Exercise-induced attenuation of treatment side-effects in patients with newly diagnosed prostate cancer beginning androgen-deprivation therapy: a randomised controlled trial

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Objectives
(i) To assess whether exercise training attenuates the adverse effects of treatment in patients with newly diagnosed prostate cancer beginning androgen-deprivation therapy (ADT), and (ii) to examine whether exercise-induced improvements are sustained after the withdrawal of supervised exercise.

Patients and Methods
In all, 50 patients with prostate cancer scheduled for ADT were randomised to an exercise group (n = 24) or a control group (n = 26). The exercise group completed 3 months of supervised aerobic and resistance exercise training (twice a week for 60 min), followed by 3 months of self-directed exercise. Outcomes were assessed at baseline, 3- and 6-months. The primary outcome was difference in fat mass at 3-months. Secondary outcomes included: fat-free mass, cardiopulmonary exercise testing variables, QRISK² (ClinRisk Ltd, Leeds, UK) score, anthropometry, blood-borne biomarkers, fatigue, and quality of life (QoL).

Results
At 3-months, exercise training prevented adverse changes in peak O₂ uptake (1.9 mL/kg/min, P = 0.038), ventilatory threshold (1.7 mL/kg/min, P = 0.013), O₂ uptake efficiency slope (0.21, P = 0.005), and fatigue (between-group difference in Functional Assessment of Chronic Illness Therapy-Fatigue score of 4.5 points, P = 0.024) compared with controls. After the supervised exercise was withdrawn, the differences in cardiopulmonary fitness and fatigue were not sustained, but the exercise group showed significantly better QoL (Functional Assessment of Cancer Therapy-Prostate difference of 8.5 points, P = 0.034) and a reduced QRISK2 score (−2.9%, P = 0.041) compared to controls.

Conclusion

Keywords
androgen-deprivation therapy, aerobic exercise, resistance training, urology, #ProstateCancer, #PCSM

Introduction
Androgen-deprivation therapy (ADT) is often the first-line treatment for locally advanced and metastatic prostate cancer. Whilst the therapeutic benefits of ADT are well-established [1], it is associated with several adverse side-effects; including increased body fat and reduced skeletal muscle mass [2]. ADT also leads to reduced cardiopulmonary fitness and functional capacity [3,4], as well as increased fatigue and incidence of metabolic syndrome [5,6]. These negative changes can increase the risk of a cardiovascular (CV) events and reduce health-related quality of life (QoL) [7,8].

Exercise has been recognised as a potential strategy for managing the adverse effects of ADT [9]. A recent meta-analysis of 15 studies showed that exercise training can improve aerobic capacity and mitigate ADT-related increases in body fat in patients with prostate cancer [10]. However, with scant exception [11], this evidence relates to the effects of exercise in patients that have already developed adverse effects from receiving long-term ADT. Given that these
adverse health effects occur rapidly in the early stages of treatment [12,13], it is pertinent to explore whether exercise administered concurrently with the initiation of ADT could retard or prevent treatment toxicities.

To date, only one study has prescribed exercise at the commencement of ADT. Cormie et al. [11] reported beneficial effects of a 3-month supervised exercise intervention on body composition, strength, blood lipid profile, cardiopulmonary fitness, and QoL in 63 patients with prostate cancer beginning ADT at a single-centre [11]. However, it is unknown whether exercise-induced improvements can be maintained over the longer-term after withdrawal of supervised exercise. This is important because treatment-associated side-effects continue to develop after the first 3 months of ADT [3,14] and reductions in strength and physical function have been observed just 3 months after the cessation of supervised exercise in older adults [15]. Therefore, the purpose of the present study was to: (i) examine whether a supervised programme of aerobic and resistance exercise training reduces treatment-related side-effects in patients with prostate cancer beginning ADT, and (ii) to determine whether any exercise-induced improvements can be sustained by encouraging patients to maintain self-directed exercise after the withdrawal of supervision.

Patients and Methods

Patients with newly diagnosed prostate cancer listed for ADT by the urology multi-disciplinary team at the Norfolk and Norwich University Hospitals NHS Foundation Trust, UK, were recruited from urology outpatient clinics from 2012 to 2014. Inclusion criteria were: histologically confirmed prostate cancer, aged 50–80 years, beginning LHRH agonist treatment with or without radiotherapy, anticipated to remain on ADT for ≥6 months, be classified as 0 or 1 according to the WHO performance status, and not achieving 150 min/week of moderate intensity physical activity during the last 6 months. Exclusion criteria were: metastatic bone disease, previously treated with ADT, involvement in any other clinical trial, prior CV event or heart failure, chronic obstructive pulmonary disease, and an absolute contraindication to exercise testing or training [16]. Written informed consent was obtained before study participation and the protocol was approved by the East of England Regional Committee. This trial was registered at ClinicalTrials.gov (trial ID: NCT03776045).

