Edith Cowan University

Research Online

Research outputs 2022 to 2026

6-1-2023

Moderators of resistance-based exercise programs' effect on sarcopenia-related measures in men with prostate cancer previously or currently undergoing androgen deprivation therapy: An individual patient data meta-analysis

Pedro Lopez
Edith Cowan University

Robert U. Newton
Edith Cowan University

Dennis R. Taaffe
Edith Cowan University

Kerri Winters-Stone

Daniel A. Galvão
Edith Cowan University

See next page for additional authors

Follow this and additional works at: https://ro.ecu.edu.au/ecuworks2022-2026

 Part of the Oncology Commons

10.1016/j.jgo.2023.101535
Lopez, P., Newton, R. U., Taaffe, D. R., Winters-Stone, K., Galvão, D. A., & Buffart, L. M. (2023). Moderators of resistance-based exercise programs' effect on sarcopenia-related measures in men with prostate cancer previously or currently undergoing androgen deprivation therapy: An individual patient data meta-analysis. Journal of Geriatric Oncology, 14(5), article 101535. https://doi.org/10.1016/j.jgo.2023.101535
This Journal Article is posted at Research Online.
https://ro.ecu.edu.au/ecuworks2022-2026/2408

Authors

Pedro Lopez, Robert U. Newton, Dennis R. Taaffe, Kerri Winters-Stone, Daniel A. Galvão, and Laurien M. Buffart

This journal article is available at Research Online: https://ro.ecu.edu.au/ecuworks2022-2026/2408

Journal of Geriatric Oncology 14 (2023) 101535

Contents lists available at ScienceDirect

Journal of Geriatric Oncology

journal homepage: www.elsevier.com/locate/jgo

Research Paper

Moderators of resistance-based exercise programs' effect on sarcopenia-related measures 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], Dennis R. Taaffe [a,b], Kerri Winters-Stone [d], Daniel A. Galvão [a,b,1], Laurien M. Buffart [a,e,*,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] Knight Cancer Institute, Oregon Health and Science University, Portland, OR, USA
[e] Department of Physiology, Radboud University Medical Center, Radboud Institute for Health Sciences, Nijmegen, Netherlands

ARTICLE INFO

Keywords:
Prostate cancer
Strength training
Sarcopenia
Muscle mass
Physical function

ABSTRACT

Introduction: Older men with prostate cancer are commonly affected by reductions in lean mass and physical function following androgen deprivation therapy (ADT). Resistance-based exercise programs are critical to counteract the musculoskeletal toxicities derived from prostate cancer treatment and aging. However, there is significant variability in the effects of exercise interventions. Examining demographic and clinical moderators of exercise effects in this patient group can assist in identifying which subgroups of patients benefit most. Therefore, we examined the effects and moderators of resistance-based exercise programs on sarcopenia-related outcomes that included lean mass, skeletal muscle index, physical function, and muscle strength in older men with prostate cancer.
Materials and Methods: Data were retrieved from the Predicting OptimaL cAncer RehabIlitation and Supportive care (POLARIS) consortium. For the present study, we included data from trials that examined the effects of supervised resistance-based exercise interventions on lean mass outcomes, muscle strength, and physical function in patients with prostate cancer previously or currently treated with ADT. Linear mixed models were undertaken to analyse the effects of resistance-based exercise programs considering the clustering of patients within studies. Effects were evaluated by regressing the study group on the post-intervention value of the outcome adjusted for the baseline value, while potential moderators were examined by adding the moderator and its interaction term into the regression model.
Results: A total of 560 patients with prostate cancer (age: 69.5 ± 7.8 yrs.; body mass index: 28.6 ± 4.0 $kg.m^{-2}$) previously or currently treated with ADT were included. Resistance-based exercise programs resulted in significant effects on whole-body and appendicular lean mass and the skeletal muscle index ($P < 0.05$), with improvements observed across different characteristics. Improvements were also observed in 400-m walk and 6-m backwards tandem walk ($P < 0.05$), with patients presenting with lower baseline levels deriving greater exercise effects on 400-m walk (−19.4 s, 95% confidence interval [CI]: −36.6 to −2.3) and 6-m backwards tandem walk tests (−3.0 s, 95% CI: −5.7 to −0.3). For relative muscle strength, significant exercise effects were observed, with greater effects in younger patients (0.35 $kg.kg^{-1}$, 95% CI: 0.22 to 0.48).
Discussion: Resistance-based exercise programs effectively improve well-known markers of sarcopenia in men with prostate cancer, with specific subgroups of patients, such as those younger and presenting with lower baseline levels of physical function, deriving greater effects on muscle strength and physical function, respectively.

