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

Abstract

Objectives: 1) To assess whether exercise training attenuates the adverse effects of treatment in newly diagnosed prostate cancer patients beginning androgen deprivation therapy (ADT), and 2) to examine whether exercise-induced improvements are sustained after the withdrawal of supervised exercise.

Patients and methods: Fifty prostate cancer patients 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 (2x/week for 60 min), followed by 3-months of self-directed exercise. Outcomes were assessed at baseline, 3-months, 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 score, anthropometry, blood-borne biomarkers, fatigue, and quality of life (QoL).

Results: At 3-months, exercise training prevented adverse changes in peak oxygen uptake (1.9 $ml.kg^{-1}.min^{-1}$, $p = 0.038$), ventilatory threshold (1.7 $ml.kg^{-1}.min^{-1}$, $p = 0.013$), oxygen uptake efficiency slope (0.21, $p = 0.005$) and fatigue (4.5, $p = 0.024$) 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 After the supervised exercise was withdrawn, the differences in cardiopulmonary fitness and fatigue were not sustained, but the exercise group showed significantly higher QoL (8.5, $p = 0.034$) and a reduced QRISK2 score (-2.9%, $p = 0.041$) compared to controls.

Conclusion: A short-term programme of supervised exercise for prostate cancer patients beginning ADT results in sustained improvements in QoL and cardiovascular event risk profile.

Key words: Prostate cancer, androgen deprivation therapy, aerobic exercise, resistance training; urology.

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 the increase risk of a cardiovascular event 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 prostate cancer patients [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 prostate cancer patients 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 this study was to: (1) examine whether a supervised programme of aerobic and resistance exercise training reduces treatment-related side-effects in prostate cancer patients beginning ADT, and (2) to determine whether any exercise-induced improvements can be sustained by encouraging patients to maintain self-directed exercise after the withdrawal of supervision. We chose outcomes

Patients and Methods

Newly diagnosed prostate cancer patients 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 luteinizing hormone-releasing hormone (LHRH) agonist treatment with or without radiotherapy, anticipated to remain on ADT for at least 6 months, be classified as 0 or 1 according to the World Health Organisation performance status, and not achieving 150 min·week^{-1} 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 cardiovascular event or heart failure, chronic obstructive pulmonary disease (COPD) 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, participants 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, 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. Participants 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 x 5 min bouts at an intensity of 11-15 on the 6-20 Borg Rating of Perceived Exertion (RPE) Scale [17], corresponding to approximately 55-85% age-predicted maximum heart rate (220 – age) [18]. Participants maintained a cadence of 50 rev·min^{-1} 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). Participants 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]. Thirty seconds of passive rest separated each exercise. 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 minutes of self-directed structured exercise or physical activity on three 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 variables, cardiovascular event 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 cardiovascular 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 (BIVA), 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]. Excessive body fat mass is associated

Cardiopulmonary fitness

An incremental cardiopulmonary exercise test (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 $W \cdot min^{-1}$ to volitional exhaustion. Patients maintained a cadence of 50-60 $rev \cdot min^{-1}$ throughout, with exhaustion defined as a $\geq$10 $rev \cdot min^{-1}$ drop in cadence for five consecutive seconds. Breath-by-breath data were recorded throughout (Ultima, CardioO2; Medical Graphics Corporation) and averaged before interpretation using a moving average (middle five of seven breaths). Peak oxygen consumption ($\dot{V}O_{2peak}$) was determined as the highest [moving average] $\dot{V}O_2$ 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^{-1} of age-predicted maximum. The ventilatory threshold (VT) was estimated using the modified V-slope method [27], which was confirmed by evaluating ventilatory equivalents and end-tidal pressures . Two analysts independently determined VT, with discrepancies of $\geq$ 7.5% resolved through discussion and consultation with a third analyst, if necessary. Ventilatory equivalents for O_2 ($\dot{V}E/\dot{V}O_2$) and CO_2 ($\dot{V}E/\dot{V}CO_2$) at VT, O_2 pulse at peak exercise, and oxygen 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, prostate specific antigen (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.