Experimental Design

This study was a single-centred, parallel groups, prospective, randomised controlled trial (RCT). After baseline testing, patients were randomly allocated 1:1 to a standard care control group or a standard care plus exercise group using a randomisation sequence created by an independent researcher (nQuery, Statistical Solutions Ltd, Boston, MA, USA). Treatment allocation was concealed from the research team until after baseline measurements were collected. Outcome assessors and data analysts were blind to treatment allocation. Outcomes were assessed at baseline, 3-months (post-intervention), and 6-months (follow-up).

Exercise Intervention

The intervention was supervised by exercise science staff in the exercise science facilities at the University of East Anglia, UK, which is adjacent to the treating hospital. Patients competed two supervised exercise sessions per week for 12 weeks upon initiating ADT. Each session lasted ~60 min and included aerobic interval exercise on a cycle ergometer (Monark 824E; Varberg, Sweden) followed by resistance training. The aerobic exercise component involved a 5 min warm-up at light resistance (50 W) followed by 6 × 5 min bouts at an intensity of 11–15 on the 6–20 Borg Rating of Perceived Exertion (RPE) Scale [17], corresponding to 55–85% of the age-predicted maximum heart rate (220 – age) [18]. Patients maintained a cadence of 50 rev/min and each 5 min bout was separated by 2.5 min of active recovery at light resistance (50 W). As patients became accustomed to the exercise, they were encouraged to progress towards the upper threshold of intensity by adding further load to the cycle ergometer flywheel. The resistance training component included six exercises that targeted the major muscle groups (dumbbell squat, modified press-up, dumbbell bent-over row, dumbbell bicep curl, short arc quad, wall squat). Patients performed 2–4 sets of 10 repetitions at 11–15 RPE, which is a valid method of monitoring resistance training intensity in this population [19]. Each exercise was separated by 30 s of passive rest. Resistance training stimuli were progressed weekly by increasing the external load and/or increasing the number of sets. In addition to the supervised exercise sessions, patients were advised to increase their habitual physical activity levels and were encouraged to engage in 30 min of self-directed structured exercise or physical activity on 3 days each week (e.g., brisk walking, cycling, home-based resistance training). After the withdrawal of supervision (i.e., after the 3-month supervised intervention had finished), patients were instructed to continue exercising and to maintain self-directed levels of physical activity.

Standard Care

The control group did not receive any supervised exercise or specific physical activity recommendations, although they were offered some supervised exercise sessions after completing the study.
Outcome Measurements

The primary outcome was difference in body fat mass at 3-months. This was chosen because body fat has shown a high propensity to increase during the initial 3 months of ADT, more so than other measures [20], which highlights the importance of targeting body fat at this stage of treatment. Secondary outcomes included fat-free mass (FFM), cardiopulmonary exercise testing (CPET) variables, CV events risk, anthropometry, blood-borne biomarkers, fatigue, and QoL. Although not clinical endpoints, these outcomes were chosen because they have been shown to be adversely affected by ADT and are related to an increased risk of mortality and/or CV disease [21–24].

Body Composition and Anthropometry

Body mass and stature were measured with a calibrated balance beam scale and a wall-mounted stadiometer, respectively. Whole-body fat mass and FFM were measured with bioelectrical impedance analysis (BIA) and concurrent bioelectrical impedance vector analysis, with a single-frequency, phase-sensitive 50 kHz analyser (BIA-101; RJL/Akern Systems, Firenze, Italy). This method is considered valid for measuring changes in body composition [25]. Waist and hip circumferences were measured with a non-stretching anthropometric tape using standard techniques [26].

Cardiopulmonary Fitness

An incremental CPET was performed on an electronically braked cycle ergometer (Excalibur Sport, Lode, Netherlands) to determine maximum exercise tolerance. Following a warm-up against no added resistance, work rate was increased by 10–20 W/min to volitional exhaustion. Patients maintained a cadence of 50–60 rev/min throughout, with exhaustion defined as a ≥10 rev/min drop in cadence for 5 s consecutively. Breath-by-breath data were recorded throughout (Ultima™, CardioO2® gas exchange analysis system; Medical Graphics Corp., Saint Paul, MN, USA) and averaged before interpretation using a moving average (middle five of seven breaths). Peak O2 consumption (VO2peak) was determined as the highest (moving average) VO2 attained during the CPET. Peak effort was confirmed by a peak respiratory exchange ratio of >1.10 and/or a peak heart rate within 10 beats/min of age-predicted maximum. The ventilatory threshold (VT) was estimated using the ed V-slope method [27], which was confirmed by evaluating ventilatory equivalents and end-tidal pressures. Two analysts independently determined VT, with discrepancies of ≥7.5% resolved through discussion and consultation with a third analyst, if necessary. Ventilatory equivalents for O2 (VE/VO2) and CO2 (VE/VCO2) at VT, O2 pulse at peak exercise, and O2 uptake efficiency slope (OUES) were also derived.

