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Pedro Lopez
Edith Cowan University

Robert U. Newton
Edith Cowan University

Dennis R. Taaffe
Edith Cowan University

Kerri Winters-Stone

Laurien M. Buffart
Edith Cowan University

See next page for additional authors

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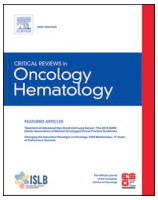

Effects and moderators of exercise medicine on cardiometabolic outcomes in men with prostate cancer previously or currently undergoing androgen deprivation therapy: An individual patient data meta-analysis

Pedro Lopez [a,b,c], Robert U. Newton [a,b,d], Dennis R. Taaffe [a,b], Kerri Winters-Stone [e,f], Laurien M. Buffart [a,f,*,1], Daniel A. Galvão [a,b,1]

[a] Exercise Medicine Research Institute, Edith Cowan University, Joondalup, Western Australia, Australia
[b] School of Medical and Health Sciences, Edith Cowan University, Joondalup, Western Australia, Australia
[c] Pleural Medicine Unit, Institute for Respiratory Health, Perth, Western Australia, Australia
[d] School of Human Movement and Nutrition Sciences, University of Queensland, St. Lucia, Queensland, Australia
[e] Knight Cancer Institute, Oregon Health and Science University, Portland, OR, USA
[f] Department of Physiology, Radboud University Medical Center, Radboud Institute for Health Sciences, Nijmegen, Netherlands

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ABSTRACT

Purpose: To examine the effects and moderators of exercise effects on cardiometabolic outcomes in men with prostate cancer previously or currently undergoing androgen deprivation therapy (ADT).
Results: Seven trials including 560 patients were examined. Exercise resulted in significant effects on whole-body and regional fat mass ($P \leq 0.001$). For whole-body fat mass, significant exercise effects were observed in patients who were unmarried (−1.4 kg, $P < 0.05$) and who presented with higher fat mass levels (−1.0 kg, $P < 0.05$). For diastolic blood pressure and low-density lipoprotein (LDL), younger (−4.7 mmHg, $P < 0.05$) and older patients (−0.2 mmol.l^{-1}, $P < 0.10$) achieved greater effects, respectively. Regarding high-density lipoprotein (HDL), patients undertaking ADT + prostatectomy + radiotherapy derived significant exercise effects (0.3 mmol.l^{-1}, $P < 0.05$).
Conclusions: Exercise effectively reduces fat mass across subgroups of men undergoing or following ADT with different characteristics. For diastolic blood pressure, HDL and LDL, groups based on age and treatment history could be specifically targeted with exercise medicine.

1. Introduction

Prostate cancer is the third most prevalent cancer worldwide, with a total of ~1.5 million new cases in 2020 (Sung et al., 2021). In clinical practice, men with localised and locally advanced prostate cancer are commonly treated with androgen deprivation therapy (ADT) (Shahinian et al., 2005; Gunner et al., 2016) along with radical prostatectomy and radiation therapy (D'Amico et al., 2008; Siddiqui et al., 2008). Although the treatments are very successful with a 5-year survival rate of nearly 100% when patients are diagnosed at an early stage, ADT results in several cardiovascular and metabolic side effects such as increases in fat mass and insulin resistance, abdominal obesity, and hypercholesterolemia (Smith et al., 2006; Galvao et al., 2008; Galvão et al., 2009). These treatment-related adverse effects impact patients' wellbeing and quality of life during and following treatment (Chambers et al., 2017) and also lead to an increased risk of diabetes and cardiovascular events (Keating et al., 2006; D'Amico et al., 2007; Tsai et al., 2007).

Exercise has been endorsed as a promising medicine for cancer patients by many professional organisations (Hayes et al., 2009; Schmitz et al., 2010; Hayes et al., 2019; Schmitz et al., 2019) and deemed very important during and following ADT in men with prostate cancer (Segal et al., 2003, 2009; Galvao et al., 2010; Bourke et al., 2014; Galvao et al., 2014; Cormie et al., 2015; Newton et al., 2019; Taaffe et al., 2019; Ndjavera et al., 2020; Bigaran et al., 2020; Lopez et al., 2021). We (Galvao et al., 2010, 2014; Cormie et al., 2015; Newton et al., 2019; Taaffe et al., 2019; Lopez et al., 2021; Wall et al., 2017; Winters-Stone

* Correspondence to: Department of Physiology, Radboud Institute for Health Sciences, Geert Grooteplein Zuid 21, 6525 EZ Nijmegen, Netherlands.
E-mail address: Laurien.Buffart@radboudumc.nl (L.M. Buffart).
[1] Shared senior authorship

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et al., 2015) and others (Segal et al., 2003, 2009; Bourke et al., 2014; Ndjavera et al., 2020; Bigaran et al., 2020), for example, have shown that exercise medicine can improve body composition and some cardiometabolic markers including blood pressure, glucose metabolism, lipid profile and inflammation in prostate cancer patients undertaking ADT at different treatment stages (Bigaran et al., 2020; Lopez et al., 2021). These outcomes are of clinical relevance as increased risk of metabolic and cardiovascular disease are experienced by patients on ADT (Galvão et al., 2009; Keating et al., 2006). Nevertheless, although the role of exercise medicine is being expanded to include patients at different disease stages (Galvão et al., 2018; Newton et al., 2018), it remains to be determined when and for whom exercise may result in clinically meaningful benefits for cardiometabolic outcomes in this population. Therefore, identifying demographic and clinical factors which can modify the exercise response of cardiometabolic outcomes (i.e., moderators of exercise effect) may help shift from *one-size-fits-all* to more targeted and tailored exercise prescriptions for men with prostate cancer (Iyengar and Jones, 2019). Additionally, it is important to identify who is effectively responding to exercise programs, given the large variability expected in patients undergoing different treatment regimens, and presenting with different demographic and clinical characteristics. This information is important for predicting patients who will likely respond to exercise and assisting clinicians and exercise professionals in recommending and prescribing exercise programs, respectively. Despite promising results derived from a few studies examining the moderators of exercise response in men with prostate cancer (Buffart et al., 2014, 2015; Taaffe et al., 2018) and previous systematic reviews with aggregate data meta-analysis (i.e., using reported mean effects and dispersion values) (Bigaran et al., 2020; Lopez et al., 2021), individual patient data (IPD) meta-analysis (i.e., merging different trial datasets rather than using reported mean effects and dispersion values) has been suggested as the preferred method to identify moderators of intervention effects (Buffart et al., 2013), Therefore, an IPD meta-analysis is likely the best method to examine demographic and clinical moderators of exercise effects in men with prostate cancer.

As a result, the present meta-analysis of individual prostate cancer patient data aims to evaluate the effects of exercise on cardiometabolic outcomes including body fat, fat mass and trunk fat mass, hip and waist circumference, cardiovascular outcomes, lipid profile, glucose metabolism and inflammation, and to identify demographic and clinical moderators of exercise effects on these outcomes in men with prostate cancer previously or currently undergoing ADT. This IPD meta-analysis is derived from data collected in the *Predicting Optimal Cancer Rehabilitation and Supportive Care* (POLARIS) study investigating the effects of exercise and psychosocial interventions in patients with cancer during and after cancer treatment (Buffart et al., 2013).