Cardiovascular event risk

The risk of a cardiovascular event in the next 10 years was estimated with the validated QRISK2 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). Participants 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 (FACIT-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 prostate cancer patients 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 participants (22 per group) were required to detect a between-group difference of 1.4 kg assuming SD = 1.6 kg, numerator df = 1, $\alpha = 0.05$ and $1\text{-}\beta = 0.8$, which was calculated using G*Power version 3.1. An attrition rate of 20% was also factored into the sample size calculation.

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-months and 6-months were assessed by analysis of covariance (ANCOVA), with baseline values as covariates. The adjusted mean differences with 95% confidence intervals 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 participants 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 prostate cancer patients 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 (Figure 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 (≥ 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 age of participants was 72 years, with a range of 63 to 79 years. On average, patients were overweight (i.e. BMI ≥ 25 kg/m^2) and had multiple comorbidities, with hypertension (46%), cardiovascular disease (36%), and musculoskeletal disorders (26%) being the most common. Two patients in the control group (8%) had a coexistent primary cancer (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 participants had a Gleason score of 7-8 (52%). The average risk of having a cardiovascular 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 found in $\dot{V}O_{2peak}$, 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 (indicative of severe hypogonadism), which was accompanied by reductions in PSA (Table 2). There was no evidence for differences in blood-borne biomarkers, body composition, cardiovascular 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 (Table 3). Despite this, the significant between-group differences in cardiorespiratory and fatigue observed at 3-months were not maintained (Table 3). However, the exercise group reported higher QoL at 6-months compared to controls. Exercise also prevented adverse changes in QRISK2 score (Table 3), indicating a reduced cardiovascular event 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 prostate cancer patients beginning ADT can be maintained after the withdrawal of supervision. The 3-month aerobic and resistance training intervention prevented adverse changes in cardiorespiratory fitness and fatigue. After the supervised exercise was withdrawn, differences in cardiorespiratory fitness and fatigue were not sustained, but the exercise group showed higher QoL and a reduced cardiovascular event risk compared to the control group. These findings have important implications for clinicians concerned with the management of ADT-related side-effects.

Our 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% confidence intervals showed that true mean difference is likely to lie somewhere between -4.9 to 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 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 prostate cancer patients receiving ADT.

Supervised exercise prevented the reduction in cardiorespiratory fitness observed in the controls, with significant differences in $\dot{V}O_{2peak}$, VT and OUES favouring the exercise group at 3-months. The adjusted mean difference in $\dot{V}O_{2peak}$ (1.9 $ml.kg^{-1}.min^{-1}$) was of a similar magnitude to that reported previously in prostate cancer patients after 3-months of aerobic and resistance training at the commencement of ADT (1.1 $ml.kg^{-1}.min^{-1}$) [11]. Although the minimal clinically important difference (MCID) in $\dot{V}O_{2peak}$ for prostate cancer patients is currently unknown, an increase of 1.8 $ml.kg^{-1}.min^{-1}$ 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 biochemical recurrence in newly diagnosed prostate cancer patients [40]. Other evidence also suggests that cardiopulmonary fitness is associated with reduced relative risk of cancer mortality and chronic disease [41, 42].

In addition to maintaining $\dot{V}O_{2peak}$, this study is the first to demonstrate 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 $\dot{V}O_{2peak}$ [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 oxygen utilisation at the muscle as opposed to $\dot{V}O_{2peak}$, which is primarily limited by delivery of oxygen 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 prostate cancer patients 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 this 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 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 prostate cancer patients 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 this 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 cardiovascular events risk, as evidence by the significant difference in QRISK2 score at 6-months (-2.9%, $p = 0.041$). This is an important finding because ADT increases the risk of acute myocardial infarction in prostate cancer patients [53]. In agreement with this result, 4-months of aerobic and resistance training has recently been shown to reduce cardiovascular event risk, as assessed using the US Framingham risk equation, in overweight early-stage breast cancer patients [54]. Convincing epidemiological evidence also shows an inverse association between regular exercise and risk of an acute cardiovascular event [55]. Thus, our findings extend those of previous studies by providing preliminary support for exercise as a countermeasure for ADT-related cardiovascular event 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 this 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 was 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 cancer patients [56-58] and older adults in general [59], which align with reasons cited in our 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 to QoL and cardiovascular event risk in prostate cancer patients commencing ADT. Our results suggest that clinicians could prescribe a short-term exercise programme at the beginning of ADT to attenuate these important treatment-related side-effects.