Biomarkers

Fasting blood samples were assessed for insulin, glucose, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides, PSA, testosterone, and sex hormone-binding globulin (SHBG) in the hospital’s accredited clinical biochemistry laboratory. The baseline sample was taken before the initial LHRH agonist injection.

CV Events Risk

The risk of a CV event in the next 10 years was estimated with the validated QRISK® 2 (ClinRisk Ltd, Leeds, UK) online calculator (https://qrisk.org/2017) [28].

Hand-grip Strength

Hand-grip strength was measured with an analogue dynamometer (Takei Scientific Instruments Ltd., Tokyo, Japan). Patients performed three maximal trials on each hand, with the highest score used for analysis.

Patient-Reported Outcomes (PROs) and Self-reported Activity

The Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire assessed disease-specific QoL. Fatigue was measured with Functional Assessment of Chronic Illness Therapy-Fatigue (FACT-Fatigue) questionnaire. Higher scores indicate better QoL and less fatigue, respectively. The Godin Leisure-Time Exercise Questionnaire (GodinQ) was used to characterise self-reported levels of physical activity [29].

Sample Size

We powered the study to identify differences in fat mass at 3-months because this was the primary outcome. To our knowledge, Cormie et al. [11] is the only previous study to have investigated the effects of exercise in patients with prostate cancer initiating ADT, reporting an adjusted mean difference in body fat mass of 1.4 kg (P = 0.001) at 3-months. An SD of 1.6 kg was obtained from the adjusted mean difference and P-value using Cochrane guidelines [30]. Therefore, 44 patients (22 per group) were required to detect a between-group difference of 1.4 kg assuming SD = 1.6 kg, numerator d.f. = 1, α = 0.05 and 1–β = 0.8, which was calculated using G*Power, version 3.1 (Heinrich-Heine-Universität, Düsseldorf, Germany). An attrition rate of 20% was also factored into the sample size calculation.
Exercise benefits in patients on ADT

Statistical Analysis

Analyses were performed by intention-to-treat using R (R Foundation for Statistical Computing, Vienna, Austria). Between-group differences in outcomes at 3- and 6-months were assessed by analysis of covariance (ANCOVA), with baseline values as covariates. The adjusted mean differences with 95% CIs are presented. Statistical significance was set at a two-tailed \( P < 0.05 \). To comply with intention-to-treat and increase precision of the estimates, missing data at 3-months \((n = 8)\) and 6-months \((n = 13)\) were multiply imputed using predictive mean matching with 20 iterations. At the end of the 20 iterations, one imputed data set was created and the process was repeated to generate 20 imputed data sets. ANCOVA models were fitted on each imputed data set, and the results from each model were then pooled into a single set of estimates and standard errors using Rubin’s rules \([31]\). For patients who had missing data at 3-months, baseline values and other covariates were entered into the imputation model. When data were missing at 6-months, baseline and 3-month endpoint values with covariates were used to impute missing values. Outcomes with missing data at baseline were not included in the analysis. Data and analyses scripts can be accessed online \([32]\).

Results

Recruitment, Retention and Adherence to the Intervention

Of the 186 patients with prostate cancer screened for eligibility, 39 did not meet the inclusion criteria due to bone metastasis or medical conditions limiting exercise. A total of 97 eligible patients declined to participate in the study for reasons including: lack of time due to work commitments and/or having a holiday planned during the study period, lack of interest, costs associated with transport and parking, and fear of delaying treatment by undergoing baseline assessments and randomisation before receiving the initial ADT injection. Hence, 50 patients enrolled on the study and were randomised (Fig. 1). At 3-months, two patients in the exercise group and two in the control group withdrew from the study due to a lack of motivation/interest. Four patients in the control group also missed the 3-month assessment time point due to conflicting schedules. A total of 13 patients missed the assessment at 6-months. All patients in the exercise group completed at least 17 out of a possible 24 supervised sessions \((\geq 70\%)\). There were no adverse events reported during training or testing.

Patient Characteristics

Demographic and medical characteristics at baseline were evenly distributed between groups (Table 1). The mean (range) age of the patients was 72 \((63–79)\) years. On average, patients were overweight \(\text{i.e., body mass index [BMI] } \geq 25 \text{ kg/m}^2\) and had multiple comorbidities, with hypertension \((46\%)\), CV disease \((36\%)\), and musculoskeletal disorders \((26\%)\) being the most common. Two patients in the control group \((8\%)\) had a coexistent primary cancer \(\text{lymphoma and rectal cancer}\). The most common patient medications were antianginal/antihypertensive drugs \((58\%)\) and statins \((52\%)\). The incidence of metastasis at baseline was 42\% and the majority of patients had a Gleason score of 7–8 \((52\%)\). The average risk of having a CV event in the next 10 years was 26.8\%. Outcomes at each time point are presented in Table 2.