2. Methods

2.1. Protocol and registration

The present study was undertaken in accordance with the *Preferred Reporting Items for Systematic review and Meta-Analyses of Individual Participant Data* (PRISMA-IPD) (Stewart et al., 2015) with registration of the POLARIS study at the *International Prospective Register of Systematic Reviews* (PROSPERO identifier: CRD42013003805) in February 2013. Further details about POLARIS are reported elsewhere (Buffart et al., 2013, 2017).

2.2. Study procedure

Data were obtained from the POLARIS database which includes randomised controlled trials (RCTs) examining the effects of exercise and/or psychosocial interventions on quality of life in adult patients with cancer (Buffart et al., 2013). All principal investigators of eligible RCTs were invited to participate in the POLARIS consortium and to share individual patient data (Buffart et al., 2017). Search strategy and data extraction have been previously described (Buffart et al., 2017). All principal investigators of RCTs signed a data sharing agreement statement agreeing with the POLARIS policies (Buffart et al., 2013), and all individual RCTs included in the POLARIS study had received approval from local ethics committees. After checking for completeness and correctness, shared databases were recoded and harmonized into the POLARIS database. For the present study, we included RCTs that examined the effects of supervised exercise interventions on cardiometabolic outcomes including body fat percentage, fat mass and trunk fat mass (assessed by dual-energy X-ray absorptiometry), waist and hip circumference, systolic and diastolic blood pressure, mean arterial pressure, resting heart rate, total cholesterol, triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), glucose, glycated haemoglobin, insulin, or C-reactive protein in men with prostate cancer previously or currently treated with ADT.

2.3. Potential demographic and clinical moderators of exercise response

Potential moderators of exercise response in men with prostate cancer were based on previous original RCTs (Buffart et al., 2014, 2015; Taaffe et al., 2018) and papers derived from the POLARIS study (Buffart et al., 2017, 2018). Demographic and clinical characteristics were only considered for further analyses when data from a sufficient number of participants were available (i.e., >50 patients per subgroup). In this case, age (continuous, and groups based on tertiles), marital status (not married vs. married), and education level (no tertiary education vs. tertiary education) were considered as demographic moderators of the exercise response. Clinical moderators of the exercise response were associated with prostate cancer treatment including baseline values (continuous, and groups based on clinical cut-off values or tertiles when clinical cut-off values were not available), body mass index (BMI; continuous, and groups based on normal weight (BMI <25 $kg.m^{-2}$), overweight (BMI ≥25 to <30 $kg.m^{-2}$) and obesity (BMI ≥30 $kg.m^{-2}$)), time since diagnosis (continuous and based on tertiles), Gleason score (groups based on 7 and ≥8), ADT duration (groups based on acute (<6 months) and chronic ADT exposure (≥6 months)) (Taaffe et al., 2018; Galvão et al., 2011) and treatment regimen (ADT alone vs. ADT + prostatectomy vs. ADT + radiotherapy vs. ADT + prostatectomy + radiotherapy). Sub-analyses on Gleason score ≤ 6, treatment with chemotherapy, and presence of metastatic disease were not undertaken given the small number of participants with data available.

2.4. Statistical analysis

One-step complete-case IPD meta-analyses were conducted to examine the effects and the demographic and clinical moderators of exercise response of body fat, fat mass and trunk fat mass, waist and hip circumference, cardiovascular outcomes, lipid profile, glucose metabolism and inflammation. Linear mixed model analyses with a two-level structure were undertaken to consider the clustering of patients within studies by using a random intercept on study level. Effects were evaluated by regressing the study group (exercise vs. control group) on the post-intervention value of the outcome adjusted for the baseline value, while moderators were examined by adding the moderator and its interaction term with the intervention into the regression model for each moderator separately. Within- and between- trial interactions were separated by centring the individual value of the covariate around the mean study value of that covariate to reduce ecological bias (Fisher et al., 2011).

Likelihood ratio test was used to compare models with and without interaction terms, and χ^2 values, degrees of freedom (df) and P-values are reported. Stratified analyses were undertaken if the interaction terms were significant ($P \leq 0.05$) or approaching statistical significance to examine potential moderators (P-value ranging from 0.05 to 0.10). When statistically significant, we report regression coefficients (β) and

95% confidence intervals (95% CI) of the intervention effect for each subgroup. All analyses were conducted in R Core Team (2013) using the package 'lme4' (Bates et al., 2015).

3. Results

Seven RCTs from the POLARIS database examined exercise intervention effects on fat mass, cardiovascular outcomes, lipid profile, glucose metabolism and inflammation in men diagnosed with prostate cancer (Galvao et al., 2010, 2014; Cormie et al., 2015; Taaffe et al., 2019; Winters-Stone et al., 2015; Newton et al., 2018; Galvao et al., 2018). After screening for patients previously or currently treated with ADT, data from 560 out of 587 men with prostate cancer enrolled in these trials were included for analysis.

3.1. Study and patient characteristics

The sample of men with prostate cancer consisted of 319 patients allocated to exercise interventions compared to 241 patients allocated to the control groups (Table 1). Average age was 69.5 ± 7.8 yrs and BMI was 28.6 ± 4.0 kg.m^{-2}. The majority of these patients were married (78.6%), without a tertiary education (71.0%) and no longer employed (70%). Furthermore, 51.4% of patients were diagnosed with fast-growing aggressive tumours (Gleason score ≥ 7) and treated with ADT only (39.1%), followed by ADT + radiotherapy (36.2%), ADT + prostatectomy (13.9%), and ADT + prostatectomy + radiotherapy (10.8%). The median duration of ADT before study commencement was 2.0 months ranging from 0 to 156 months, with 58.2% of the patients receiving ADT during the study intervention and 41.8% receiving ADT before the intervention. Patient characteristics are presented in Table 1, while baseline and post-assessment values of fat mass, cardiovascular outcomes, lipid profile, glucose metabolism and inflammation are presented in Table 1 and Table S2 (Supplementary material).

All studies included had undertaken resistance-based exercise programs and predominantly prescribed combined resistance and aerobic exercise (Galvao et al., 2010, 2014; Cormie et al., 2015; Newton et al., 2019), followed by resistance training plus impact-loading (Newton et al., 2019; Winters-Stone et al., 2015), and multimodal exercise programs involving resistance training and aerobic exercise with either impact-loading (Taaffe et al., 2019) or flexibility training (Galvao et al., 2018). Studies were designed to compare the exercise interventions vs. usual care control (Galvao et al., 2010; Cormie et al., 2015; Galvao et al., 2018), wait-list control (Newton et al., 2019; Taaffe et al., 2019), or physical activity material (Galvao et al., 2014) and attention control group (Winters-Stone et al., 2015). One study compared multiple exercise interventions (Newton et al., 2019). The duration of the exercise interventions ranged from 12 to 48 weeks (Table S1, Supplementary material). The median attendance was 97.2% (interquartile range: 81.9–100.0%).

