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Obesity and low levels of physical activity impact on cardiopulmonary fitness in older men after treatment for prostate cancer

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Abstract

The purpose of this study was to compare fitness parameters and cardiovascular disease risk of older and younger men with prostate cancer (PCa) and explore how men's fitness scores compared to normative age values. 83 men were recruited post-treatment and undertook a cardiopulmonary exercise test (CPET), sit-to-stand, step-and-grip strength tests and provided blood samples for serum lipids and HbA1c. We calculated waist-to-hip ratio, cardiovascular risk (QRISK2), Charlson comorbidity index (CCI) and Godin leisure-time exercise questionnaire [GLTEQ]. Age-group comparisons were made using normative data. Men > 75 years, had lower cardiopulmonary fitness, as measured by VO_2 Peak (ml/kg/min) 15.8 ± 3.8 $p < 0.001$, and lower grip strength(28.6±5.2 kg $p < 0.001$) than younger men. BMI ≥30kg/m^2 and higher blood pressure all contributed to a QRisk2 score indicative of 20% chance of cardiovascular risk within 10 years (mean: 36.9–6.1) $p < 0.001$. Age, BMI and perceived physical activity were significantly associated with lower cardiopulmonary fitness. Men with PCa > 75 years had more cardiovascular risk factors compared to normative standards for men of their age. Although ADT was more frequent in older men, this was not found to be associated with cardiopulmonary fitness, but obesity and low levels of physical activity were. Secondary prevention should be addressed in men with PCa to improve men's overall health.

KEYWORDS
cardiopulmonary fitness, cardiovascular risk, obesity, older person, prostatic neoplasm, secondary prevention

1 | INTRODUCTION

Prostate cancer (PCa) is the most common male cancer, affecting approximately 1.3 million men worldwide (Bray et al., 2018). In the UK, more than 48,000 new PCa cases were registered in 2015–2017, with prevalence being highest in men aged 75 to 79 years, and this is predicted to rise by 12% by 2030 (CancerResearchUK, 2015–17). Older men with PCa, defined as those men 70 years of age and older (Boyle et al., 2019), have been reported to have less favourable outcomes in observational studies, possibly due to later diagnosis, conservative treatment and adverse effects of treatment (Bechis et al., 2011; Pettersson et al., 2018; Vernooij et al., 2019; Yang et al., 2017). As life expectancy increases, we are likely to see the burden of PCa cancer in older men increase and need to consider their complex health needs (Droz et al., 2014; WHO, 2018). Older men with PCa are more likely to have comorbidities, with more than 30% of men diagnosed having one or more co-existing chronic illnesses (Roy et al., 2018). Diabetes, cardiovascular disease (CVD) and hypertension can impact on PCa treatment decisions and treatment-related adverse effects (Bradley et al., 2014; Søgaard et al., 2013). Men over 70 are also more likely to be treated conservatively with androgen deprivation therapy (ADT), which may have adverse consequences for their physical and psychological health (Bourke et al., 2013).

Studies have shown an association between all-cause mortality and ADT in men with PCa (Davis et al., 2015; Keating et al., 2013; O'Farrell et al., 2015). While ADT is highly effective as a component of combined modality therapy, its use, and specifically, the use of gonadotrophin-releasing hormone (GnRH) agonists, has been associated with the development of sarcopenic obesity and cardiometabolic risk factors, including dyslipidaemia, insulin resistance and elements of metabolic syndrome (Collier et al., 2011; Morote et al., 2015; Turner et al., 2017). An association between ADT and increased risk of CVD and mortality has been recognised in multiple studies (Bosco et al., 2014; Nguyen et al., 2011; Weaver et al., 2013; Zhao et al., 2014) but CVD and links with increased mortality remain contentious in clinical practice. One possible reason for this, is that the outcomes of observational studies have not been confirmed in clinical trials of PCa treatment, including those with ADT (Scailteux et al., 2017). Clinical trials have often excluded men 65 years or older and those with pre-existing cardiometabolic risk factors, which may increase their susceptibility to the adverse effects of ADT, and have been more focused on younger, healthier patient populations, in comparison with observational studies (Hutchins et al., 1999; Kennedy-Martin et al., 2015; Thompson et al., 2017).

Regarding adverse effects associated with ADT, there is a growing body of evidence that lifestyle interventions (exercise and dietary advice) have significant potential for secondary prevention to reduce treatment-related cardiovascular risk (Gardner et al., 2014; Owen et al., 2017; Redig & Munshi, 2010; Wall, 2016) and all-cause mortality (Dickerman et al., 2019). Exercise and nutritional interventions have also been shown to counteract sarcopenic obesity (Trouwborst et al., 2018) in the non-cancer population so have potential for use in men with PCa to reduce obesity, risk of diabetes and cardiovascular disease.