Outcomes at 3-months

Exercise prevented the decline in cardiopulmonary fitness, with significant between-group differences in \(\text{V}O_2\text{peak, VT, and OUES (Table 3)}\). Exercise also prevented the increase in fatigue observed in the control group, as indicated by a significantly higher FACIT-Fatigue score. As expected, serum testosterone concentrations declined in both groups \(\text{indicative of severe hypogonadism}\), which was accompanied by reductions in PSA concentrations (Table 2). There was no evidence for differences in blood-borne biomarkers, body composition, CV disease risk, or hand-grip strength (Table 3).

Outcomes at 6-months

After the withdrawal of supervision, the exercise group maintained self-directed levels of exercise, as evidenced by the between-group difference in GodinQ scores (Table 3). Despite this, the significant between-group differences in cardiopulmonary fitness and fatigue observed at 3-months were not maintained (Table 3). However, the exercise group reported better QoL at 6-months compared to controls. Exercise also prevented adverse changes in QRISK2 score (Table 3), indicating a reduced CV events risk compared to the control group. There was no evidence for differences in blood-borne biomarkers, body composition, or hand-grip strength (Table 3).

Discussion

This is the first study to assess whether the effects of supervised exercise in patients with prostate cancer beginning ADT can be maintained after the withdrawal of supervision. The 3-month aerobic and resistance training intervention prevented adverse changes in cardiopulmonary fitness and fatigue. After the supervised exercise was withdrawn, differences in cardiopulmonary fitness and fatigue were not sustained, but the exercise group showed higher QoL and a reduced CV events risk compared to the control group. These findings have important implications
Assessed for eligibility ($n = 186$)

- Excluded ($n = 136$)
  - Not meeting inclusion criteria ($n = 39$)
  - Declined to participate ($n = 97$)

Randomised ($n = 50$)

- Allocated to exercise group ($n = 24$)
  - Received allocated intervention ($n = 24$)

- Allocated to control group ($n = 26$)
  - Received allocated intervention ($n = 26$)

- Withdrew from study ($n = 2$)
  - Lack of motivation ($n = 2$)

- Withdrew from study ($n = 2$)
  - Lack of interest ($n = 2$)
  - Missed assessment ($n = 4$)
  - Conflicting schedules ($n = 4$)

Completed assessment ($n = 22$)

- Completed assessment ($n = 18$)

3-months

- Analysed by intention to treat ($n = 24$)
  - Missing baseline data for grip strength ($n = 1$), PSA ($n = 1$), fat mass ($n = 1$), SHBG ($n = 2$), insulin ($n = 2$), and FFM ($n = 1$).

6-months

- Analysed by intention to treat ($n = 26$)
  - Missing baseline data for testosterone ($n = 1$), VT ($n = 1$), grip strength ($n = 2$), fat mass ($n = 2$), SHGB ($n = 2$), insulin ($n = 1$), FFM ($n = 2$), and FACT-P ($n = 1$).
for clinicians concerned with the management of ADT-related side-effects.

Our present data showed no evidence for an effect of exercise on fat mass in men commencing ADT, which was our primary outcome. Although the adjusted mean difference favoured the exercise group at 3-months (−1.9 kg), the 95% CIs showed that the true mean difference is likely to lie somewhere between −4.9 and 0.9 kg, indicating a high level of uncertainty. The current literature-base is equivocal with regard to the effect of exercise on adiposity in hypogonadal men. Segal et al. [33] reported that 6 months of resistance training, but not aerobic training, prevented increases in body fat percentage observed in control groups. Recently, Dawson et al. [34] reported that 3 months of resistance training reduced body fat percentage compared with controls, yet there was no effect of exercise on whole-body fat mass. Conversely, four RCTs have shown no differences between exercise and control groups for any measure of adiposity [35–38]. Thus, our present findings are in line with the existing evidence-base, showing an uncertain effect of short-term exercise programmes on body fat. Further research should explore the inclusion of other strategies alongside exercise (e.g., calorie restriction) to promote meaningful reductions in fat mass in patients with prostate cancer receiving ADT.