3.2. Effects and moderators of exercise on fat mass outcomes

Exercise resulted in a significant overall decrease in body fat percentage (−0.8%, 95% CI: −1.1 to −0.5, P < 0.001), fat mass (−0.8 kg, 95% CI: −1.1 to −0.4, P < 0.001) and trunk fat mass (−0.4 kg, 95% CI: −0.7 to −0.2, P = 0.001) compared with control groups, while no significant effects were observed for waist (−0.1 cm, 95% CI: −1.0 to 0.8, P = 0.885) or hip circumference (−0.3 cm, 95% CI: −1.1 to 0.5, P = 0.493). Marital status significantly moderated the exercise intervention effect on fat mass (P = 0.041) with unmarried patients deriving greater effects from exercise on fat mass (β = −1.4 kg, 95% CI: −2.5 to −0.3, P = 0.006) compared to patients who were married (β = −0.6 kg, 95% CI: −1.0 to −0.2, P = 0.003; Fig. 1 and Table 2). Furthermore, baseline levels of fat mass approached statistical significance to moderate the exercise intervention effects on fat mass (P = 0.091). Exercise intervention effects were statistically significant for patients presenting with

Table 1
Participant characteristics.

Characteristics	Resistance-based exercise groups (n = 319)	Control groups (n = 241)
Demographic		
Age, mean ± SD, yrs[a]	69.6 ± 7.7	69.4 ± 7.8
Age categories, n (%)		
≤ 66 yrs	88 (27.6%)	72 (29.9%)
> 66–73 yrs	134 (42.0%)	86 (35.7%)
> 73 yrs	95 (29.8%)	(79 (32.8%)
Married, n (%)[a]	249 (78.1%)	191 (79.3%)
Tertiary education, n (%)[a]	88 (27.6%)	52 (21.6%)
Current employed, n (%)[a]	75 (23.5%)	81 (33.6%)
Current smoker, n (%)[a]	13 (4.1%)	8 (3.3%)
Clinical		
BMI, mean ± SD, kg.m^{-2} [a]	28.2 ± 4.0	29.1 ± 4.0
BMI categories, n (%)		
Normal weight (BMI <25 kg.m^{-2})	58 (18.2%)	35 (14.5%)
Overweight (BMI ≥25 to <30 kg.m^{-2})	168 (52.7%)	118 (49.0%)
Obese (BMI ≥30 kg.m^{-2})	92 (28.8%)	87 (36.1%)
Time since diagnosis, median (IQR), mo[a]	7.0 (4.0–58)	7.0 (4.0–39.0)
Number of medications, median (IQR)[a]	3.0 (1.0–5.0)	3.0 (2.0–5.0)
Number of comorbidities, median (IQR)[a, b]	0.0 (0.0–1.0)	1.0 (0.0–1.0)
PSA, median (IQR), ng.ml^{-1} [a]	0.6 (0.1–3.1)	0.8 (0.1–4.2)
Testosterone level, median (IQR), nmol.l^{-1} [a]	1.7 (0.8–9.3)	3.3 (0.8–12.7)
Gleason score, mean ± SD[a]	7.6 ± 1.1	7.6 ± 1.1
Gleason categories, n (%)[a]		
Slow growing (Gleason ≤6)	15 (4.7%)	15 (6.2%)
Fast growing, moderately aggressive (Gleason= 7)	78 (24.5%)	49 (20.3%)
Fast growing, aggressive (Gleason ≥8)	91 (28.5%)	70 (29.0%)
ADT, n (%)		
Before intervention	121 (37.9%)	113 (46.9%)
During intervention	198 (62.1%)	128 (53.1%)
ADT duration, median (IQR), mo[a]	3.0 (2.0–6.0)	3.0 (2.0–6.0)
Treatment regimen[a]		
ADT only	123 (38.6%)	83 (34.4%)
ADT + prostatectomy	40 (12.5%)	33 (13.7%)
ADT + radiotherapy	102 (32.0%)	89 (36.9%)
ADT + prostatectomy + radiotherapy	36 (11.3%)	21 (8.7%)
Chemotherapy, n (%)[a]	8 (2.5%)	6 (2.5%)
Metastasis, n (%)	25 (7.8%)	16 (6.6%)
Cardiometabolic outcomes		
Baseline levels, mean ± SD		
Body fat%[a]	28.6 ± 5.3	29.7 ± 5.2
Fat mass, kg[a]	24.6 ± 7.7	26.0 ± 7.6
Trunk fat mass, kg[a]	13.3 ± 4.7	14.0 ± 4.4
Waist circumference, cm[a]	99.3 ± 10.9	101.2 ± 10.7
Hip circumference, cm[a]	101.2 ± 8.2	103.1 ± 7.3
Systolic blood pressure, mmHg[a]	139.7 ± 16.2	138.6 ± 15.4
Diastolic blood pressure, mmHg[a]	78.3 ± 8.4	79.3 ± 9.2
Mean arterial pressure, mmHg[a]	98.8 ± 9.7	99.1 ± 10.3
Resting heart rate, beats.min^{-1} [a]	67.6 ± 11.9	72.8 ± 44.8
Total cholesterol, mmol.l^{-1} [a]	4.6 ± 1.1	4.6 ± 1.0
Triglycerides, mmol.l^{-1} [a]	1.3 ± 0.6	1.4 ± 0.7
HDL, mmol.l^{-1} [a]	1.3 ± 0.4	1.3 ± 0.4
LDL, mmol.l^{-1} [a]	2.9 ± 1.0	2.8 ± 0.9
Glucose, mmol.l^{-1} [a]	5.8 ± 1.3	5.7 ± 1.0
Glycated haemoglobin, %[a]	6.0 ± 0.7	5.9 ± 0.6
Insulin, mU.l^{-1} [a]	9.5 ± 5.3	11.8 ± 16.0
C-reactive protein, mg.l^{-1} [a]	2.5 ± 4.1	2.4 ± 4.6

ADT, Androgen deprivation therapy; BMI, body mass index; IQR, interquartile range; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PSA, prostate-specific antigen; SD, standard deviation; a, Missing values: age, n = 6; married, n = 15; tertiary education, n = 23; current employed, n = 12; current smoker, n = 92; BMI, n = 2; Time since diagnosis, n = 96; number of medications, n = 75; number of comorbidities, n = 147; prostate-specific antigen, n = 101; testosterone, n = 101; Gleason score, n = 242; AST duration, n = 9; treatment regimen, n = 33; chemotherapy, n = 64; body fat, n = 139; fat mass, n = 139; trunk fat mass, n = 177; waist circumference, n = 145; hip circumference, n = 228; systolic blood pressure, n = 310; diastolic blood pressure, n = 310; mean arterial pressure, n = 310; resting heart rate, n = 291; total

cholesterol, n = 181; triglycerides, n = 182; HDL, n = 317; LDL, n = 319; glucose, n = 188; glycated haemoglobin, n = 279; insulin, n = 218; C-reactive protein, n = 269; b, cardiovascular disease, diabetes, dyslipidaemia, hypertension, and osteoporosis; c, including radiotherapy undertaken before and during studies intervention

> 27.1 kg of fat mass (β = −1.0 kg, 95% CI: −1.8 to −0.1, P = 0.022) and between 21.1 and 27.1 kg (β = −0.7, 95% CI: −1.3 to −0.2, P = 0.006), while those presenting with values < 21.1 kg did not experience significant reductions in fat mass following exercise (β = −0.4 kg, 95% CI: −1.0 to 0.2, P = 0.154; Fig. 1 and Table 2). Finally, although a moderating effect from education levels in the exercise effects on hip circumference approached statistical significance (P = 0.056), the intervention effects in each of the subgroups based on education levels were not statistically significant (no tertiary education: β = −0.4 cm, 95% CI: −1.3 to 0.5, P = 0.418; tertiary education: β = 1.2 cm, 95% CI: −0.6 to 3.0, P = 0.190). Other demographical and clinical characteristics did not significantly moderate the exercise intervention effects on body fat, fat mass or trunk fat mass outcomes (Table 2).