The aim of this study was to compare the fitness and CVD risk of older and younger patient's with PCa with the hypothesis being that older men with PCa have lower fitness and higher CVD risk compared to younger men with PCa. Thereby raising the profile of the importance of lifestyle interventions for secondary prevention in this population.

2 | METHODS

2.1 | Study design and recruitment

A cross-sectional study design was undertaken with patients recruited from two UK cancer centres (Surrey and Newcastle). This study was approved by NHS Health Research Authority (REC Ref14/LO/0495) data was collected from 23/7/2014 to 31/7/2015. All participant's provided informed written consent. Physical and health assessments were carried out in clinical and laboratory settings.

2.2 | Study population

Men were eligible to take part in the study if they were treated 3–36 months post-diagnosis, with stable PSA, <0.4ng/ml for surgical and radiotherapy patients <10ng/ml and androgen deprivation therapy (ADT). Men were recruited if they had one or more of three risk factors; BMI <18.5 or >25 Kg/m^2; elevated blood pressure and or receiving ADT. We purposely recruited men at higher risk of chronic health problems as these men were potentially more in need of secondary prevention. Men were excluded if they had a history of myocardial infarction or pulmonary disease or were receiving active treatment (except ADT). Adverse risk from engaging in physical activity was assessed during a prior medical check using the Physical Activity Readiness Questionnaire (Adams, 1999) and those individuals deemed 'at risk' were excluded from the cardiopulmonary fitness assessment but were still included in the study. A study population and strobe diagram are presented in Figure 1.

2.3 | Data collection

Demographic data including age, ethnicity, employment and smoking status were obtained using a demographics questionnaire, completed at the start of assessment. Cancer treatment and Charlson Comorbidity Index (CCI) (Charlson et al., 1987) were obtained from medical records and reviewed by a medical practitioner. Self-perceived physical activity levels were measured prior to assessment by the Godin Leisure Time Exercise Questionnaire (Amireault et al., 2015) this contains 3 core items regarding the frequency of strenuous, moderate and mild physical activity in periods of 15 minutes or more during a 7-day period. The scores are multiplied by weight and summed into an overall score that ranges between 0 and 119 metabolic equivalents of task (METs)/ minutes of physical activity per week.

2.4 | Cardiovascular and metabolic assessments

Blood pressure, weight, body mass index (BMI), waist and hip circumference were assessed. Nonfasted blood samples were evaluated for HbA1c, serum cholesterol (total, HDL, LDL) and triglycerides. HbA1c

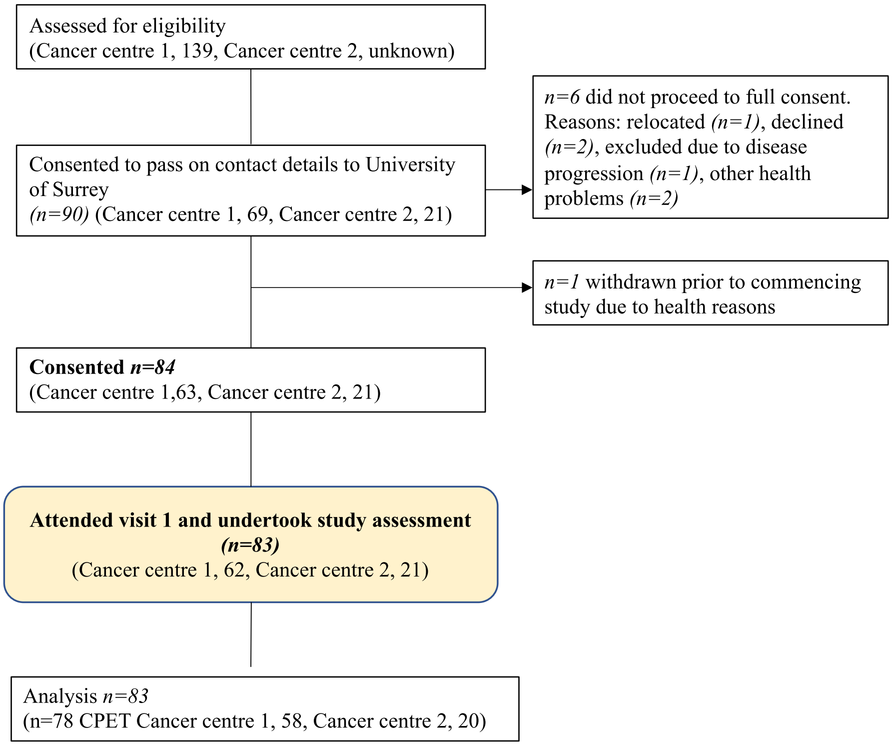


FIGURE 1 Strobe diagram of sample and data collection

was measured by a commercially available enzyme-linked immunosorbent assay (ELISA). Similarly, serum cholesterol and triglycerides were measured by commercially available enzymatic colorimetric assays. All blood sample analysis and diagnostic assays were provided by an accredited clinical laboratory. Cardiovascular risk was calculated using QRISK2, a validated prediction algorithm based on the metabolic indices above, BMI, age, blood pressure and socioeconomic indicators, to estimate the percentage risk of a cardiovascular event within the next 10 years (Collins & Altman, 2010). Body composition was measured with bioelectrical impedance analysis (BIA) as measured with the BodyStat 1500 with spot electrodes placed on the hands and feet and analysis conducted of % body fat (Gonzalez et al., 2018).