Supervised exercise prevented the reduction in cardiopulmonary fitness observed in the controls, with significant differences in VO_{2peak}, VT, and OUES favouring the exercise group at 3-months. The adjusted mean difference in VO_{2peak} (1.9 mL/kg/min) was of a similar magnitude to that reported previously in patients with prostate cancer after 3 months of aerobic and resistance training at the commencement of ADT (1.1 mL/kg/min) [11]. Although the minimal clinically important difference (MCID) in VO_{2peak} for patients with prostate cancer is currently unknown, an increase of 1.8 mL/kg/min following 6 months of exercise training has been associated with improved PSA-doubling time (R^2 0.41, P < 0.003) [39]. This finding suggests a link between improved cardiopulmonary exercise capacity and prostate cancer progression, which is consistent with the reported inverse relationship between vigorous physical activity and cancer incidence [40].

Table 1 Baseline characteristics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Exercise group (n = 24)</th>
<th>Control group (n = 26)</th>
<th>Total (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (SD)</td>
<td>71.4 (5.4)</td>
<td>72.5 (4.2)</td>
<td>72.0 (4.8)</td>
</tr>
<tr>
<td>Body mass, kg, mean (SD)</td>
<td>84.0 (11.2)</td>
<td>83.8 (9.6)</td>
<td>83.9 (10.3)</td>
</tr>
<tr>
<td>BMI, kg/m², mean (SD)</td>
<td>28.4 (3.1)</td>
<td>27.7 (3.4)</td>
<td>28.0 (3.3)</td>
</tr>
<tr>
<td>Gleason score, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤6</td>
<td>2 (8)</td>
<td>0 (0)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>7–8</td>
<td>13 (54)</td>
<td>13 (50)</td>
<td>26 (52)</td>
</tr>
<tr>
<td>9–10</td>
<td>9 (38)</td>
<td>13 (50)</td>
<td>22 (44)</td>
</tr>
<tr>
<td>PSA level, ng/mL, median [IQR]</td>
<td>23.7 [16,38]</td>
<td>18.3 [11,75]</td>
<td>20.3 [14,63]</td>
</tr>
<tr>
<td>Tumour grade, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Locally advanced</td>
<td>11 (46)</td>
<td>8 (31)</td>
<td>19 (38)</td>
</tr>
<tr>
<td>Metastatic</td>
<td>11 (46)</td>
<td>10 (38)</td>
<td>21 (42)</td>
</tr>
<tr>
<td>Past smoker, n (%)</td>
<td>9 (38)</td>
<td>10 (38)</td>
<td>19 (38)</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>4 (17)</td>
<td>2 (8)</td>
<td>6 (12)</td>
</tr>
<tr>
<td>QRISK2, %, mean (SD)</td>
<td>27.6 (10.8)</td>
<td>26.0 (7.6)</td>
<td>26.8 (9.2)</td>
</tr>
<tr>
<td>Number of comorbidities, mean (SD)</td>
<td>2.2 (1.6)</td>
<td>2.9 (1.8)</td>
<td>2.6 (1.7)</td>
</tr>
<tr>
<td>CV disease, n (%)</td>
<td>8 (33)</td>
<td>10 (38)</td>
<td>18 (36)</td>
</tr>
<tr>
<td>Type 2 diabetes, n (%)</td>
<td>4 (17)</td>
<td>2 (8)</td>
<td>6 (12)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>10 (42)</td>
<td>13 (50)</td>
<td>23 (46)</td>
</tr>
<tr>
<td>Hyperlipidaemia, n (%)</td>
<td>4 (17)</td>
<td>7 (27)</td>
<td>11 (22)</td>
</tr>
<tr>
<td>Lung disease, n (%)</td>
<td>3 (13)</td>
<td>5 (19)</td>
<td>8 (16)</td>
</tr>
<tr>
<td>Kidney disease, n (%)</td>
<td>2 (8)</td>
<td>4 (15)</td>
<td>6 (12)</td>
</tr>
<tr>
<td>Coexistent primary cancer, n (%)</td>
<td>0 (0)</td>
<td>2 (8)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>MSK disorder, n (%)</td>
<td>7 (29)</td>
<td>6 (23)</td>
<td>13 (26)</td>
</tr>
<tr>
<td>Erectile dysfunction, n (%)</td>
<td>2 (8)</td>
<td>2 (8)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>GORD, n (%)</td>
<td>3 (13)</td>
<td>4 (15)</td>
<td>7 (14)</td>
</tr>
<tr>
<td>Number of medications, mean (SD)</td>
<td>3.5 (3.2)</td>
<td>4.0 (3.0)</td>
<td>3.8 (3.1)</td>
</tr>
<tr>
<td>Anti-anginal/antihypertensive, n (%)</td>
<td>14 (58)</td>
<td>15 (58)</td>
<td>29 (58)</td>
</tr>
<tr>
<td>Antidiabetic, n (%)</td>
<td>4 (17)</td>
<td>2 (8)</td>
<td>6 (12)</td>
</tr>
<tr>
<td>Antithrombotic, n (%)</td>
<td>5 (21)</td>
<td>2 (8)</td>
<td>7 (14)</td>
</tr>
<tr>
<td>Statin, n (%)</td>
<td>10 (42)</td>
<td>16 (62)</td>
<td>26 (52)</td>
</tr>
<tr>
<td>Acid reducer, n (%)</td>
<td>3 (13)</td>
<td>11 (42)</td>
<td>14 (28)</td>
</tr>
<tr>
<td>Anti-inflammatory, n (%)</td>
<td>7 (29)</td>
<td>11 (42)</td>
<td>18 (36)</td>
</tr>
<tr>
<td>Antidepressant, n (%)</td>
<td>2 (8)</td>
<td>5 (19)</td>
<td>7 (14)</td>
</tr>
</tbody>
</table>

