Committee and all participants provided written informed consent.

### 2.2. Study design and random assignment

This was a three-armed RCT. Primary endpoints were bone mineral density and cardiovascular capacity [11], which will be reported

elsewhere, with secondary endpoints including physical function and self-reported patient outcomes. Potential participants were primarily identified by their treating urologist/oncologist and referred to the study coordinator to confirm eligibility, describe the study, and obtain informed consent. Study patients underwent a familiarisation session that included correct exercise technique followed by baseline testing comprising physical tests, questionnaires, and a venous blood sample. Following baseline assessment, participants were stratified according to time on ADT (< 6 mo or ≥ 6 mo) and randomly allocated to: impact loading + resistance training (ILRT), aerobic + resistance training (ART), or to usual care/delayed exercise (DEL) by computer random assignment.

### 2.3. Exercise training program

ILRT was undertaken twice weekly in University-affiliated exercise clinics for 12 mo. Sessions were supervised with up to 10 participants. The impact-loading component consisted of a series of bounding, skipping, drop jumping, hopping, and leaping activities that produced ground reaction forces of 3.4–5.2 times body weight, and was progressive in nature. Specific details on progression are described elsewhere [11]. Resistance training consisted of six principal exercises that targeted the major upper and lower body muscle groups: chest press, seated row, shoulder press, leg press, leg extension, and leg curl, with supplementary exercises. Patients performed two to four sets of each exercise at an intensity of 6–12 RM (maximal weight that can be lifted 6–12 times). In addition, the ILRT group undertook home training twice weekly that consisted of two to four rotations of skipping/hopping/leaping/drop jumping [11]. ART underwent supervised exercise in the clinic twice weekly for the initial 6 mo. The aerobic-based component consisted of 20–30 min of exercise at 60–75% of estimated maximal heart rate using various modes which included walking/jogging and cycling or rowing on stationary ergometers. Resistance exercise during the initial 6 mo was the same as that undertaken in the ILRT regimen. In addition, participants were encouraged to undertake home-based aerobic activity such as walking or cycling with the goal to accumulate 150 min/wk of aerobic activity. For the 2nd 6 mo, patients were provided with a home-based maintenance program similar to our previous report [12]. DEL were provided with a printed booklet with information about exercise for the initial 6 mo, followed by 6 mo of twice weekly supervised exercise on a cycle ergometer at an intensity of ~70% maximal heart rate and flexibility exercises in the clinic. During the 12-mo study period, ILRT, ART, and DEL were asked to maintain customary physical activity and dietary patterns.

### 2.4. Fatigue and vitality

Study endpoints of fatigue and vitality were assessed at baseline, 6 mo, and 12 mo. Fatigue was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30; Table 1). Fatigue is a three-item symptom subscale with higher scores representing greater fatigue [13]. Vitality (energy level and fatigue) was assessed with the Short Form-36 Health Survey (SF-36; Table 1) [14]. The Vitality scale of the SF-36 is a four-item subdomain measure with scores ranging from 0 to 100, with higher values indicating more vitality [15].

**Table 1 – Fatigue subscale questions from the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 36 and the Vitality scale questions from the Short Form-36 Health Survey**

Fatigue subscale questions	
During the past wk (4-point scale from “Not At All” to “Very Much”):	
Did you need to rest?	
Have you felt weak?	
Were you tired?	
Vitality scale questions	
How much of the time during the past 4 wk (5-point scale from “All of the Time” to “None of the Time”):	
Did you feel full of life?	
Did you have a lot of energy?	
Did you feel worn out?	
Did you feel tired?	

### 2.5. Other measures

The 400-m walk was used as a measure of cardiovascular fitness [5,12,16] and muscle strength was assessed using the 1-RM method [17]. Strength is reported as the sum of the chest press and leg press, representative of upper- and lower-body strength, respectively. Percent body fat was determined using dual-energy x-ray absorptiometry. PSA and total testosterone were assessed by an accredited laboratory. Nutritional status was assessed by the Mini Nutritional Assessment [18] and self-reported physical activity by the Leisure Score Index of the Godin Leisure-Time Exercise Questionnaire [19].