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Conflicts of interest statement

The authors have no potential conflicts of interest to disclose

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503 **Figure legends**

504 **Figure 1**. Participant flowchart. FACT-P = Functional Assessment of Cancer Therapy-
505 Prostate; FFM = fat-free mass; PSA = protein specific antigen; SHBG = sex hormone binding
506 globulin; VT = ventilatory threshold.

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Table 1. Baseline characteristics

	Exercise (n = 24)	Control (n = 26)	Total (n = 50)
Age (years)	71.4 ± 5.4	72.5 ± 4.2	72.0 ± 4.8
Body mass (kg)	84.0 ± 11.2	83.8 ± 9.6	83.9 ± 10.3
BMI (kg/m^2)	28.4 ± 3.1	27.7 ± 3.4	28.0 ± 3.3
Gleason score			
≤ 6	2 (8)	0 (0)	2 (4)
7-8	13 (54)	13 (50)	26 (52)
9-10	9 (38)	13 (50)	22 (44)
PSA (ng/mL)	23.7 [16, 38]	18.3 [11, 75]	20.3 [14, 63]
Tumour grade			
Locally advanced	11 (46)	8 (31)	19 (38)
Metastatic	11 (46)	10 (38)	21 (42)
Past smoker	9 (38)	10 (38)	19 (38)
Current smoker	4 (17)	2 (8)	6 (12)
QRISK®2 (%)	27.6 ± 10.8	26.0 ± 7.6	26.8 ± 9.2
Number of comorbidities	2.2 ± 1.6	2.9 ± 1.8	2.6 ± 1.7
Cardiovascular disease	8 (33)	10 (38)	18 (36)
Type 2 diabetes	4 (17)	2 (8)	6 (12)
Hypertension	10 (42)	13 (50)	23 (46)
Hyperlipidaemia	4 (17)	7 (27)	11 (22)
Lung disease	3 (13)	5 (19)	8 (16)
Kidney disease	2 (8)	4 (15)	6 (12)
Coexistent primary cancer	0 (0)	2 (8)	2 (4)
MSK disorder	7 (29)	6 (23)	13 (26)
Erectile dysfunction	2 (8)	2 (8)	4 (8)
GORD	3 (13)	4 (15)	7 (14)
Number of medications	3.5 ± 3.2	4.0 ± 3.0	3.8 ± 3.1
Antianginal/antihypertensive[1]	14 (58)	15 (58)	29 (58)
Antidiabetic	4 (17)	2 (8)	6 (12)
Antithrombotic	5 (21)	2 (8)	7 (14)
Statin	10 (42)	16 (62)	26 (52)
Acid reducer	3 (13)	11 (42)	14 (28)

Anti-inflammatory	7 (29)	11 (42)	18 (36)
Anti-depressant	2 (8)	5 (19)	7 (14)

BMI = body mass index; GORD = gastro-oesophageal reflux disease; MSK = musculoskeletal; PSA = prostate specific antigen; SHGB = sex hormone binding globulin.

Data are presented as mean ± SD, median [IQR], or number of participants (percentage of participants).

[1]α-blockers, β-blockers, angiotensin II receptor blockers, diuretics, nitrates, calcium channel blockers, or ACE inhibitors.