3.3. Effects and moderators of exercise on cardiovascular outcomes

Exercise did not promote significant overall effects on systolic or diastolic blood pressure, mean arterial pressure or resting heart rate (P = 0.210 – 0.940; Table 3). Age moderated the exercise effect on diastolic blood pressure (P = 0.069). The exercise intervention effects were statistically significant in younger patients (<66 yrs: β = −4.7 mmHg, 95% CI: −8.0 to −1.4, P = 0.007) but not in those aged 66–73 yrs (β = 2.7 mmHg, 95% CI: −1.6 to 7.1, P = 0.211) or > 73 yrs (β = 0.1 mmHg, 95% CI: −3.3 to 3.5, P = 0.940; Fig. 2, Table 3). Other demographic and clinical characteristics did not significantly moderate the exercise intervention effects on cardiovascular outcomes (Table 3).

3.4. Effects and moderators of exercise on lipid profile

Exercise effects on total cholesterol, triglycerides, HDL and LDL in men with prostate cancer were not statistically significant (P = 0.179 – 0.737; Table 4). Time since diagnosis significantly moderated the exercise intervention effect on total cholesterol (P = 0.021), although the exercise intervention effects within subgroups based on ≤ 4 months since diagnosis (β = −0.2 mmol.l^{-1}, 95% CI: −0.4 to 0.1, P = 0.199), > 4–18 months (β = 0.0 mmol.l^{-1}, 95% CI: −0.2 to 0.2, P = 0.971) and > 18 months (β = 0.2 mmol.l^{-1}, 95% CI: −0.1 to 0.6, P = 0.200) were not statistically significant following exercise. Furthermore, baseline levels of triglycerides significantly moderated the exercise effects on triglycerides (P = 0.018), indicating that patients with higher baseline values showed larger reductions. However, groups based on baseline triglyceride levels (clinically defined borderline high values, >1.7 mmol.l^{-1}: β = −0.3 mmol.l^{-1}, 95% CI: −0.6 to 0.1, P = 0.148; normal values: β = 0.0 mmol.l^{-1}, 95% CI: −0.1 to 0.1, P = 0.891) were not statistically significant. The moderator effect of education levels approached statistical significance (P = 0.092), but exercise intervention effects within each subgroup of education levels (no tertiary education: β = 0.0 mmol.l-1, 95% CI: −0.1 to 0.1, P = 0.779; tertiary education: β = −0.1 mmol.l-1, 95% CI: −0.4 to 0.1, P = 0.209) were not statistically significant.

Time since diagnosis potentially moderated the exercise intervention effects on HDL (P = 0.064), with larger increases in patients who were longer since diagnosis. However, exercise intervention effects within subgroups based on time since diagnosis such as ≤ 4 months (n = 53, β = −0.0 mmol.l^{-1}, 95% CI: −0.1 to 0.0, P = 0.351) and > 4–18 months (n = 75, β = 0.1 mmol.l^{-1}, 95% CI: −0.0 to 0.2, P = 0.116) were not statistically significant. Groups based on > 18 months since diagnosis were not examined given the insufficient number of cases for HDL. Furthermore, a significant moderation effect from treatment regimen (P = 0.023) was observed. Patients treated with ADT + prostatectomy + radiotherapy had greater increases in HDL following exercise (β = 0.3 mmol.l^{-1}, 95% CI: 0.1–0.5, P = 0.007), while those undertaking ADT + prostatectomy (β = −0.2 mmol.l^{-1}, 95% CI: −0.4 to 0.0, P = 0.086) experienced a modest reduction in HDL levels. In those patients undertaking ADT only (β = 0.0 mmol.l^{-1}, 95% CI: −0.1 to 0.1, P = 0.489) and ADT + radiotherapy (β = 0.0 mmol.l^{-1}, 95% CI: −0.1 to 0.1, P = 0.919), exercise effects were not statistically significant (Fig. 3 panel A). Regarding LDL, age significantly moderated the exercise intervention effects (P = 0.008), with reductions in older patients (β = −0.2 mmol.l^{-1}, 95% CI: −0.4 to 0.0, P = 0.091), while a significant increase was observed in patients < 66 yrs (β = 0.3 mmol.l^{-1}, 95% CI: 0.0–0.6, P = 0.041), and no significant intervention effects in patients aged between 66 and 73 yrs (β = −0.0 mmol.l^{-1}, 95% CI: −0.2 to 0.2, P = 0.923) (Fig. 3 panel B).

3.5. Effects and moderators of exercise on glucose metabolism and inflammation

No significant differences in glucose, glycated haemoglobin, insulin or C-reactive protein were found between exercise and control groups (P = 0.337 – 0.724; Table 5). Education level was a significant moderator of the exercise effects on insulin (P = 0.018). However, groups

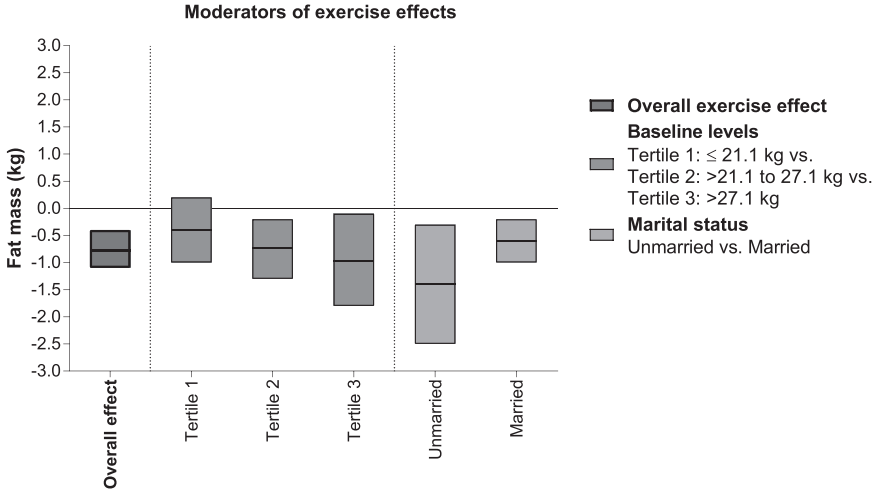

Fig. 1. Exercise intervention effects on fat mass stratified for subgroups based on baseline values of fat mass and marital status. Data are presented as mean difference and 95% confidence intervals.

Table 2
Effects and moderators of exercise effects on body fat, fat mass, trunk fat mass, and waist and hip circumference in men with prostate cancer.