### 2.6. Statistical analyses and sample size calculation

The sample size estimate for the RCT was based on projected changes in the primary outcomes of bone mineral density and cardiorespiratory

capacity [11]. To achieve 90% power at an  $\alpha$  level of 0.05 (two-tailed) and account for an attrition rate of up to 35%, 65 patients per group were required. For fatigue and vitality, assuming a minimally important difference (MID) of 5 points for fatigue [20] and for vitality [21], ~69 patients per group were required for fatigue (~51 patients for 80% power), and ~42 patients per group for vitality. Data were analysed using IBM SPSS Version 21 (IBM Corp., Armonk, NY, USA). Analyses included standard descriptive statistics, chi-square, one-way analysis of variance, and one-way and two-way (group x time) repeated measures analysis of variance. Follow-up tests were performed if the interaction or main effect for time was significant. Where appropriate, the Bonferroni post-hoc procedure for multiple comparisons was used to locate the source of significant differences. Trend analysis was performed using linear regression and entering quartiles of fatigue and vitality at baseline as an ordinal variable. Intention to treat was utilised for all analyses using maximum likelihood imputation of missing values (expectation maximisation). Tests were two-tailed with an  $\alpha$  level of 0.05 applied as the criterion for statistical significance.

## 3. Results

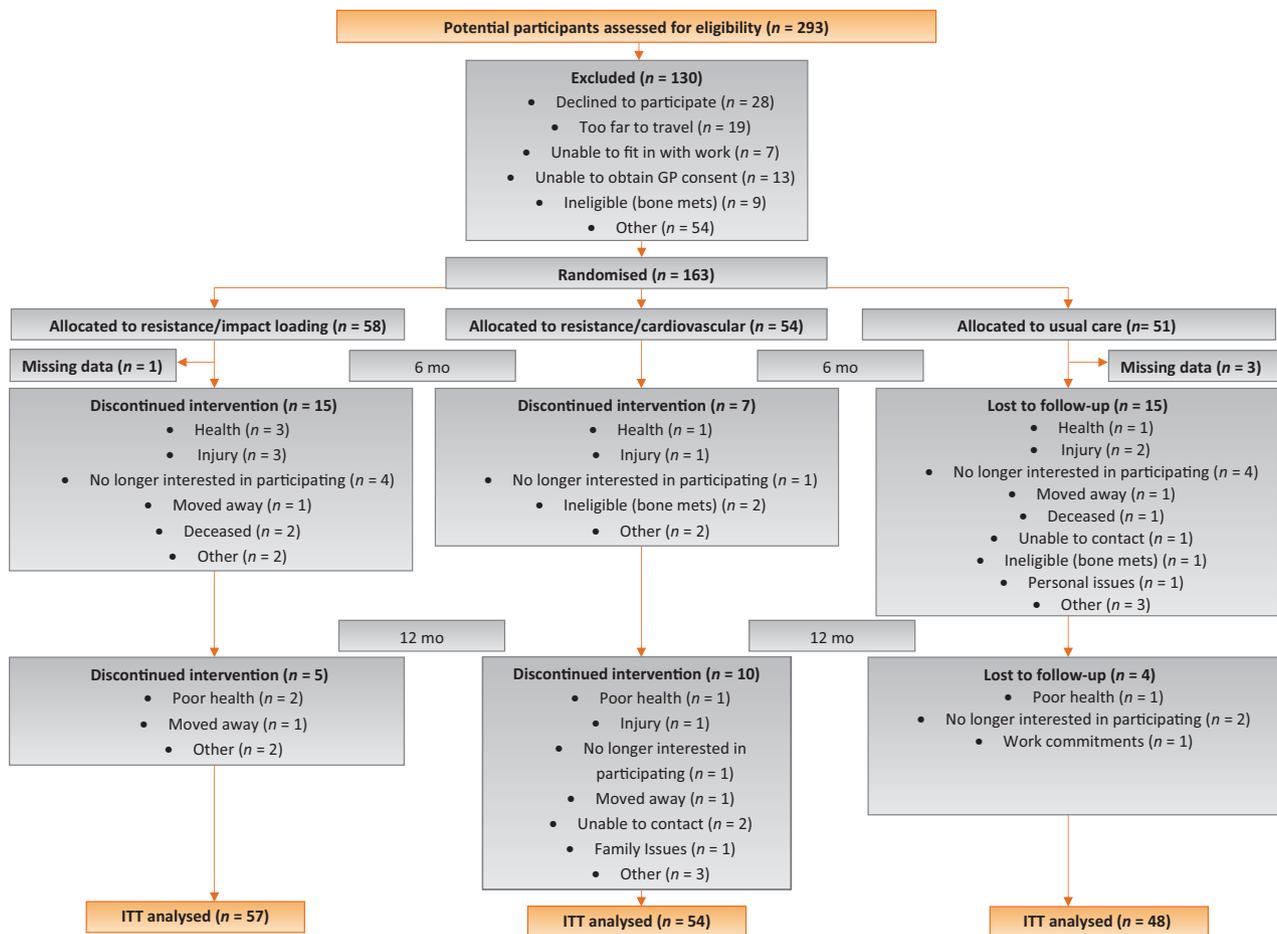
### 3.1. Patients characteristics

There were no significant differences among groups at baseline (Table 2). The median (interquartile range) time for entry into the study since diagnosis was 8 (4–73) mo, 9 (4–47) mo, and 8 (4–40) mo, and for time on ADT 3 (2–4) mo, 3 (2–4) mo, and 2 (2–4) mo for ILRT, ART, and DEL, respectively. Of the 163 participants, four men had missing data at baseline for both fatigue and vitality resulting in a study group of 159 men in this report. Of these 159 parti-