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

	Exercise (n = 24)			Control (n = 26)		
	Baseline	3-months	6-months	Baseline	3-months	6-months
Body composition						
Fat mass (kg)	24.3 ± 5.3	21.7 ± 7.4	22.7 ± 6.8	23.3 ± 8.3	22.7 ± 7.7	24.1 ± 7.6
FFM (kg)	58.2 ± 7.1	58.9 ± 5.7	59.3 ± 6.7	59.1 ± 7.3	58.2 ± 5.4	58.2 ± 6.9
Body mass (kg)	84.0 ± 11.2	82.2 ± 10.7	82.1 ± 10.1	83.8 ± 9.6	82.9 ± 9.7	83.9 ± 9.3
Waist circumference (cm)	107 ± 11	108 ± 8	108 ± 7	106 ±7	107 ± 8	110 ± 8
Waist to hip ratio	1.03 ± 0.06	1.02 ± 0.05	1.03 ± 0.05	0.99 ± 0.05	1.02 ± 0.05	1.02 ± 0.06
Blood biomarkers						
PSA (ng/mL)	25.8 [25.7]	1.8 [2.5]	0.53 [1.4]	18.3 [63.5]	0.9 [3.1]	0.41 [2.0]
Total cholesterol (mmol/L)	4.7 ± 0.98	4.9 ± 0.85	5.1 ± 0.91	4.9 ± 0.95	5.0 ± 1.1	5.2 ± 0.99
HDL-C (mmol/L)	1.2 ± 0.23	1.3 ± 0.20	1.3 ± 0.22	1.3 ± 0.29	1.3 ± 0.28	1.4 ± 0.34
LDL-C (mmol/L)	2.9 ± 0.94	3.0 ± 0.78	3.2 ± 0.94	3.0 ± 0.86	3.1 ± 0.94	3.2 ± 0.94
Triglycerides (mmol/L)	1.3 ± 0.61	1.3 ± 0.56	1.4 ± 0.45	1.3 ± 0.56	1.3 ± 0.64	1.3 ± 0.54
Testosterone (nmol/L)	15.1 ± 5.4	0.57 ± 0.48	0.45 ± 0.28	14.8 ± 6.6	0.43 ± 0.38	0.31 ± 0.19
SHBG (nmol/L)	41.5 [16.8]	46.1 [26.7]	51.0 [28.9]	41.0 [16.5]	47.8 [29.0]	45.6 [23.3]
Insulin (pmol/L)	65.0 [63.0]	74.8 [60.5]	60.9 [65.4]	61.0 [105]	63.9 [67.7]	90 [94.7]
Glucose (mmol/L)	5.6 [0.63]	5.6 [1.3]	5.8 [0.92]	5.9 [1.1]	5.8 [1.0]	5.7 [0.74]
PROs						

FACT-P	119 ± 19	123 ± 22	126 ± 15	123 ± 16	123 ± 19	120 ± 16
FACIT-Fatigue	41.8 ± 10.2	41.8 ± 11.2	43.7 ± 8.6	42.9 ± 8.4	38.5 ± 11.9	39.9 ± 9.3
GodinQ	29.0 ± 20.9	43.7 ± 21.9	40.0 ± 19.8	32.0 ± 26.3	36.0 ± 21.3	31.3 ± 19.3
CPET variables						
$\dot{V}O_{2peak}$ ($ml.kg^{-1}.min^{-1}$)	23.5 ± 5.4	23.2 ± 5.1	21.9 ± 4.8	22.4 ± 5.8	20.4 ± 5.3	20.2 ± 4.7
VT ($ml.kg^{-1}.min^{-1}$)	12.1 ± 2.2	13.1 ± 2.4	11.8 ± 1.8	11.9 ± 2.2	11.3 ± 2.2	11.1 ± 2.3
$\dot{V}E/VCO_2$	30.4 ± 4.3	30.4 ± 3.3	30.9 ± 3.7	31.3 ± 4.6	33.0 ± 4.9	33.2 ± 4.6
$\dot{V}E/VO_2$	27.7 ± 4.5	28.5 ± 3.4	29.2 ± 4.0	29.2 ± 4.0	30.6 ± 4.1	30.8 ± 4.6
O_2 pulse (ml/beat)	13.6 ± 3.0	13.3 ± 2.6	12.4 ± 2.2	12.9 ± 2.3	11.9 ± 2.7	11.9 ± 2.5
OUES	2.17 ± 0.50	2.09 ± 0.42	2.01 ± 0.39	2.11 ± 0.55	1.85 ± 0.33	1.87 ± 0.34
Muscle strength						
Hand grip (kg)	35.0 ± 6.8	34.2 ± 5.3	33.9 ± 6.5	36.3 ± 6.1	35.0 ± 6.7	34.1 ± 5.7
CV event risk						
QRISK2(%)	27.7 ± 10.8	27.2 ± 10.8	25.8 ± 9.8	26.0 ± 7.6	26.2 ± 7.2	27.4 ± 7.7

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; LDL-C = low-density lipoprotein cholesterol; OUES = oxygen uptake efficiency slope; PROs = patient reported outcomes; PSA = prostate specific antigen; SHGB = sex hormone binding globulin; VT = ventilatory threshold; VCO_2 = carbon dioxide output; $\dot{V}E$ = minute ventilation; VO_2 = oxygen uptake; $\dot{V}O_{2peak}$ = peak oxygen uptake.