2.5 | Grip strength and sit to stand test

Grip strength was selected as a measure of upper body strength, with participants being asked to complete three squeezes of a dynamometer per hand for five seconds and with scores being averaged. A 30-second chair sit-to-stand time was selected as a measure of lower body muscle strength (Jones et al., 1999). Participants were asked to rise as quickly as possible to a full standing position and return to full sitting position as many times as possible within 30 seconds, while keeping arms folded across their chest.

2.6 | Cardiopulmonary fitness

The cardiopulmonary exercise test (CPET) is a continuous, incremental exercise test to volitional exhaustion, carried out on an electronic cycle ergometer. CPET provides a direct measurement of aerobic capacity and peak oxygen consumption ($V0_2$Peak) that is reflective of aerobic physical fitness (Scott et al., 2015). CPET is a gold standard assessment for evaluating pre-operative cardiopulmonary fitness (Smith et al., 2009). CPET has been evaluated for reliability and validity in men prior to surgery for PCa (Scott et al., 2015).

Pedalling frequency was self-selected within a range of 60-90 rpm, with the program. After a two-minute warm-up against no resistance (0 Watt) the intensity of exercise was increased by 20–30 Watts/minute. Men were encouraged to continue cycling to volitional exhaustion or until a plateau in oxygen consumption as observed. Heart rate (HR) and volume of oxygen ($V0_2$) consumed during exercise (ml/kg/min) were measured. Peak oxygen consumption ($V0_2$Peak) was calculated as the consecutive 20 second period of gas exchange data in the last minute before volitional exhaustion (Nusair, 2017). Men were not included in the CPET analysis if they were unable to reach $V0_2$ Peak or if the CPET test was stopped for safety reasons.

All results from the physical fitness assessments were compared with population norms (Aspenes et al., 2011; Massy-Westropp et al., 2011; Reuter et al., 2011; Strassmann et al., 2013), before being classified against age-matched normative values into low (below the age-specific norm), moderate (within age norms) or high (above age norms).

2.7 | Statistical methods

Descriptive statistics were conducted to describe the sample. Men were stratified according to age <65, 65–75 and >75 years to be able to compare to normative values. Mean and standard deviation were

TABLE 1 Demographic and treatment characteristics across age groups for men with prostate cancer

	Study Population *n* = 83	<65 years *n* = 22 (26.5%)	65–75 *n* = 47 (56.6%)	>75 years *n* = 14 (16.8%)
Cancer centre				
Centre 1 n (%)	62 (74.7)	15 (68.2)	37 (78.7)	10 (71.4)
Centre 2 n (%)	21 (25.3)	7 (31.8)	10 (21.3)	4 (28.6)
Age (Years)				
Mean (SD)	68.2 (7.4)	58.6 (4.4)	69.5 (2.9)	78.7 (2.0)
Ethnicity n (%)				
Caucasian	80 (96.4)	20 (90.9)	46 (97.9)	14 (100.0)
Black British	3 (3.6)	2 (9.1)	1 (2.1)	0 (0.0)
Retired n (%)				
Yes	19 (22.9)	8 (36.4)	11 (23.4)	0 (0.0)
No	54 (65.1)	8 (36.4)	35 (74.5)	11 (78.6)
Missing	10 (12)	6 (27.3)	1 (2.1)	3 (21.4)
Treatment (men had combined treatments)				
Surgery	53 (63.9)	17 (77.3)	33 (72.2)	3 (21.4)
Radiotherapy	26 (31.3)	4 (18.2)	12 (25.5)	10 (71.4)
Brachytherapy	3 (3.6)	0 (0.0)	3 (0.0)	0 (0.0)
Adjuvant ADT	32 (38.6)	6 (27.3)	15 (31.9)	11 (78.6)
ADT<6 months	7 (8.4)	0 (0)	3 (3.6)	4 (4.8)
ADT>24 months	25 (30.1)	6 (7.2)	5 (6.0)	7 (8.4)
Time from treatment (years)				
Median (IQR)	0.8 (1.0)	0.8 (0.8)	0.8 (1.0)	0.3 (0.9)
Charlson co-morbidity index CCI (IQR)				
Median (IQR)	6 (3)	5 (3)	6 (1)	8 (3)
Diabetes	7 (8.4)	1 (4.5)	2 (4.2)	4 (28.6)
Statins	14 (16.8)	2 (2.4)	11 (13.2)	1 (1.2)
Smoking status N (%)				
Non-smoker	45 (54.2)	13 (59.1)	27 (57.4)	5 (35.7)
Ex-smoker	27 (32.5)	5 (22.7)	18 (38.3)	4 (28.6)
Current smoker	4 (4.8)	2 (9.1)	1 (2.1)	1 (7.1)
Missing	7 (8.4)	2 (9.1)	1 (2.1)	4 (28.6)
Body Mass Index (BMI) Kg/m^{2}[a]	28.9 (SD3.4)	29.8(4.1)	28.5(3.2)	29.1(2.8)
Normal	5 (6.0)	3 (13.6)	2 (4.2)	0 (0.0)
Overweight	53 (63.9)	10 (45.5)	34 (72.3)	9 (64.3)
Obese	25 (30.1)	9 (40.9)	11 (23.4)	5 (35.7)
Godin leisure-time exercise questionnaire (GLTEQ) Mean (SD)	26.3 (22.7)	40.7 (31.0)	23.7(19.3)	16 (11.2)