**Table 2 – Participant characteristics (mean  $\pm$  standard deviation)**

	ILRT (n = 57)	ART (n = 54)	DEL (n = 48)	p value
Age (y)	68.9 $\pm$ 9.1	69.0 $\pm$ 9.3	68.4 $\pm$ 9.1	0.947
Height (cm)	173.6 $\pm$ 5.8	173.2 $\pm$ 6.8	171.6 $\pm$ 5.2	0.215
Weight (kg)	84.4 $\pm$ 11.2	84.9 $\pm$ 15.6	88.4 $\pm$ 15.4	0.316
Body fat (%)	28.1 $\pm$ 4.8	27.3 $\pm$ 5.9	29.6 $\pm$ 5.0	0.086
Gleason score	7.7 $\pm$ 1.4	8.0 $\pm$ 0.9	7.8 $\pm$ 1.0	0.548
Cancer stage grouping				
Localised, N (%)	52 (91.2)	50 (92.6)	45 (93.8)	0.887
Nodal metastases, N (%)	5 (8.8)	4 (7.4)	3 (6.3)	
Bone metastases, N (%)	0 (0)	0 (0)	0 (0)	
PSA (ng/ml)	1.3 $\pm$ 2.1	1.0 $\pm$ 1.8	1.3 $\pm$ 2.4	0.730
Testosterone (pg/ml)	0.8 $\pm$ 1.1	1.1 $\pm$ 2.6	1.3 $\pm$ 3.4	0.536
MNA	27.2 $\pm$ 2.3	27.6 $\pm$ 2.2	27.6 $\pm$ 1.8	0.633
Godin LSI	20.6 $\pm$ 16.5	23.5 $\pm$ 20.7	21.8 $\pm$ 16.0	0.698
Employed, N (%)	22 (38.6)	17 (31.5)	19 (39.6)	0.571
Married, N (%)	44 (77.2)	42 (77.8)	43 (89.6)	0.720
Current smoker, N (%)	3 (5.3)	3 (5.6)	3 (6.3)	0.822
ADT + antiandrogen, N (%)	27 (47.4)	30 (55.6)	27 (56.3)	0.586
ADT time (mo)	4.2 $\pm$ 4.5	5.3 $\pm$ 7.6	3.7 $\pm$ 3.7	0.320
Radiation, N (%)	49 (86.0)	50 (92.6)	40 (83.8)	0.341
Prostatectomy, N (%)	20 (35.1)	15 (27.8)	12 (25.0)	0.497
Other conditions				
CVD, N (%)	4 (7.0)	3 (5.6)	2 (4.2)	0.819
Hypertension, N (%)	20 (35.1)	15 (27.8)	23 (47.9)	0.104
Dyslipidaemia, N (%)	11 (19.3)	14 (25.9)	10 (20.8)	0.682
Diabetes, N (%)	5 (8.8)	7 (13.0)	8 (16.7)	0.475

ADT = androgen deprivation therapy; ART = aerobic + resistance training; DEL = usual care/delayed exercise; ILRT = impact-loading + resistance training; LSI = Leisure Score Index; PSA = prostate specific antigen; MNA = Mini Nutritional Assessment with malnourished <17, undernourished 17–23.5, well-nourished >23.5; Godin LSI, with a moderate-to-strenuous LSI  $\geq$ 24 classed as active and  $\leq$ 23 classed as insufficiently active.