Data are presented as mean ± SD or median [IQR]

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

	3-months		6-months	
	Adjusted mean difference (95% CI)	*p*	Adjusted mean difference (95% CI)	*p*
Body composition				
Fat mass (kg)	-1.9 (-4.9, 0.93)	0.18	-2.2 (-5.5, 1.1)	0.18
FFM (kg)	1.2 (-1.2, 3.7)	0.32	1.4 (-2.9, 5.8)	0.51
Body mass (kg)	-0.98 (-2.7, 0.70)	0.25	-2.0 (-4.1, 0.08)	0.061
Waist circumference (cm)	-0.32 (-3.0, 2.4)	0.82	-2.1 (-5.4, 1.3)	0.22
Waist to hip ratio	-0.01 (-0.04, 0.02)	0.48	0.00 (-0.04, 0.03)	0.80
Blood biomarkers				
PSA (ng/mL)	-0.74 (-27.7, 26.2)	0.96	-3.1 (29.8, 23.6)	0.82
Total cholesterol (mmol/L)	0.09 (-0.25, 0.42)	0.61	0.12 (-0.22, 0.45)	0.49
HDL-C (mmol/L)	0.07 (-0.04, 0.19)	0.21	0.01 (-0.11, 0.13)	0.81
LDL-C (mmol/L)	-0.02 (-3.0, 0.25)	0.87	0.02 (-0.43, 0.46)	0.94
Triglycerides (mmol/L)	-0.04 (-0.28, 0.21)	0.77	0.09 (-0.15, 0.32)	0.46
Testosterone (nmol/L)	0.14 (-0.12, 0.41)	0.28	0.14 (-0.02, 0.29)	0.084
SHBG (nmol/L)	1.6 (-6.2, 9.4)	0.68	9.8 (-3.0, 22.6)	0.13
Insulin (pmol/L)	10.8 (-7.4, 29.1)	0.24	-14.8 (-39.7, 10.1)	0.23
Glucose (mmol/L)	0.27 (-0.11, 0.65)	0.16	0.28 (-0.13, 0.68)	0.18
PROs				
FACT-P	4.1 (-4.5, 12.6)	0.34	8.5 (0.67, 16.3)	0.034
FACIT-Fatigue	4.5 (0.62, 8.4)	0.024	4.2 (-1.3, 9.7)	0.13
GodinQ	9.1 (-2.7, 20.9)	0.12	10.2 (0.74, 19.7)	0.035
CPET variables				
$\dot{V}O_{2peak}$ ($ml.kg^{-1}.min^{-1}$)	1.9 (0.16, 3.7)	0.034	0.95 (-1.0, 3.0)	0.34
VT ($ml.kg^{-1}.min^{-1}$)	1.6 (0.38, 2.9)	0.012	0.73 (-0.32, 1.8)	0.17
$\dot{V}E/VCO_2$	-2.1 (-4.2, 0.02)	0.052	-1.8 (-4.0, 0.46)	0.11
$\dot{V}E/VO_2$	-1.3 (-3.4, 0.71)	0.19	-0.63 (-2.8, 1.5)	0.56
O_2 pulse (ml/beat)	0.98 (-0.25, 2.2)	0.12	0.13 (-1.0, 1.3)	0.81
OUES	0.21 (0.07, 0.35)	0.005	0.11 (-0.07, 0.29)	0.23

Strength				
Hand grip (kg)	0.46 (-1.5, 2.5)	0.65	1.0 (-0.67, 2.7)	0.23
CV event risk				
QRISK2 (%)	-0.46 (-2.8, 1.9)	0.68	-2.9 (-5.8, 0.13)	0.041

95% CI = confidence interval; 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; LDL-C = low-density lipoprotein cholesterol; OUES = oxygen uptake efficiency slope; *p* = p-value; PROs = patient reported outcomes; PSA = prostate specific antigen; SHGB = sex hormone binding globulin; VT = ventilatory threshold; VCO_2 = carbon dioxide output; $\dot{V}E$ = minute ventilation; VO_2 = oxygen uptake; $\dot{V}O_{2peak}$ = peak oxygen uptake.

[a]Data are adjusted for baseline values.