* Corresponding author at: 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

https://doi.org/10.1016/j.jgo.2023.101535
Received 14 November 2022; Received in revised form 24 April 2023; Accepted 16 May 2023
Available online 23 May 2023
1879-4068/© 2023 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

1. Introduction

Prostate cancer is the second most prevalent cancer in men worldwide, with ~1.5 million new cases in 2020 [1]. For patients with localised and locally advanced prostate cancer, chemical castration (i.e., androgen deprivation therapy [ADT]) is commonly prescribed with radical prostatectomy and radiation therapy [2,3], resulting in a five-year survival rate approaching 100%. However, declines in the musculoskeletal system, including reductions in lean mass and physical function, are extensively documented following ADT [4–6]. These are associated with an increased risk of falls and fractures, and physical disability throughout treatment [7]. In addition, these treatment-related adverse events in combination with aging and a sedentary lifestyle increase the risk of sarcopenia, i.e., progressive and generalised loss of skeletal muscle mass and muscle strength or function [6], reducing functional independence and the quality of life of older men with prostate cancer.

Exercise programs, specifically those comprising resistance training, are critical to counteract the musculoskeletal adverse effects derived from prostate cancer treatment [8–16]. We [8–16] and others [17,18] have previously demonstrated that resistance-based exercise programs (i.e., interventions including resistance training as one of the components) can improve lean mass and physical function, with most patients, even those chemically castrated [4], positively responding to this exercise modality [19]. These outcomes are clinically important due to their association with overall survival in patients with cancer [20,21]. Nevertheless, although most patients respond favourably to exercise [19], it remains unknown precisely when and for which specific subgroups exercise benefits may be most beneficial during or following ADT. For example, it remains to be determined if demographic and clinical characteristics such as age, baseline levels (pre-intervention) of lean mass, physical function and muscle strength, body mass index, time since diagnosis, and time of exposure to ADT affect the response to exercise in men with prostate cancer. In addition, the effect of exercise prescription characteristics such as exercise type and total number of sessions need to be better explored in this population. Identifying whether the exercise effects on lean mass and physical function differ by patient or intervention characteristics (e.g., moderators of intervention effect) may help inform targeted and tailored strategies to prevent sarcopenia-related physical disabilities in older patients with prostate cancer.

To date, previous systematic reviews with aggregate data meta-analysis (i.e., using reported mean effects and dispersion values) have examined the effects of exercise on lean mass and physical function in patients with prostate cancer [15,16]. However, these studies are limited by their inability to examine variations in exercise effects by patient characteristics. Individual patient data (IPD) meta-analysis, merging individual patient data from multiple trial datasets rather than reported mean effects and dispersion values, has been considered the preferred method to investigate variations in effects across subgroups of patients [22]. Therefore, the present IPD meta-analysis aims to evaluate the effects of resistance-based exercise programs on sarcopenia-related outcomes, including whole-body and appendicular lean mass, muscle strength, and physical function tests. These outcomes are commonly used in exercise trials and strongly associated with a variety of clinical endpoints in patients with cancer [20,21]. In addition, we aimed to identify clinical and exercise prescription moderators of resistance-based exercise effects on these outcomes in older patients previously or currently undergoing ADT for prostate cancer.

2. Materials and Methods

2.1. Protocol and Registration

The present IPD meta-analysis is a secondary report of the *Predicting Optimal Cancer Rehabilitation and Supportive care* (POLARIS) study, a consortium that pooled individual patient data from randomised controlled trials (RCTs) examining the effects of exercise and/or psychosocial interventions on quality of life in adult patients with cancer [22]. POLARIS was previously registered at the International Prospective Register of Systematic Reviews (PROSPERO identifier: CRD42013003805) and the current analysis is within the overall scope of the project. The present study was undertaken in accordance with the Preferred Reporting Items for Systematic review and Meta-Analyses of Individual Participant Data (PRISMA-IPD) statement [23].