**Fig. 1 – Consolidated standards of reporting trials diagram.** ITT = intention to treat; Mets = metastasis.

Participants, three men had missing data for fatigue and one participant had missing data for vitality, resulting in 156 participants for fatigue and 158 for vitality in the analyses. Men in the study were primarily, if not all, Caucasian. During the trial, 34 men in ILRT, 31 in ART, and 29 in DEL received radiation therapy in conjunction with ADT ( $p = 0.949$ ). No men were on or progressed during the trial to chemotherapy. In the 1st 6 mo of the study 37 men withdrew with an additional 19 at 12 mo for a total of 56 men (Fig. 1). Nutritional status did not differ among groups over the 12-mon period ( $p = 0.245$ ) nor was there a significant interaction for physical activity among groups ( $p = 0.063$ ). There was no significant change in PSA ( $p = 0.103$ ) or testosterone ( $p = 0.083$ ) during the study period. Attendance at the supervised sessions was 65% and 69% for ILRT at 6 mo and 12 mo, respectively, 69% for ART for the 1st 6-mo period, and 63% for DEL for the 6–12 mo period.

### 3.2. Fatigue and vitality

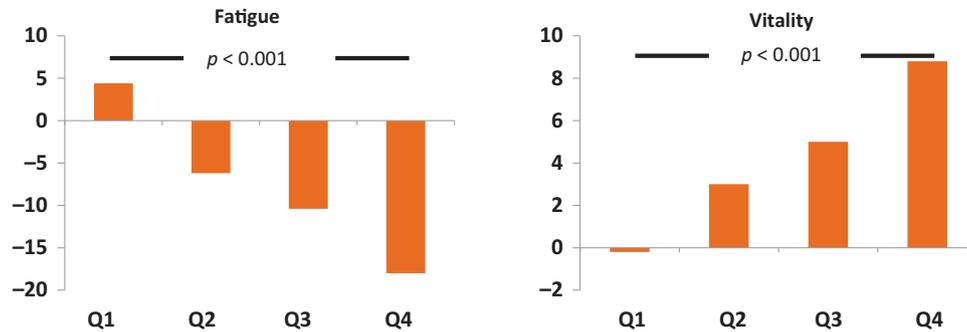
There was no difference among groups for fatigue ( $p = 0.498$ ) or vitality ( $p = 0.723$ ) at baseline (Table 3). With training, there was no significant interaction ( $p = 0.304$ ) but a significant effect for time ( $p < 0.001$ ) with fatigue reduced

( $p = 0.005$ ) in ILRT at 6 mo and 12 mo by  $\sim 5$  points, and in ART ( $p = 0.005$ ) and DEL ( $p = 0.022$ ) by  $\sim 5$  points at 12 mo. Similarly, there was no significant interaction ( $p = 0.525$ ) but a significant effect for time ( $p < 0.001$ ) with vitality increasing for all groups ( $p \leq 0.001$ ) at 12 mo by  $\sim 4$  points. There was no change in fatigue or vitality during the initial 6-mo usual care period for DEL. When levels of fatigue and vitality were examined by quartiles, those with the highest levels of fatigue and lowest levels of vitality at baseline responded the best to exercise such that there was a progressive decrease in fatigue ( $p_{\text{trend}} < 0.001$ ) and increase

**Table 3 – Fatigue and vitality at baseline, 6 mo, and 12 mo**

	Baseline	6 mo	12 mo	<i>p</i> value	
Fatigue					
ILRT	27.9 ± 20.7	22.2 ± 15.4	22.5 ± 16.6	0.005	B > 6, 12
ART	23.4 ± 18.1	21.9 ± 18.4	17.7 ± 15.0	0.005	B, 6 > 12
DEL	25.8 ± 20.2	24.6 ± 17.7	20.3 ± 15.3	0.022	B, 6 > 12
Vitality					
ILRT	50.0 ± 10.8	51.9 ± 8.0	54.6 ± 8.5	<0.001	B, 6 < 12
ART	51.5 ± 10.7	52.7 ± 9.8	55.3 ± 8.7	0.001	B, 6 < 12
DEL	50.3 ± 10.0	50.1 ± 9.7	53.9 ± 8.1	<0.001	B, 6 < 12

ART = aerobic + resistance training; B = baseline; DEL = usual care/delayed exercise; ILRT, impact-loading + resistance training.