[a]BMI categorisation for men: Normal 18.5–24.9 Overweight 25–29.9 Obese >30.

used for normally distributed variables, median and interquartile range for non-normally distributed variables and count and percentage for categorical variables. ANOVA was used to test for differences between the age groups. Univariate analysis was used to explore demographic and treatment factors that could be associated with cardiopulmonary fitness. Multivariate analysis with stepwise linear regression and backward elimination was used to investigate strength of association of factors with cardiopulmonary fitness (CPET $V0_2$ Peak). Data were imputed using a multiple imputation method with 5 data sets. The results presented for univariate and multivariate regression analyses are based on pooled results from imputed datasets. The regression analyses were also performed using complete cases and this yielded the same results (sensitivity analysis). Statistical significance was considered at 0.05 level. Data were entered checked for quality and managed in Excel. All data pre-processing and statistical analyses were performed in R statistical software version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria). Multiple imputation and pooled regression analyses were performed using the MICE package in R.

3 | RESULTS

A total of 83 men participated in the study at the two centres in the UK (Surrey and Newcastle), their characteristics are presented in Table 1. Data are presented across three age groups men <65 years of age (n = 22, 26.5%), 65-75y (n = 47, 56.6%) and >75y (n = 14, 16.8%). The mean age of men was 68.2 ± 7.4 y. Most men were Caucasian (96.4%) and still in employment (65.1%). The majority of men were treated with surgery (63.9%), radiotherapy (31.3%) or ADT either as an adjuvant or standalone (38.6%). Most of the men (25, 30.1%) were on ADT for 24 months with 7 (8.4%) receiving short-course ADT (<6 months). The majority of men had comorbidities with a median CCI of 6 (IQR 3). Type II diabetes was present in 7 (8.4%) men, 4 of which were in the >75 age group. Statins (HMG-CoA reductase inhibitors) were taken by 14 (16.8%) of the men for lipid modification of which only 1 was in the >75 age group. Most men were non-smokers (54.2%) with only 4 (4.8%) active smokers and the remaining men having quitted smoking. On average men were overweight with a mean BMI of 28.9 Kg/m^2± 3.4, with no significant differences between age groups. Men had low overall levels of perceived physical activity as recorded by GLTEQ.

Central obesity was a consistent finding across age groups (p = 0.653, Table 2), with the overall mean waist-to-hip ratio of 0.97 ± 0.06 with 72 (86.7%) men at or above the recommended NHS 0.9 ratio for good health for men, and a higher proportion in men >75 years group. The percentage body fat was 29.4 ± 3.8, with men of >75 years having significantly more fat than the other age groups (mean of 31.7 ± 4.2) (p = 0.026). Total serum cholesterol (TC) (4.8 mmol/L ± 0.4), HDL-cholesterol (1.4 mmol/L, ±0.4) and the TC/HDL ratio (3.6) were similar and within reference ranges across age groups.

Men who were >75 years and with a higher BMI and lower physical activity levels, in the multivariate analysis were more likely to have poorer cardiopulmonary fitness (p < 0.001). Factors such as ADT, when compared with other factors, were not associated with poorer cardiopulmonary fitness (Table 3).

Men <65 years had lower mean risk of cardiovascular events (12 ± 8.5), which was significantly higher for men who were >75 years (36.9 ± 6.1)(p < 0.001). A QRisk2 of >10% in an individual would be considered a clinical indicator for further formal assessment and medical intervention, and such scores are suggestive that

TABLE 2 Clinical assessment data characterised by men's age and grouped into subcategories <65, 65–75, >75. Expressed as mean (SD) unless otherwise specified (significance defined as p < 0.05)