GORD, gastro-oesophageal reflux disease; IQR, interquartile range; MSK, musculoskeletal. *-blockers β-blockers, angiotensin II receptor blockers, diuretics, nitrates, calcium channel blockers, or angiotensin-converting enzyme (ACE) inhibitors.
In addition to maintaining VO2peak, the present study is the first to show that supervised exercise prevents the reduction in VT in patients receiving ADT. This is an important finding because VT predicts clinical outcomes in the oncological setting independent of body mass index [43]. Moreover, the VT is not influenced by patient volition [27], and therefore, the improvement occurred independent of motivational factors during the CPET. Furthermore, VT is limited by the rate of O2 utilisation at the muscle as opposed to VO2peak, which is primarily limited by delivery of O2 to the muscle [44], although this could be influenced by age-related diseases such as sarcopenia. As such, VT represents a unique peripheral muscle adaptation in response to exercise training.

The exercise group reported less fatigue than controls at 3-months. The between-group difference in FACIT-Fatigue score (4.5 points) is clinically relevant given that the MCID has been estimated at 3 points [45]. This finding agrees with a systematic review showing a beneficial effect of exercise on fatigue in patients with prostate cancer treated with ADT [46]. In fact, improved fatigue following exercise is amongst the most consistent findings in exercise-oncology research [47]. The biological mechanisms underpinning the beneficial effects of exercise on fatigue are not completely understood, but may be related to its anti-inflammatory effect on cancer-related systemic inflammation [48].

An important and novel aspect of the present study was the 6-month follow-up after the withdrawal of supervised exercise. This allowed us to determine whether exercise-induced improvements were maintained in the longer-term, which is important because side-effects of ADT continue to develop throughout treatment [3] and reductions in physical function occur just 3 months after the cessation of supervised exercise in older adults [15]. Despite the maintenance of self-directed exercise, as evidenced by the GodinQ, the exercise-induced improvements in cardiopulmonary fitness and fatigue were not sustained at 6-months. Exercise is often performed at a lower intensity when it is unsupervised compared to when it is performed under supervision [15]. As a consequence, the intensity of self-directed exercise after the withdrawal of supervision may have been inadequate to sustain the benefits observed at