	Body fat%		Fat mass, kg		Trunk fat mass, kg		Waist circumference, cm		Hip circumference, cm	
	χ^2 (df), P-value	β (95% CI)	χ^2 (df), P-value	β (95% CI)	χ^2 (df), P-value	β (95% CI)	χ^2 (df), P-value	β (95% CI)	χ^2 (df), P-value	β (95% CI)
Overall exercise effect	Reference	-0.8[a] (−1.1 to −0.5)	Reference	-0.8[a] (−1.1 to −0.4)	Reference	-0.4[a] (−0.7 to −0.2)	Reference	-0.1 (−1.0 to 0.8)	Reference	-0.3 (−1.1 to 0.5)
Demographic moderators										
Baseline levels	0.27 (1), 0.606		2.85 (1), 0.091[d]		0.03 (1), 0.871		0.01 (1), 0.922		1.63 (1), 0.201	
≤ 21.1 kg		-		-0.4 (−1.0 to 0.2)		-		-		-
> 21.1–27.1 kg		-		-0.7[e] (−1.3 to −0.2)		-		-		-
> 27.1 kg		-		-1.0[e] (−1.8 to −0.1)		-		-		-
Age continuous	0.30 (1), 0.586		0.71 (1), 0.400		0.47 (1), 0.492		0.24 (1), 0.627		1.15 (1), 0.283	
Marital Status	2.51 (1), 0.113		4.19 (1), 0.041[c]		0.55 (1), 0.460		0.65 (1), 0.421		0.09 (1), 0.768	
Not married		-		-1.4[e] (−2.5 to −0.3)		-		-		-
Married		-		-0.6[c] (−1.0 to −0.2)		-		-		-
Education level	0.18 (1), 0.673		0.03 (1), 0.867		0.00 (1), 0.974		0.36 (1), 0.547		3.65 (1), 0.056[d]	
No tertiary education		-		-		-		-		-0.4 (−1.3 to 0.5)
Tertiary education		-		-		-		-		1.2 (−0.6 to 3.0)
Clinical moderators										
BMI continuous	0.05 (1), 0.821		1.03 (1), 0.310		0.00 (1), 0.970		1.35 (1), 0.245		1.73 (1), 0.188	
Time since diagnosis	0.20 (1), 0.658		0.01 (1), 0.906		0.04 (1), 0.839		2.29 (1), 0.130		0.00 (1), 0.984	
Gleason score	0.02 (1), 0.897		1.20 (1), 0.273		1.11 (1), 0.291		0.00 (1), 0.983		0.49 (1), 0.483	
ADT duration	0.07 (1), 0.796		0.13 (1), 0.723		1.39 (1), 0.238		0.78 (1), 0.378		1.01 (1), 0.315	
Treatment regimen	1.03 (3), 0.795		2.70 (3), 0.440		0.97 (3), 0.808		5.66 (3), 0.129		1.30 (3), 0.729	

ADT, Androgen deprivation therapy; BMI, body mass index; a, P-value ≤ 0.05 derived from overall effect; b, P-value ranging from.05 to.10 derived from overall effect; c, P-value ≤ 0.05 derived from interaction terms with the likelihood ratio test; d, P-value ranging from.05 to.10 derived from interaction terms with the likelihood ratio test; e, P-value ≤ 0.05 derived from within-subgroup effect; f, P-value ranging from.05 to.10 derived from within-subgroup effect.

based on education levels did not present significant differences between exercise and control groups (no tertiary education: 0.4 $mU.l^{-1}$, 95% CI: −1.0 to 1.8, P = 0.556; tertiary education: −2.0 $mU.l^{-1}$, 95% CI: −5.3 to 1.3, P = 0.238). Other demographic and clinical characteristics did not significantly moderate the exercise intervention effects on glucose metabolism and inflammation (P = 0.207 – 0.982).

4. Discussion

In this IPD meta-analysis, we examined the effects and moderators of exercise interventions on cardiometabolic health in men with prostate cancer. There were four main findings: 1) exercise significantly reduced body fat (whole body and trunk fat mass), with greater reductions in fat mass in men who were unmarried; 2) age was a significant moderator of exercise effects on diastolic blood pressure, with greater reductions observed in younger than older men; 3) exercise intervention effects on HDL were significant for men undertaking ADT + prostatectomy + radiotherapy but not for those undergoing other ADT-treatment regimens (i.e., ADT alone, ADT + prostatectomy, and ADT + radiotherapy); and 4) exercise-induced reductions in LDL were greater in older men compared to younger patients. These results highlight that specific subgroups of men with prostate cancer previously or currently treated with ADT may benefit the most from exercise medicine when targeting cardiometabolic outcomes.

Increases in fat mass are quite substantial and can achieve 2 kg during the first year of androgen suppression in men with prostate cancer (Galvao et al., 2008). In the present study, we observed a reduction of 0.8 kg in fat mass and these are in accordance with previous aggregate data meta-analyses in men with prostate cancer (Bigaran et al., 2020; Lopez et al., 2021) indicating that exercise is an effective strategy to counteract this adverse effect of ADT. In addition, the lack of moderating effect on body fat percentage and trunk fat mass indicates that these benefits may be experienced by patients with prostate cancer of different demographic and clinical characteristics. Nevertheless, our findings also provide evidence that unmarried prostate cancer patients experience greater reductions in fat mass following exercise than those who were married, although married patients also had a significant reduction in fat mass following exercise. This result is in accordance

Table 3
Effects and moderators of exercise effects on systolic and diastolic blood pressure, mean arterial pressure, and resting heart rate in men with prostate cancer.

	Systolic blood pressure, mmHg		Diastolic blood pressure, mmHg		Mean arterial pressure, mmHg		Resting heart rate, beats.min^{-1}	
	χ^2 (df), P-value	β (95% CI)	χ^2 (df), P-value	β (95% CI)	χ^2 (df), P-value	β (95% CI)	χ^2 (df), P-value	β (95% CI)
Overall exercise effect	Reference	2.1 (−1.2 to 5.5)	Reference	0.1 (−2.2 to 2.4)	Reference	0.8 (−1.6 to 3.1)	Reference	3.4 (−4.0 to 10.9)
Demographic moderators								
Baseline levels	0.01 (1), 0.907		1.62 (1), 0.203		2.09 (1), 0.148		0.02 (1), 0.891	
Age continuous	0.34 (1), 0.562		3.30 (1), 0.069[d]		2.18 (1), 0.140		0.34 (1), 0.562	
≤ 66 yrs		-		-4.7[e] (−8.0 to −1.4)		-		-
> 66–73 yrs		-		2.7 (−1.6 to 7.1)		-		-
> 73 yrs		-		0.1 (−3.3 to 3.5)		-		-
Marital Status	0.13 (1), 0.715		0.00 (1), 0.984		0.02 (1), 0.882		0.15 (1), 0.704	
Education level	0.00 (1), 0.991		0.11 (1), 0.745		0.03 (1), 0.854		0.40 (1), 0.525	
Clinical moderators								
BMI continuous	0.48 (1), 0.489		0.80 (1), 0.372		0.02 (1), 0.878		0.07 (1), 0.789	
Time since diagnosis	2.64 (1), 0.104		0.30 (1), 0.589		1.15 (1), 0.283		0.81 (1), 0.368	
Gleason score	0.39 (1), 0.531		0.22 (1), 0.640		0.03 (1), 0.875		0.00 (1), 0.974	
ADT duration	0.00 (1), 0.993		0.88 (1), 0.349		0.38 (1), 0.538		0.53 (1), 0.467	
Treatment regimen	3.53 (3), 0.318		1.17 (3), 0.760		1.61 (3), 0.658		1.09 (3), 0.780	

ADT, Androgen deprivation therapy; BMI, body mass index; a, P-value ≤ 0.05 derived from overall effect; b, P-value ranging from.05 to.10 derived from overall effect; c, P-value ≤ 0.05 derived from interaction terms with the likelihood ratio test; d, P-value ranging from.05 to.10 derived from interaction terms with the likelihood ratio test; e, P-value ≤ 0.05 derived from within-subgroup effect; f, P-value ranging from.05 to.10 derived from within-subgroup effect.