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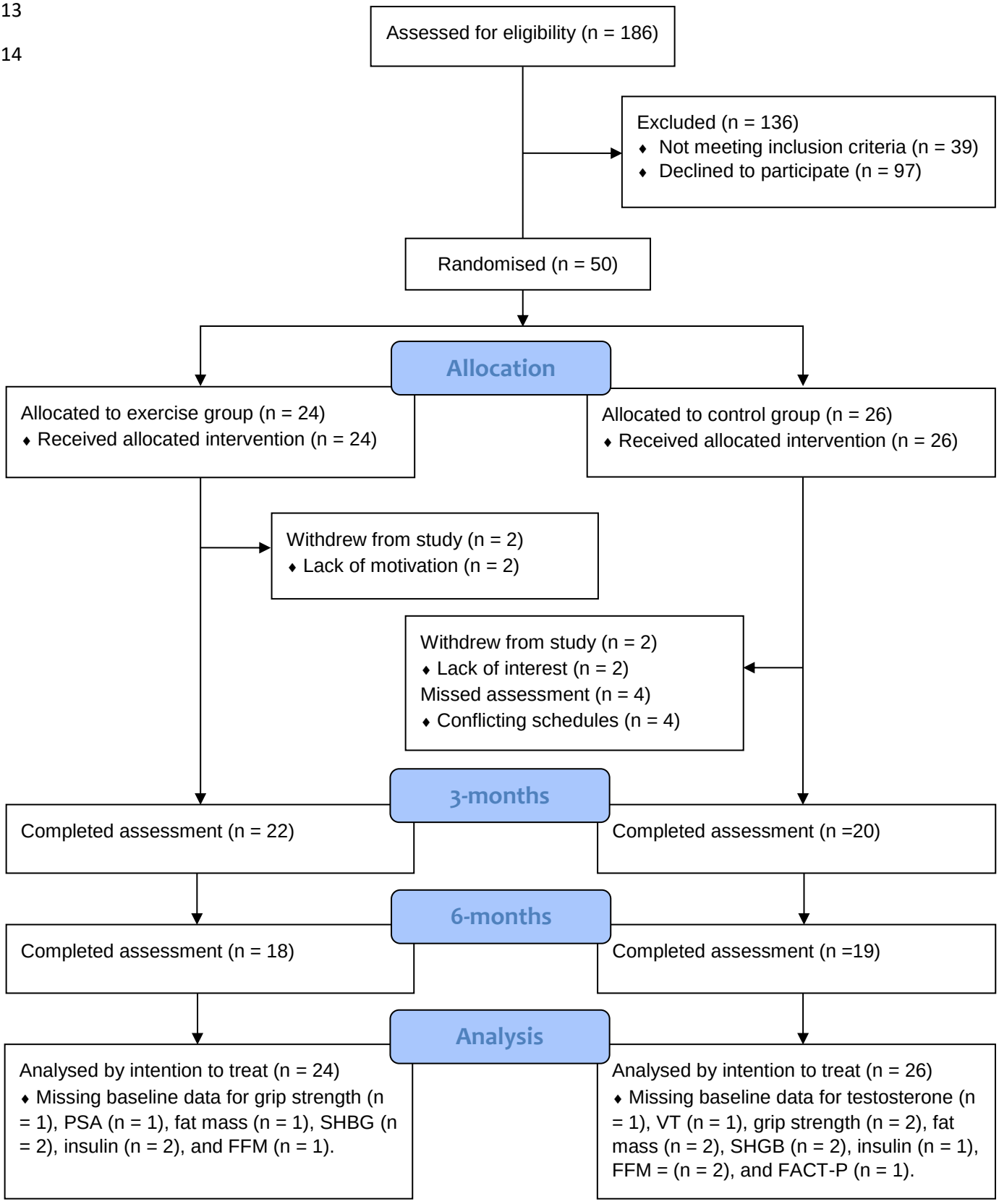
Assessed for eligibility (n = 186)
Excluded (n = 136)
♦ Not meeting inclusion criteria (n = 39)
♦ Declined to participate (n = 97)
Randomised (n = 50)
Allocation
Allocated to exercise group (n = 24)
♦ Received allocated intervention (n = 24)
Allocated to control group (n = 26)
♦ Received allocated intervention (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)
3-months
Completed assessment (n = 22)
Completed assessment (n =20)
6-months
Completed assessment (n = 18)
Completed assessment (n =19)
Analysis
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).
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).