**Fig. 2 – Change in fatigue (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 36) and vitality (Short Form-36) with 6–12 mo exercise according to baseline status. Quartile 1 (Q1) least fatigued and highest vitality to quartile 4 (Q4) most fatigued and least vitality. Fatigue cut-points were 22 for Q2, 33 for Q3, and 44 for Q4. For vitality, cut-points were 58 for Q2, 51 for Q3, and 44 for Q4. The *p* value is for trend analysis.**

in vitality ( $p_{\text{trend}} < 0.001$ ) with exercise (Fig. 2). Sensitivity analysis was conducted using complete cases [22] with no change in the results for vitality and although for fatigue there was a significant main effect for time ( $p = 0.003$ ) with the magnitude of difference within groups over time similar, with the reduction in sample size and hence statistical power the only significant difference was for ART ( $p = 0.032$ ).

**3.3. Other measures and adverse events**

For cardiorespiratory fitness, there was no significant interaction ( $p = 0.216$ ) but a significant effect for time ( $p < 0.001$ ) with fitness improved ( $p = 0.008$ ) in ILRT at 12 mo by ~14 s and in ART ( $p < 0.001$ ) by ~13 s at 12 mo, with the change in DEL of ~11 s at 12 mo approaching significance ( $p = 0.063$ ; Table 4). Notably, there was no change in cardiorespiratory fitness during the nonexercise period for DEL. For muscle strength, there was a significant interaction ( $p < 0.001$ ) with strength progressively increasing at 6 mo and 12 mo ( $p < 0.001$ ) in ILRT, increasing during the initial 6-mo supervised phase in ART ( $p < 0.001$ ) with no change thereafter, and no change between baseline and 6 mo in DEL but a difference by 12 mo following exercise

( $p < 0.001$ ). No adverse effects from exercise resulted in any participants having to withdraw from the study. Two men in ILRT withdrew within the 1st 6 mo due to compressed spinal discs and shoulder issues, although the person developed shoulder issues prior to commencing exercise training. Two men in ART had cardiovascular problems, one in the 1st 6 mo and one in the 2nd 6 mo, with one requiring heart bypass surgery while another participant in ART developed back pain. Two men withdrew from DEL in the 1st 6 mo due to difficulty walking and the other required back surgery.

**4. Discussion**

To our knowledge, this is the first year-long RCT to evaluate the effects of different exercise modalities on fatigue in prostate cancer patients undergoing ADT. There were two important findings: (1) all exercise modalities (resistance + impact loading, aerobic + resistance, aerobic only) had a beneficial effect on fatigue and vitality, and (2) those with the highest levels of fatigue and lowest vitality improved the most with exercise.

A substantial proportion of PCa patients will receive ADT as part of their treatment. Prevalence of clinically-relevant fatigue in these patients has been reported as ~40% [2,23]. The fatigue scores from the EORTC QLQ-C30 in our cohort are similar to the reference values for men with PCa aged 60–69 y ( $25.2 \pm 26.6$ ) [24]. Vitality has also been shown to decline during ADT. In a population-based sample of men with PCa followed for 1 y, Alibhai et al [25] reported vitality was substantially lower in ADT-treated compared with non-ADT patients. A more recent prospective study also showed changes in vitality following 12 mo of ADT with rapid declines during the initial 3 mo [26].

Short-term exercise trials have shown the efficacy of combined resistance and aerobic exercise, or as sole training modes, to improve fatigue in men undergoing radiation therapy/ADT for PCa [5,7,8]. We have also shown improvements in vitality following a 12-wk exercise intervention [5]. Here we extend these findings by providing data on the largest exercise trial undertaken with men undergoing ADT

**Table 4 – Cardiovascular fitness and muscle strength at baseline, 6 mo, and 12 mo**

	Baseline	6 mo	12 mo	<i>p</i> value	
Cardiovascular fitness (s)					
ILRT	274.6 ± 56.1	264.3 ± 47.7	260.8 ± 48.7	0.008	B > 12
ART	269.6 ± 50.9	254.8 ± 41.7	256.8 ± 47.7	<0.001	B > 12
DEL	278.8 ± 52.5	276.3 ± 53.8	268.3 ± 47.1	0.063	
Muscle strength (kg)					
ILRT	161.2 ± 57.6	188.9 ± 63.5	199.4 ± 65.5	<0.001	B < 6 < 12
ART	163.8 ± 61.3	193.5 ± 66.0	191.8 ± 64.8	0.001	B < 6, 12
DEL	168.8 ± 73.7	177.1 ± 70.0	187.5 ± 76.8	<0.001	B < 12