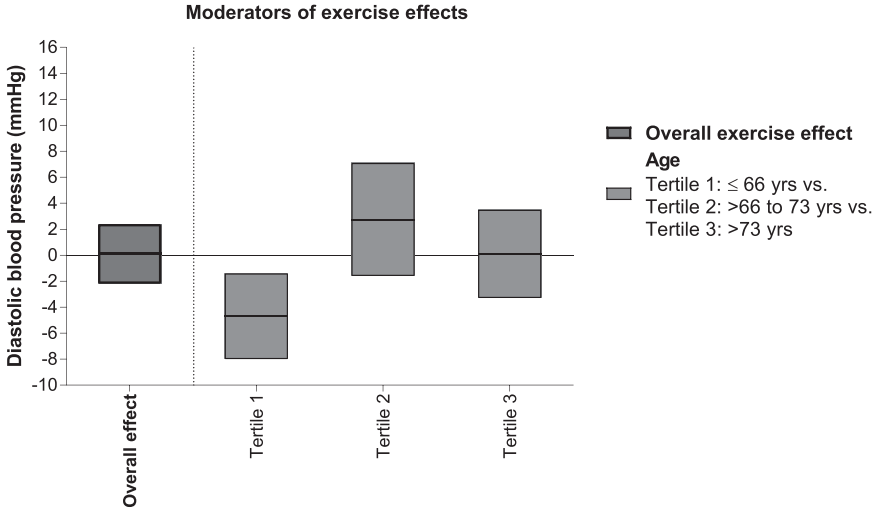

Fig. 2. Exercise intervention effects on diastolic blood pressure stratified for subgroups based on age. Data are presented as mean difference and 95% confidence intervals.

with previous studies examining the moderating effect of marital status on quality of life indicating that unmarried cancer patients benefit more from exercise (Courneya et al., 2008, 2009) or examining only patients with prostate cancer who were married (Winters-Stone et al., 2016). As a result, we suggest that due to the lack of social support at home, unmarried cancer patients may be more engaged throughout supervised exercise programs and therefore derive greater effects on fat mass. Although both unmarried and married participants achieved similar attendance throughout the program (median of 92.4% and 97.2%, respectively), differences may still occur in terms of exercise compliance (i.e., dosage of exercise completed by patients) or even nutritional aspects.

The positive trend observed for those with greater baseline values to experience greater reductions in fat mass with exercise is of interest and worthy of comment. We have recently demonstrated that obese men with prostate cancer can experience a substantial reduction in fat mass following 12 weeks of a resistance-based exercise program allied with nutrition intervention (Wilson et al., 2021). Nevertheless, although we observed an important reduction in fat mass following exercise only programs, the combination of exercise with nutrition interventions including caloric restriction and protein supplementation (Wilson et al., 2021) could result in greater effects for those patients who are obese. This information is of importance given that changes of − 0.8 kg are modest and may not be meaningful to this subgroup of patients during ADT. Moreover, although previous exploratory studies indicate a moderating effect from ADT duration on fat mass (Taaffe et al., 2018; Galvão et al., 2011), we did not observe an effect in our sample of men with prostate cancer at different disease stages. The reasons for this may be related to the different characteristics of our sample compared to previous studies including only patients currently or previously treated with ADT and radiotherapy (Galvao et al., 2010; Taaffe et al., 2018; Galvão et al., 2011). Therefore, our findings are that patients likely experience similar benefits for fat mass regardless of their accompanying treatments and current or prior ADT exposure.

Table 4
Effects and moderators of exercise effects on total cholesterol, triglycerides, and high- and low-density lipoproteins in men with prostate cancer.

	Total cholesterol, mmol.l^{-1}		Triglycerides, mmol.l^{-1}		HDL, mmol.l^{-1}		LDL, mmol.l^{-1}	
	χ^2 (df), P-value	β (95% CI)	χ^2 (df), P-value	β (95% CI)	χ^2 (df), P-value	β (95% CI)	χ^2 (df), P-value	β (95% CI)
Overall exercise effect	Reference	0.0 (−0.1 to 0.2)	Reference	-0.0 (−0.2 to 0.1)	Reference	0.0 (−0.0 to 0.1)	Reference	0.0 (−0.1 to 0.2)
Demographic moderators								
Baseline levels	1.89 (1), 0.169		5.60 (1), 0.018[c]		0.35 (1), 0.552		0.00 (1), 0.952	
≤ 1.7 mmol.l^{-1}		-		0.0 (−0.1 to 0.1)		-		-
> 1.7 mmol.l^{-1}		-		-0.3 (−0.6 to 0.1)		-		-
Age continuous	0.34 (1), 0.558		2.29 (1), 0.131		1.36 (1), 0.243		6.99 (1), 0.008[c]	
≤ 66 yrs		-		-		-		0.3[e] (0.0–0.6)
> 66–73 yrs		-		-		-		-0.0 (−0.2 to 0.2)
> 73 yrs		-		-		-		-0.2 [f] (−0.4 to 0.0)
Marital Status	0.05 (1), 0.817		0.56 (1), 0.453		0.03 (1), 0.860		0.07 (1), 0.797	
Education level	0.14 (1), 0.713		2.84 (1), 0.092[d]		1.10 (1), 0.295		0.30 (1), 0.584	
No tertiary education		-		0.0 (−0.1 to 0.1)		-		-
Tertiary education		-		-0.1 (−0.4 to 0.1)		-		-
Clinical moderators								
BMI continuous	0.54 (1), 0.461		1.88 (1), 0.170		1.07 (1), 0.301		0.10 (1), 0.751	
Time since diagnosis	5.29 (1), 0.021[c]		0.03 (1), 0.872		3.44 (1), 0.064[d]		0.06 (1), 0.802	
≤ 4 months		-0.2 (−0.4 to 0.1)		-		-0.0 (−0.1 to 0.0)		
> 4–18 months		0.0 (−0.2 to 0.2)		-		0.1 (−0.0 to 0.2)		
> 18 months		0.2 (−0.1 to 0.6)		-		-		
Gleason score	2.36 (1), 0.124		0.39 (1), 0.533		0.47 (1), 0.493		2.27 (1), 0.132	
ADT duration	0.36 (1), 0.549		0.01 (1), 0.935		0.10 (1), 0.752		0.17 (1), 0.678	
Treatment regimen	3.59 (3), 0.310		1.67 (3), 0.643		9.50 (3), 0.023[c]		1.43 (3), 0.699	
ADT only		-		-		0.0 (−0.1 to 0.1)		-
ADT + prostatectomy		-		-		-0.2 [f] (−0.4 to 0.0)		-
ADT + radiotherapy		-		-		0.0 (−0.1 to 0.1)		-
ADT + prostatectomy + radiotherapy		-		-		0.3[e] (0.1–0.5)		-