Age subgroups	All (n = 83)	<65 years n = 22 (26.5%)	65–75 n = 47 (56.6%)	>75 years n = 14 (16.8%)	p (between age groups)
Waist/Hip Ratio	0.97 (0.06)	0.96 (0.08)	0.97 (0.05)	0.97 (0.05)	0.653
Waist/Hip ratio ≥0.9 N (%)	72 (86.7)	16 (72.7)	42 (89.3)	14 (100)	0.046
Body composition (% body fat)	29.4 (3.8)	27.0 (3.8)	29.9 (3.2)	31.7(4.2)	0.026
HbA1c mmol/mol	41.0 (8.3)	40.2 (11.2)	39.7 (5.5)	46.1 (9.3)	0.034
People without diabetes HbA1c mmol/mol	39.2 (5.3)	38.2 (6.4)	39.0 (4.5)	42.5 (5.5)	0.099
Total serum cholesterol (TC) (mmol/l)	4.8 (0.9)	4.7 (0.7)	4.6 (0.7)	4.8 (0.9)	0.282
HDL- cholesterol (mmol/l)	1.4 (0.4)	1.3 (0.3)	1.4 (0.4)	1.4 (0.2)	0.514
TC: HDL ratio	3.6 (1.0)	4.0 (1.3)	3.5 (0.9)	3.6 (0.8)	0.625
Serum triglycerides (mmol/l)	1.8 (0.8)	1.6 (0.5)	1.8 (0.8)	2.4 (1.1)	0.034
CPET Peak VO_2 (ml/kg/min) (n = 78)[a]	20.7 (6.3)	24.9 (7.8)	20.3 (5.1)	15.8 (3.8)	<0.001
Grip strength (kg)	38.4 (8.4)	42.3 (5.6)	39.5 (8.2)	28.6 (5.2)	<0.001
Chair Sit-to-Stand	13.6 (4.1)	14.8 (4.5)	13.7 (3.9)	11.2 (2.9)	0.036
Systolic blood pressure (mm Hg)	135.7 (15.3)	136.1 (18.6)	133.8 (12.5)	141.6 (17.8)	0.240
Diastolic blood pressure (mm Hg)	81.4 (10)	87.8 (9.6)	80.1 (9.2)	77.1 (10.2)	0.005
Calculated 10-year risk of CVD event (QRisk2)	20.4 (10.1)	12 (8.5)	19.9 (5.7)	36.9 (6.1)	<0.001

Note: Reference values.

HbA1c normal is below 42 mmol/mol, prediabetes 42 to 47 mmol/mol, Diabetes 48 mmol/mol (refs).

Non-fasting serum blood: triglycerides healthy below <1.8 mmol/L; HDL should be >1 mmol/L; TC/HDL ratio above 6 is considered high; TC below 5.0; LDL below 3.(refs).

Waist-to-hip ratio <0.9 for men is considered healthy (refs).

[a]Those men able to reach $V0_2$ peak and complete CPET assessment.

TABLE 3 Univariate and multivariate linear regressions. A final model obtained with stepwise linear regression and backward elimination using *p*-value of 0.05 as cut-off. Investigating factors that are associated with cardiopulmonary fitness VO_2 Peak as measured by the cardiopulmonary exercise test (CPET). Final equation CPET_VO2_Peak = 66.70 − 0.36 × Age (years) − 0.81 × BMI +0.07 × GLTEQ score

Independent variable	Coefficient estimate	Standard error	*p*-value	95% Confidence interval	
				Lower	Upper
Univariate analysis					
Age (years)	−0.40	0.08	<0.001	−0.57	−0.24
Ethnicity (Black British)	−4.18	3.65	0.256	−11.46	3.09
Retired (yes)	2.37	1.56	0.133	−0.74	5.49
Diabetes (yes)	−4.52	2.42	0.066	−9.34	0.31
Charlson comorbidity score	−0.95	0.32	0.004	−1.59	−0.31
BMI Kg/m^2	−0.78	0.20	<0.001	−1.17	−0.38
Smoking status (Ex-smoker)	−1.93	1.47	0.190	−4.86	1.01
Smoking status (Current smoker)	−0.41	3.23	0.899	−6.86	6.03
GLTEQ score	0.11	0.03	0.001	0.04	0.17
ADT (yes)	−3.40	1.38	0.016	−6.15	−0.65
Surgery (yes)	3.21	1.41	0.025	0.41	6.01
Radiotherapy including brachy (yes)	−3.13	1.42	0.030	−5.95	−0.30
Time from treatment (years)	1.09	0.99	0.276	−0.89	3.07
Waist-to-hip ratio	−24.33	12.36	0.054	−49.10	0.45
Body composition, fat %	−0.74	0.16	<0.001	−1.06	−0.42
Multivariate model					
Age (years)	−0.37	0.11	0.002	−0.59	−0.15
Ethnicity (Black British)	−6.21	3.12	0.051	−12.45	0.04
Retired (yes)	−0.24	1.40	0.865	−3.03	2.55
Diabetes (yes)	−0.47	2.11	0.824	−4.71	3.76
Charlson comorbidity score	0.19	0.38	0.625	−0.58	0.95
BMI Kg/m^2	−0.73	0.23	0.002	−1.18	−0.27
Smoking status (Ex-smoker)	−1.41	1.19	0.241	−3.79	0.97
Smoking status (Current smoker)	0.13	2.65	0.962	−5.21	5.47
GLTEQ score	0.05	0.03	0.069	0.00	0.11
ADT (yes)	−2.06	1.78	0.254	−5.64	1.52
Surgery (yes)	−0.45	1.86	0.812	−4.21	3.32
Radiotherapy including brachy (yes)	−0.11	1.78	0.953	−3.74	3.53
Time from treatment (years)	−0.12	1.05	0.914	−2.31	2.08
Waist-to-hip ratio	4.28	11.43	0.710	−18.71	27.27
Body composition, fat %	−0.18	0.20	0.369	−0.59	0.22
Final model with backward elimination					
Age (years)	−0.36	0.07	<0.001	−0.50	−0.21
BMI Kg/m^2	−0.81	0.16	<0.001	−1.14	−0.48
GLTEQ score	0.07	0.03	0.010	0.02	0.12