## Table 2 Outcomes at baseline, 3- and 6-months.

<table>
<thead>
<tr>
<th></th>
<th>Exercise group (n = 24)</th>
<th>Control group (n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>3-months</td>
</tr>
<tr>
<td>Body composition, mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fat mass, kg</td>
<td>24.3 (5.3)</td>
<td>21.7 (7.4)</td>
</tr>
<tr>
<td>FFM, kg</td>
<td>58.2 (7.1)</td>
<td>58.9 (5.7)</td>
</tr>
<tr>
<td>Body mass, kg</td>
<td>84.0 (11.2)</td>
<td>82.2 (10.7)</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>107 (11)</td>
<td>108 (8)</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>1.03 (0.06)</td>
<td>1.02 (0.05)</td>
</tr>
<tr>
<td>Blood biomarkers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSA level, ng/mL, median [IQR]</td>
<td>25.8 [25.7]</td>
<td>1.8 [2.5]</td>
</tr>
<tr>
<td>Total cholesterol, mEq/L, mean (SD)</td>
<td>4.7 (0.98)</td>
<td>4.9 (0.85)</td>
</tr>
<tr>
<td>HDL-C, mEq/L, mean (SD)</td>
<td>1.2 (0.23)</td>
<td>1.3 (0.20)</td>
</tr>
<tr>
<td>LDL-C, mEq/L, mean (SD)</td>
<td>2.9 (0.94)</td>
<td>3.0 (0.78)</td>
</tr>
<tr>
<td>Triglycerides, mEq/L, mean (SD)</td>
<td>1.3 (0.61)</td>
<td>1.3 (0.56)</td>
</tr>
<tr>
<td>Testosterone, mEq/L, mean (SD)</td>
<td>15.1 (5.4)</td>
<td>0.57 (0.48)</td>
</tr>
<tr>
<td>ShBG, mEq/L, median [IQR]</td>
<td>41.5 [16.8]</td>
<td>46.1 [26.7]</td>
</tr>
<tr>
<td>Insulin, mEq/L, median [IQR]</td>
<td>65.0 [60.0]</td>
<td>74.8 [60.5]</td>
</tr>
<tr>
<td>Glucose, mM, median [IQR]</td>
<td>5.6 [0.63]</td>
<td>5.6 [1.3]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PROs, mean (SD)</th>
<th>FACT-P</th>
<th>FACT-Fatigue</th>
<th>GodinQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>119 (19)</td>
<td>123 (22)</td>
<td>126 (15)</td>
<td>123 (16)</td>
</tr>
<tr>
<td>41.8 (10.2)</td>
<td>41.8 (11.2)</td>
<td>43.7 (8.6)</td>
<td>42.9 (8.4)</td>
</tr>
<tr>
<td>29.0 (20.9)</td>
<td>43.7 (21.9)</td>
<td>40.0 (19.8)</td>
<td>32.0 (26.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CPET variables, mean (SD)</th>
<th>VO2peak, mL/kg/min</th>
<th>VT, mL/kg/min</th>
<th>VE/VO2</th>
<th>VE/VEO2</th>
<th>O2 pulse, mL/beat</th>
<th>OUES</th>
</tr>
</thead>
<tbody>
<tr>
<td>23.5 (5.4)</td>
<td>23.2 (5.1)</td>
<td>21.9 (4.8)</td>
<td>22.4 (5.8)</td>
<td>20.4 (5.3)</td>
<td>20.2 (4.7)</td>
<td>11.9 (2.2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Muscle strength, mean (SD)</th>
<th>Hand grip, kg</th>
<th>QRS2, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>35.0 (6.8)</td>
<td>34.2 (5.3)</td>
<td>33.9 (6.5)</td>
</tr>
<tr>
<td>27.7 (10.8)</td>
<td>27.2 (10.8)</td>
<td>25.8 (9.8)</td>
</tr>
</tbody>
</table>
Exercise benefits in patients on ADT

Table 3 Adjusted mean differences in outcomes at 3- and 6-months.

<table>
<thead>
<tr>
<th>Variable</th>
<th>3-months</th>
<th>6-months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted mean difference (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td><strong>Body composition</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fat mass, kg</td>
<td>−1.9 (−4.9, 0.93)</td>
<td>0.18</td>
</tr>
<tr>
<td>FFM, kg</td>
<td>1.2 (−1.2, 3.7)</td>
<td>0.32</td>
</tr>
<tr>
<td>Body mass, kg</td>
<td>−0.98 (−2.7, 0.70)</td>
<td>0.25</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>−0.32 (−3.0, 2.4)</td>
<td>0.82</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>−0.01 (−0.04, 0.02)</td>
<td>0.48</td>
</tr>
<tr>
<td><strong>Blood biomarkers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSA level, ng/mL</td>
<td>−0.74 (−27.7, 26.2)</td>
<td>0.96</td>
</tr>
<tr>
<td>Total cholesterol, mM</td>
<td>0.09 (−0.25, 0.42)</td>
<td>0.61</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>0.07 (−0.04, 0.19)</td>
<td>0.21</td>
</tr>
<tr>
<td>LDL-C, mmol/L</td>
<td>−0.02 (−3.0, 0.25)</td>
<td>0.87</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>−0.04 (−0.28, 0.21)</td>
<td>0.77</td>
</tr>
<tr>
<td>Testosterone, nmol/L</td>
<td>0.14 (−0.12, 0.41)</td>
<td>0.28</td>
</tr>
<tr>
<td>SHBG, nmol/L</td>
<td>1.6 (−6.2, 9.4)</td>
<td>0.68</td>
</tr>
<tr>
<td>Insulin, pmol/L</td>
<td>10.8 (−7.4, 29.1)</td>
<td>0.24</td>
</tr>
<tr>
<td>Glucose, mM</td>
<td>0.27 (−0.11, 0.65)</td>
<td>0.16</td>
</tr>
<tr>
<td><strong>PROs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FACT-P</td>
<td>4.1 (−4.5, 12.6)</td>
<td>0.34</td>
</tr>
<tr>
<td>FACIT-Fatigue</td>
<td>4.5 (0.62, 8.4)</td>
<td>0.024</td>
</tr>
<tr>
<td>GodinQ</td>
<td>9.1 (−2.7, 20.9)</td>
<td>0.12</td>
</tr>
<tr>
<td><strong>CPET variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VO2peak, mL/kg/min</td>
<td>1.9 (0.16, 3.7)</td>
<td>0.034</td>
</tr>
<tr>
<td>VT, mL/kg/min</td>
<td>1.6 (0.38, 2.9)</td>
<td>0.012</td>
</tr>
<tr>
<td>VE/VO2</td>
<td>−2.1 (−4.2, 0.02)</td>
<td>0.052</td>
</tr>
<tr>
<td>VE/VCO2</td>
<td>−1.3 (−3.4, 0.71)</td>
<td>0.19</td>
</tr>
<tr>
<td>Qo2 pulse, mL/beat</td>
<td>0.98 (−0.25, 2.2)</td>
<td>0.12</td>
</tr>
<tr>
<td>OUES</td>
<td>0.21 (0.07, 0.35)</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand grip, kg</td>
<td>0.46 (−1.5, 2.5)</td>
<td>0.65</td>
</tr>
<tr>
<td><strong>CV events risk</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QRISK2, %</td>
<td>−0.46 (−2.8, 1.9)</td>
<td>0.68</td>
</tr>
</tbody>
</table>