ADT, Androgen deprivation therapy; BMI, body mass index; a, P-value ≤ 0.05 derived from overall effect; b, P-value ranging from.05 to.10 derived from overall effect; c, P-value ≤ 0.05 derived from interaction terms with the likelihood ratio test; d, P-value ranging from.05 to.10 derived from interaction terms with the likelihood ratio test; e, P-value ≤ 0.05 derived from within-subgroup effect; f, P-value ranging from.05 to.10 derived from within-subgroup effect.

Contrary to previous aggregate data meta-analyses indicating positive exercise effects on blood pressure in men with prostate cancer (Bigaran et al., 2020), or even in the general population (Oliver-Martínez et al., 2020; Cornelissen and Smart, 2013), we did not observe a significant exercise effect on blood pressure in the present analysis. The reasons for exercise alone not being sufficient to reduce systolic or diastolic blood pressure in men with prostate cancer undergoing ADT are unclear but may be associated with the lack of substantial decrease in body weight. This factor was previously associated with improved cardiovascular health in this population following a weight-loss intervention (Wilson et al., 2020). Moreover, despite the lack of overall effect from exercise on diastolic blood pressure, our findings are that younger patients had a reduction in diastolic blood pressure following exercise. This result may be related to the higher diastolic blood pressure values observed at baseline in the younger subgroup of patients (81.3 mmHg vs. 77 mmHg), although a clear moderating effect from baseline values was not observed in the analyses. In addition, most older patients with prostate cancer present with cardiometabolic comorbidities (Galvão et al., 2009), such as hypertension or peripheral artery disease, and usually undertake statins, and vasodilators, among others, and these are likely to mask exercise effects on blood pressure. Therefore, for those patients who are younger and presenting with high diastolic blood pressure, exercise may be a strategy to reduce the cardiovascular stress during prostate cancer treatment, although the administration of ADT seems to cause only a modest increase in blood pressure (Smith et al., 2008).

Men with prostate cancer undergoing ADT are at increased risk of diabetes and cardiovascular disease given that fat mass and fasting insulin levels increase as well as adverse treatment-related changes in blood lipids and arterial stiffness (Smith et al., 2006, 2002; Dockery

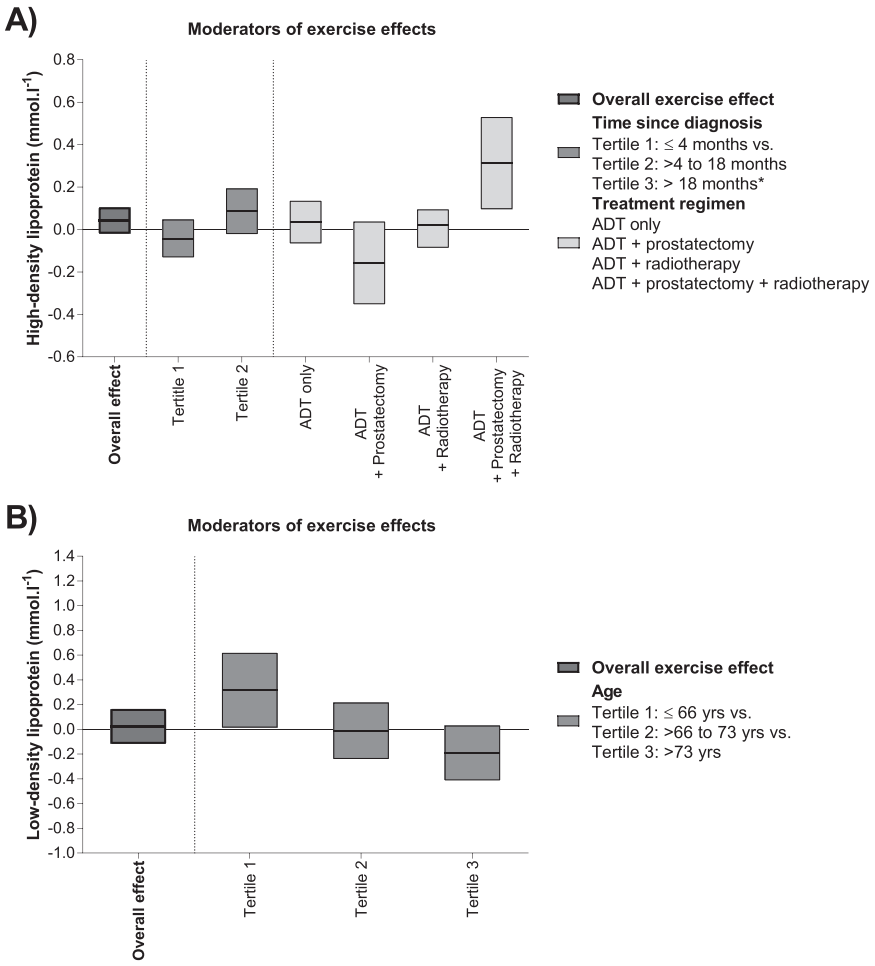

Fig. 3. Exercise intervention effects on HDL stratified for subgroups based on time since diagnosis and treatment regimen (panel A), and LDL stratified for subgroups based on age (panel B). Data are presented as mean difference and 95% confidence intervals. * , Data not shown given the small number of participants with data available.

Table 5
Effects and moderators of exercise effects on glucose, glycated haemoglobin, insulin, and C-reactive protein in men with prostate cancer.

	Glucose, mmol.l^{-1}		Glycated haemoglobin, %		Insulin, mU.l^{-1}		C-reactive protein, mg.l^{-1}	
	χ^2 (df), P-value	β (95% CI)	χ^2 (df), P-value	β (95% CI)	χ^2 (df), P-value	β (95% CI)	χ^2 (df), P-value	β (95% CI)
Overall exercise effect	Reference	0.1 (−0.5 to 0.8)	Reference	-0.0 (−0.1 to 0.0)	Reference	-0.3 (−1.5 to 1.0)	Reference	-0.7 (−2.2 to 0.8)
Demographic moderators								
Baseline levels	0.90 (1), 0.343		0.34 (1), 0.559		0.04 (1), 0.839		0.88 (1), 0.348	
Age continuous	0.32 (1), 0.573		0.00 (1), 0.952		0.01 (1), 0.923		0.16 (1), 0.689	
Marital Status	0.34 (1), 0.561		0.00 (1), 0.982		0.05 (1), 0.827		0.09 (1), 0.760	
Education level	0.76 (1), 0.383		0.90 (1), 0.343		5.60 (1), 0.018[c]		0.34 (1), 0.559	
No tertiary education		-		-		0.4 (−1.0 to 1.8)		-
Tertiary education		-		-		-2.0 (−5.3 to 1.3)		-
Clinical moderators								
BMI continuous	0.08 (1), 0.782		0.02 (1), 0.879		0.60 (1), 0.440		0.62 (1), 0.433	
Time since diagnosis	0.40 (1), 0.527		0.01 (1), 0.943		0.01 (1), 0.925		0.14 (1), 0.710	
Gleason score	0.12 (1), 0.732		0.60 (1), 0.440		0.01 (1), 0.928		1.26 (1), 0.262	
ADT duration	0.04 (1), 0.843		0.01 (1), 0.917		0.12 (1), 0.726		0.36 (1), 0.563	
Treatment regimen	0.79 (3), 0.853		3.63 (3), 0.305		0.40 (3), 0.934		4.55 (3), 0.207	