Abbreviations: ADT, androgen deprivation therapy; BMI, body mass index; GLTEQ, Godin leisure-time exercise questionnaire.

older men were at much higher risk of future cardiovascular events (NICE, 2014). There was no difference between the proportion of men in this sample with QRisk2 scores above >20% risk of 10 year CVD, and a normal, aged-matched sample of men taken from across the UK (Collins & Altman, 2012)(Graph 1.)

Cardiopulmonary fitness ($V0_2$ Peak) was significantly lower for men who were >75 years in comparison with men <65 years (15.8 ± 3.8 versus 24.9 ± 7.8 ml/kg/min; p < 0.001). Grip strength was also higher for men under 65 years, who had a mean score of 42.3 ± 5.6 kg compared with 28.6 ± 5.2 kg for those >75 years (p < 0.001). Sit to stand scores were similar across age ranges, with a mean of 14.8 ± 4.5 for men <65 years, compared with a mean of 11.2 ± 2.9 for men who were >75 years (Table 2). Compared with normative scores, 70% (14) of men in <65 years, 41.3% in the 65–75 age group and 53.8% in the >75-year group had grip strength classified as low and below age-specific normative values (Graph 2). Classifications followed a similar pattern with the sit-to-stand test, with 65%, 52.2% and 53.8% classified as being in the low group (below age normative values) for men in the <65 years, 65–75 years and >75 years group, respectively (Graph 3).

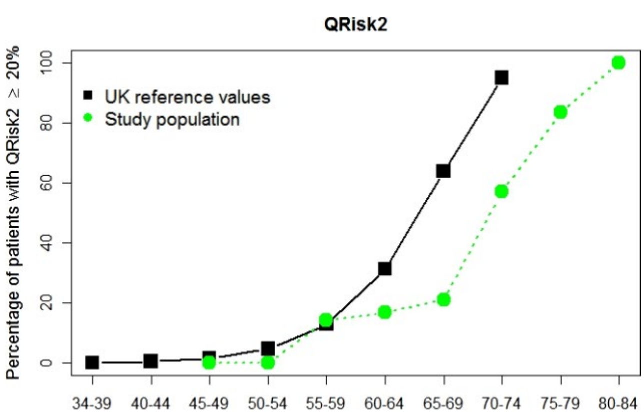
4 | DISCUSSION

The aim of this study was to compare the fitness and CVD risk of older and younger PCA patients. Compared with younger men <75 years, men >75 years with PCa had greater variability in the measures of physical fitness, metabolic health and obesity. Although ADT was more frequently prescribed for those men >75 years, ADT was not found to be associated with cardiopulmonary fitness, but BMI and low levels of physical activity were. This study contributes to the evidence for inclusion of lifestyle interventions and secondary prevention for men >75 years with PCa in clinical practice to reduce comorbidities and reverse metabolic and physical fitness declines.