ART = aerobic + resistance training; B = baseline; DEL = usual care/delayed exercise; ILRT = impact-loading + resistance training. Cardiovascular fitness determined by the 400-m walk; muscle strength equals the sum for the chest press and leg press exercises.

for PCa by examining the long-term effects of exercise and potential impact of different exercise modalities. We found that all exercise modalities had a similar effect on fatigue and vitality following the intervention. In a recent systematic review on fatigue instruments, the MID reported for the EORTC QLQ-C30 ranged from 3.0–19.7 points [20]. The mean differences for our exercise regimens was ~5 points with those in quartiles 3 and 4 at baseline having a change of 10 or more points. Similarly, it has been recommended that the MID in vitality using the SF-36 is 5 points [21]. The mean change for each of the three exercise regimens was ~4 points, with quartiles 3 and 4 gaining a mean of 5 points or more. This result is important as it provides practical information to guide the prescription of exercise in men with PCa to mitigate cancer-related fatigue.

We have recently reported that only ~12% of Australian PCa survivors are meeting sufficient exercise levels [27]. It appears that supervised exercise undertaken at moderate- to high-intensity, irrespective of modality (eg, aerobic, resistance, or impact) has a beneficial effect on fatigue. Moreover, those with higher levels of fatigue/lower levels of vitality responded the best to exercise such that there was a progressive decrease in fatigue and increase in vitality with exercise. As a result, fatigued patients are likely to benefit most from any form of structured supervised exercise when undertaken at appropriate intensity and dose. From this we propose that screening patients on ADT for fatigue and directing tailored and prescribed exercise interventions to these men should be part of the prostate cancer care pathway.

During the nonexercise period for the delay group there was no change in fatigue or vitality and no change in cardiorespiratory fitness or muscle strength. Conversely, with exercise improvements were observed in physical functioning as they were in ILRT and ART, and these were accompanied by changes in fatigue and vitality. Cardiorespiratory fitness changes as determined by the 400-m walk [28], although not substantial [16], would at least provide a greater safety margin before thresholds for disability are encountered, hence may potentially be clinically meaningful (especially for men in poorer condition than those in the present study).

Our study has several features that are worthy of comment. This is the largest and longest exercise trial in PCa patients undergoing ADT examining different exercise modalities including resistance, impact loading and aerobic training. Fatigue was assessed using the EORTC QLQ-C30 fatigue subscale which is a validated measure, widely used, and recommended for use in trials to measure cancer-related fatigue [29]. However, the generalisability of the data may be limited given that participants volunteered to participate in an exercise trial, were generally quite healthy, and predominantly were married and nonsmokers. In addition, a potential confounding factor was the group nature of the supervised sessions resulting in the sharing of common experiences and the camaraderie which may have developed, impacting on the outcomes of the study. Finally, men in this study were primarily in the initial year of ADT, therefore results may not be generalisable to men receiving ADT for a longer duration.

## 5. Conclusions

In conclusion, in the largest year-long exercise intervention study in men with PCa undergoing ADT, all exercise programs had comparable effects on reducing fatigue and enhancing vitality. However, the benefits were small to nonexistent for those least fatigued at baseline and as such an involved intervention should primarily be considered for those who are most fatigued. Encouraging fatigued patients to undertake exercise at adequate intensity, regardless of mode, will likely aid in reducing or attenuating the adverse effects of ADT on fatigue and vitality. Screening all men on ADT for fatigue and providing an exercise intervention is warranted.

**Author contributions:** Dennis R. Taaffe had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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*Acquisition of data:* Taaffe, Newton, Wall, Bolam, Galvão.

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*Critical revision of the manuscript for important intellectual content:* Taaffe, Newton, Spry, Joseph, Gardiner, Chambers, Bolam, Wall, Cormie, Galvão.

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*Obtaining funding:* Taaffe, Newton, Spry, Joseph, Gardiner, Galvão.

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*Other:* None.

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