ADT, Androgen deprivation therapy; BMI, body mass index; a, P-value ≤ 0.05 derived from overall effect; b, P-value ranging from.05 to.10 derived from overall effect; c, P-value ≤ 0.05 derived from interaction terms with the likelihood ratio test; d, P-value ranging from.05 to.10 derived from interaction terms with the likelihood ratio test; e, P-value ≤ 0.05 derived from within-subgroup effect; f, P-value ranging from.05 to.10 derived from within-subgroup effect.

et al., 2003). In the present study, exercise was not effective in improving total cholesterol, triglycerides, HDL and LDL, nor glucose metabolism and inflammation. However, benefits in HDL and LDL may be observed in specific circumstances. First, prostate cancer patients treated with ADT + prostatectomy + radiotherapy derived greater benefits in HDL following exercise compared to patients treated with ADT only, or ADT + prostatectomy or + radiotherapy. This result was somewhat unexpected since substantial increases in HDL were previously reported in patients initiating treatment with ADT (Smith et al., 2008) as well as after a weight loss program comprising a low-carbohydrate diet and aerobic exercise (Freedland et al., 2019). Although the reasons for this are unknown, this result seems not to be explained by changes in fat mass or other metabolic markers, or demographic and clinical moderators of exercise effects in the present study. Therefore, additional studies are necessary to investigate if ADT associated with other treatments for prostate cancer alters the blood lipid sensitivity to changes following exercise. Finally, contrary to the moderating effect of age on diastolic blood pressure following exercise, older men with prostate cancer tended to experience greater exercise reductions in LDL compared to younger patients. As far as we are aware, this result is novel and has not been reported in previous systematic reviews or meta-analyses examining the effect of exercise on LDL (Leon and Sanchez, 2001; Kelley et al., 2005; Costa et al., 2019; Kite et al., 2019). Although the reasons for such changes in HDL and LDL are unclear, these results are of clinical importance for patients treated with ADT + prostatectomy + radiotherapy and older patients as even modest HDL increases (0.026 $mmol.l^{-1}$) and LDL reductions (−1%) may result in a lowered risk of coronary heart and cardiovascular disease (Leon and Sanchez, 2001; Program, 1993). This information is important to identify patients likely to have favourable responses in lipid profile following exercise programs.

This is the first IPD meta-analysis concerning the effects of exercise on cardiometabolic outcomes in men with prostate cancer. The strengths of the present study include a large number of patients on ADT ($n = 560$), the wide range of cardiometabolic outcomes, as well as the examination of a number of demographic and clinical moderators of exercise effects. However, some limitations are worthy of comment. First, we did not perform further analyses on patients with a Gleason score ≤ 6, or those undertaking chemotherapy and those with metastatic disease due to the small number of participants with these characteristics. Therefore, it remains unclear whether patients with low-grade disease or very advanced disease may similarly benefit from exercise interventions. Second, the POLARIS study was not specifically designed to investigate exercise effects on cardiometabolic outcomes or even to target these outcomes in men with prostate cancer. As a result, the data available in the POLARIS database may not reflect the whole body of evidence on the efficacy of exercise on cardiometabolic outcomes (i.e., data availability bias) (Ahmed et al., 2012). Third, most trials included were conducted in Australia (i.e., six out of seven trials), and therefore, our findings may not apply to other Western Regions (e.g., United States, Canada, European countries). Fourth, information on nutritional components were assessed only in two of the seven trials, and therefore, not included in this report. Finally, the sample size available for moderation analyses was not consistent and may have limited the power to detect further moderators of the exercise effects.

In conclusion, exercise medicine effectively reduces fat mass across subgroups of men previously or currently treated with ADT with different demographic and clinical characteristics. However, for diastolic blood pressure, HDL and LDL, specific sub-groups of patients seem to respond more favourably than others, and these groups based on age and treatment history could be specifically targeted with exercise therapy. These results are of clinical relevance and indicate the need to further identify who will respond to a given exercise stimulus in order to assist clinicians in recommending exercise programs and assist exercise professionals in improving the delivery of targeted and tailored exercise medicine in men with prostate cancer.

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Sponsors were not involved in the study design, analysis or interpretation of data, manuscript writing and decision to submit the manuscript for publication.

Conflict of Interests Statement

None to declare.

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Contributorship

Conception and design: Pedro Lopez, Robert U. Newton, Dennis R. Taaffe, Laurien M. Buffart, and Daniel A. Galvão; Acquisition, analysis, or interpretation of data: Pedro Lopez, Robert U. Newton, Dennis R. Taaffe, Kerri Winters-Stone, Laurien M. Buffart, and Daniel A. Galvão; Drafting of the manuscript: Pedro Lopez, Robert U. Newton, Dennis R. Taaffe, Kerri Winters-Stone, Laurien M. Buffart, and Daniel A. Galvão; Critical revision of the manuscript for important intellectual content: Pedro Lopez, Robert U. Newton, Dennis R. Taaffe, Kerri Winters-Stone, Laurien M. Buffart, and Daniel A. Galvão.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.critrevonc.2023.103995.

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Pedro Lopez, PhD, is a postdoctoral fellow at the Pleural Medicine Unit (Institute for Respiratory Health, Western Australia, Australia). He is an exercise physiologist and data scientist with an established record and training in physical activity and exercise to improve objectively measured and patient-reported outcomes in cancer patients.

Robert U. Newton, PhD, DSc, AEP, CSCS*D, FACSM, ESSAF, FNSCA, is a Professional Research Fellow in the Exercise Medicine Research Institute at Edith Cowan University.

Dennis R. Taaffe, PhD, DSc, MPH, is a Professor in the Exercise Medicine Research Institute at Edith Cowan University with research interests in exercise oncology and exercise gerontology.

Kerri M Winters-Stone, PhD, FACSM. Kerri Winters-Stone is a Fellow of the American College of Sports Medicine and a Professor and Co-Lead of the Cancer Prevention and Control Program in the Knight Cancer Institute of Oregon Health and Science University, Oregon, USA.

Laurien M. Buffart, PhD, is an Assistant Professor in the Department of Physiology at Radboud University Medical Center with research interests in exercise oncology, quality of life and clinical outcomes.

Daniel A. Galvão, PhD, is a Professor and Director of the Exercise Medicine Research Institute at Edith Cowan University.