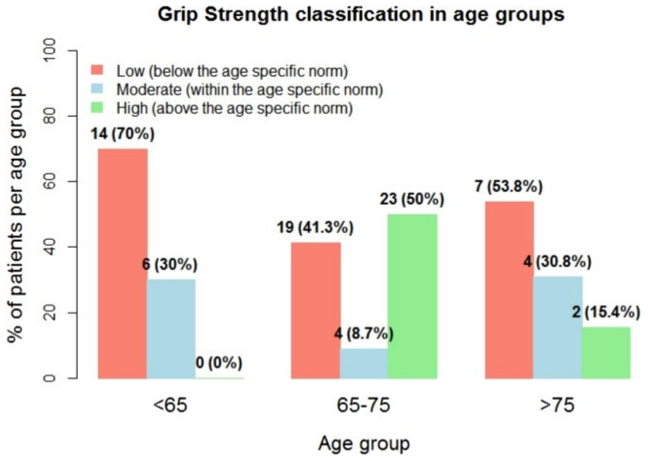
Obesity and low levels of physical activity were associated with men's poor level of cardiopulmonary fitness. Many of the men were overweight (BMI 25–29.9 kg/m^2) and had an increased waist-to-hip ratio (>0.9), indicating central adiposity. Studies suggest that obesity after PCa is associated with higher PCa specific mortality (PCSM) in men with locally advanced disease (Bonn et al., 2014; Efstathiou et al., 2007; Vidal et al., 2017). In a recent analysis of deaths in men after PCa, Troeschel et al., (2020) found that post-diagnosis obesity (BMI ≥30 kg/m^2) was a risk factor for PCa recurrence. Compared with men having a healthy weight, men who were obese had a 29% (95% CI 0.96 to 1.67) increased risk of PCSM and a 23% (95% CI1.11 to 1.35) increased risk of mortality from all-causes. Post-diagnosis weight gain (>5% of body weight) was also associated with a higher risk of PCSM, similar to that found in other studies (Bonn et al., 2014). Many of the men in our study had central adiposity, as measured by waist-to-hip ratio, and with levels of HbA1c indicative of pre-diabetes, all of which could have contributed to metabolic health risks associated with their PCa (Shlomai et al., 2016). While ADT-related cardiometabolic risk shares several of the components of metabolic syndrome (Di Sebastiano et al., 2018), ADT adverse effects are distinct in that it develops more rapidly and is characterised by an accumulation of subcutaneous adipose tissue and sarcopenia (Turner et al., 2017). This impacts on men's body composition which is characterised by a loss of skeletal muscle and accumulation of body fat (Morote et al., 2015).

Exercise and dietary strategies to reduce sarcopenic obesity in metabolic syndrome have been identified but few look at these in combination (Trouwborst et al., 2018). A systematic review of current nutritional strategies for cardiometabolic complications of ADT identified that existing evidence for the beneficial role of diet in the prevention of ADT-related cardiometabolic risk was limited (Turner et al., 2017). Thus, strategies to reduce obesity in men following PCa treatment are clearly needed. However, we know little about the amount of weight loss that is required to elicit improvements in cancer outcomes or how ADT-related effects on body weight may contribute to this (Turner et al., 2017).

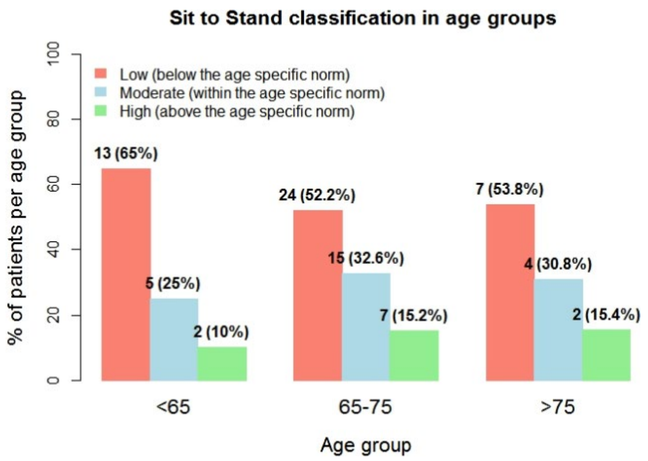
Predicted cardiovascular risk was elevated in our sample, with those in the 65–75 age group having risk scores that would reflect the need for formal assessment and lifestyle intervention, and those in the >75-year group in a range needing medical assessment and secondary prevention (NICE, 2014). Out of the sample, 14 (16.8%) of the men were prescribed statins with only 1 of the men >75 years. Elevated blood pressure, multiple comorbidities and raised BMI all contributed to the prediction of 10-year risk of a cardiovascular event. A recent registry study of 20,216 PCa survivors recorded a 30% increased risk of cardiovascular events in men on ADT (adjusted HR = 1.3, 95%CI = 1.2,1.4), especially in those on GnRH agonists and Degarilix (adjusted HR = 1.5 95% CI = 1.2,1.9)(Cardwell et al., 2020). These results are of importance because the incidence of ADT-induced cardiovascular mortality has been shown to be significantly higher in men with pre-existing CVD (Gupta et al., 2018; Hu et al., 2020). Age was also shown to be a significant factor in increasing CVD risk in those without cancer, but men who had prolonged use of ADT (more than 2 years) were found to have increased CVD at age 74 years (OR 1.9, 95% CI 1.0–3.5) and men with comorbidities had even greater CVD (OR 8.1,95% CI4.3–15.5) than men



GRAPH 1 QRisk 2 and percentage of patients above >20% QRisk compared to reference population



GRAPH 2 Upper body strength as measured by grip strength compared to age-specific norms based on data from (Massy-Westropp et al., 2011)



GRAPH 3 Lower body strength across age groups compared to age-specific norms based on data from Strassmans study (Strassmann et al., 2013)

without comorbidities (Morgans et al., 2015). In our study, elevated cardiovascular risks may have existed prior to the diagnosis of PCa, as shown in the comparison of QRisk2 data for our sample and that of the UK (Graph 1). As a tool, this metric may underestimate CVD risk in men with PCa due to the increased cardiometabolic complications of ADT, which are not taken into account in the QRisk2 score. Despite this limitation, QRisk2 could be a useful tool in urology clinics for reviewing pre-existing CVD risk factors before starting ADT.