Abbreviations: BIA, bioelectrical impedance analysis; BMI, body mass index; CPET, cardiopulmonary exercise test; CV, cardiovascular; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue; FACT-P, Functional Assessment of Cancer Therapy-Prostate; FFM, fat-free mass; GodinQ, Godin Leisure-Time Exercise Questionnaire; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; MCID, minimal clinically important difference; OUES, O2 uptake efficiency slope; PRO, patient-reported outcome; RCT, randomised controlled trial; RPE, Borg Rating of Perceived Exertion; SHBG, sex hormone-binding globulin; VCO2, CO2 output; VE, minute ventilation; VO2, O2 uptake; VO2peak, peak O2 uptake VT, ventilatory threshold. *Data are adjusted for baseline values.

3-months, and this would need to be addressed in future research.

Despite this, maintaining self-directed exercise after the supervised exercise was withdrawn attenuated the adverse effects that ADT had on QoL. Specifically, the adjusted mean difference (8.5 points) in FACT-P at 6-months favoured the exercise group; a difference that is clinical meaningful [49]. A meta-analysis of three studies previously showed that exercise has a moderately beneficial effect (standardised mean difference 0.36) on disease-specific QoL in patients with prostate cancer undergoing ADT [50]. Secondary to increasing patient longevity, maintaining patient QoL is a key objective for physicians prescribing treatment for diseases such as prostate cancer [51]. Indeed, there have been calls for clinicians to provide supportive care alongside standard therapy to optimise the management of advanced prostate cancer [52]. The findings of the present RCT suggest that a short-term programme of supervised exercise training commenced at the beginning of ADT is an effective, non-pharmacological strategy for preventing treatment-related reductions in QoL.

Regular exercise also prevented the adverse effect of ADT on CV events risk, as evidence by the significant difference in QRISK2 score at 6-months (−2.9%,  = 0.041). This is an important finding because ADT increases the risk of acute myocardial infarction in patients with prostate cancer [53]. In agreement with this result, 4-months of aerobic and resistance training has recently been shown to reduce CV events risk, as assessed using the USA Framingham risk equation, in overweight patients with early-stage breast cancer [54]. Convincing epidemiological evidence also shows an inverse association between regular exercise and risk of an acute CV event [55]. Thus, our present findings extend those of previous studies by providing preliminary support for exercise as a countermeasure for ADT-related CV events risk. It should be acknowledged, however, that despite showing a reduction in risk compared to controls, the exercise group still reported a mean QRISK2 score of 25.8% at 6-months, which is considered high risk [28].
There were some limitations to the present study. The intervention involved a 3-month programme of supervised exercise led by exercise specialists, which may not be deliverable within healthcare systems. In addition, there were a high number of eligible patients whom declined to participate in the study. Lack of time, financial costs, and transport difficulties are commonly cited exercise barriers in patients with cancer [56–58] and older adults in general [59], which align with reasons cited in our present study. Therefore, it is reasonable to suggest that a more pragmatic approach (such as home-based exercise or a shorter period of supervision with follow-on remote support) could circumvent these barriers and increase study recruitment. Future studies should seek to better understand how to improve participation of this patient group in exercise training programmes. Another limitation is that the trial was only powered to detect differences in fat mass and may not have been adequately powered to detect differences in some of the secondary outcomes. Furthermore, using self-report questionnaires to assess physical activity can be prone to subjective bias, although anecdotal evidence from the patients helped confirm that the exercise group maintained self-directed exercise after the supervised exercise intervention was withdrawn.

In conclusion, 3 months of supervised aerobic and resistance training followed by 3 months of self-directed exercise provided a sustained benefit in QoL and CV events risk in patients with prostate cancer commencing ADT. Our present results suggest that clinicians could prescribe a short-term exercise programme at the beginning of ADT to attenuate these important treatment-related side-effects.

Acknowledgements
The authors would like to thank all participants for volunteering to take part in this study.

Conflict of Interest
The authors have no potential conflicts of interest to disclose.

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