Decline in skeletal muscle mass and function is a common problem in older cancer patients which can negatively affect physical function and cancer outcomes (Handforth et al., 2014; Owen et al., 2019; Williams et al., 2020). The significant difference between mean grip strength declined as a result of increasing age, when compared with normative data, 70% of the scores for men <65 years were below age-matched norms, compared to 53% in the >75 years group. Furthermore, over 50% of men in all subgroups were below age-matched norms for lower body muscle strength, as evidenced by scores from the sit-to-stand test. This difference may reflect our measurement techniques, for example using leg extension and vertical bench press tests would have provided greater precision. In a recent longitudinal study of men aged 70 to 88 years with PCa, it was found that prior to adjuvant ADT and radiotherapy, there was a high prevalence of skeletal muscle disorders (Couderc et al., 2020). This study highlighted the need for better assessment of skeletal muscle prior to ADT, and implementation of appropriate exercise and nutrition interventions. Additionally, skeletal muscle loss has also been found to increase in prolonged use of ADT which impacts on physical fitness up to 3 years after treatment (Smith et al., 2012) but was not associated in our study with cardiopulmonary fitness. Resistance training and other forms of physical activity during ADT have been shown to reduce body fat, maintain skeletal muscle mass and insulin sensitivity (Winters-Stone et al., 2015). Exercise has also been shown to ameliorate a range of ADT-related side effects, including fatigue and impaired health-related quality of life (Cormie & Zopf, 2018) and can improve cardiovascular risk profile (Ndjavera et al., 2020). Additionally, multimodality interventions that integrate several factors such as Mediterranean diet, weight reduction and exercise provide positive benefits (Demark-Wahnefried et al., 2018; Zuniga et al., 2020).

The cardiopulmonary fitness of men >75 years was poorer than younger age groups. The large discrepancy between the average peak VO_2 value recorded for PCa patients >75 years and those <65 years was notable. However, the results are even more alarming when compared with age-matched norms. Normative data for $V0_2$ peak oxygen uptake reported by Aspenes *et al.* (Aspenes et al., 2011) show that the average values for older PCa patients in the present study were only 52% of those for the most inactive men >70 years. Furthermore, PCa patients in the <65 years age group only achieved an average score that was 72% of that for the most inactive men in the age range of 60–69 years. This suggests there is an urgent need for exercise interventions aimed at improving aerobic fitness in PCa patients of all ages but particularly for older patients. In a review of 27 RCTs, including a meta-analysis of 19 pooled studies on physical activity in cancer survivors, Grimmett et al. (Grimmett et al., 2019) found that existing data suggest that exercise interventions are effective in achieving only modest increases in physical activity at least 3 months post-intervention. Furthermore, exercise interventions were less likely to be effective in older cancer survivors, who would gain benefit from the provision of greater support, particularly those with physical limitations who are less likely to engage in exercise (Weller et al., 2019). However, initiating exercise and nutritional interventions prior to PCa treatment via prehabilitation (Faithfull et al., 2019) may be more effective than providing interventions after cancer treatment when metabolic and cardiovascular changes have already occurred.

A potential study limitation we encountered was that we invited men into the study who were identified as having pre-existing risk factor for CVD, such as elevated BP, BMI>25kg/m^2 and/or receiving ADT. Our sample may therefore not reflect the wider PCa population. We were also not able to compare our data against a non-PCa population of men using our methodology but relied on normative values generated in prior studies, future work would benefit from having normative controls. Despite this limitation, our study draws attention to the missed opportunities for health promotion in men with PCa. Large scale studies demonstrate that men with PCA are at greater risk for incident cardiovascular disease (Troeschel et al., 2020), diabetes mellitus (Zaorsky et al., 2017), osteoporosis and functional decline (Winters-Stone et al., 2017). Our study reflects the need to address how the adverse effects of treatment are superimposed on existing levels of co-morbidity and identifies those most in need of assessment and secondary prevention.

5 | CONCLUSION

We found that men with PCa >75 years had more cardiovascular risk factors, poorer physical function and lower strength compared to normative standards for men of their age. Fitness parameters were worse in older men with PCa than younger patients but to a far greater extent than in normal ageing, thereby raising the profile of the importance of lifestyle interventions in this population. This study indicates the need for proper individualised assessment of fitness parameters in men who are >75 years for an exercise and dietary prescription. Opportunities to integrate secondary prevention as part of PCa treatment are also important for ameliorating the long-term health consequences of PCa and its treatments.

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CONFLICT OF INTEREST

Sara Faithfull is a trustee of Prostate Cancer UK. All other authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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