2.2. Study Procedure

We utilised data from the POLARIS database for the present study, a continuously updated database of individual patient data from exercise randomised controlled trials [22]. Details about the POLARIS study, such as search strategy and data extraction, and methodology, are reported elsewhere [22,24]. Briefly, a total of 34 RCTs evaluating the effects of exercise in patients with cancer (~70% were breast cancer followed by male genitourinary, haematological, gastrointestinal, gynaecological, and respiratory tract) were included in the first wave of data sharing. All principal investigators of eligible RCTs were invited to participate in the POLARIS consortium and to share individual patient data [24]. Prior to sharing, all principal investigators of RCTs signed a data sharing agreement statement agreeing with the POLARIS policies [22], 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 data from RCTs available within the POLARIS database [22,24] that examined the effects of supervised resistance-based exercise interventions (i.e., interventions including resistance training as one of the components) on sarcopenia-related markers, including whole-body and appendicular lean mass, the skeletal muscle index, upper- and lower-limb relative muscle strength, 400-m walk test, chair rise test, 6-m fast walk, and 6-m backwards tandem walk in patients with prostate cancer previously or currently treated with ADT. In addition, we included two additional RCTs in men with prostate cancer [12,14], that were part of the second wave of data sharing. The trials included did not have any age limit as part of the exclusion criteria.

2.3. Resistance-Based Exercise Programs

All included studies had implemented resistance-based exercise programs, with exercise prescribed two to three times per week for ~60 min per session under supervision and consisted of small groups of up to 10 participants. The duration of the programs ranged from 12 to 48 weeks [8–14]. A total of 179 patients (32%) undertook combined resistance and aerobic exercise [8–10,13], followed by 86 patients (15%) undertaking resistance training plus impact-loading [11,13], and 54 patients (10%) undertaking multimodal exercise programs involving resistance training and aerobic exercise with either impact-loading [14] or flexibility training [12]. Detailed descriptions of the exercise programs and their progression have been published elsewhere [8–14]. Briefly, resistance training comprised exercises for the major upper and lower body muscle groups (i.e., chest press, lat pulldown, seated row, leg press, leg extension, and leg curl), with patients instructed to perform 1 to 4 sets of each exercise at an intensity of 6 to 12 repetition maximum (i.e., the heaviest weight that can be lifted 6–12 times). Aerobic exercise was also prescribed two to three times per week and consisted of various modes such as walking or jogging on a treadmill, cycling or rowing on a stationary ergometer, and exercising on an elliptical cross-trainer at an intensity of 60% to 85% of estimated maximum heart rate for 15 to 40 min [25–27]. Impact-loading exercise was prescribed two [11,13] or three times [14] per week and consisted of a series of skipping, bounding, drop jumping, hopping, or leaping activities [13,14] or a series of two-footed jumps from the ground with weighted vests [11]. All

sessions commenced with a warmup comprising low-level aerobic exercise and concluded with a cooldown of stretching exercises. Participants were also encouraged to undertake home-based training consisting of aerobic activities [9,10] or aerobic and impact-loading exercise according to their group assignment [14].

2.4. Outcome Measures

All studies included measured whole-body and appendicular lean mass using dual-energy X-ray absorptiometry (DXA) [8–14]. From these outcomes, appendicular lean mass was normalised to height squared to derive the skeletal muscle index, which is an effective method to eliminate difference in appendicular lean mass associated with height and ethnicity in older adults [28]. For muscle strength measures, studies used the 1-repetition maximum (1-RM) test for the chest press [8–14] and leg press [8–11,13,14] utilising machine-based equipment (Cybex, Cybex International Inc., US; Vectra, Vectra Fitness Inc., US) to derive upper- and lower-limb relative muscle strength, which were then normalised to body weight [29]. The relative muscle strength is an effective method to eliminate differences in muscle strength due to body weight and has been used as a measure of sarcopenia often reported in older adults [30] as well as patients with cancer [29]. The physical function tests included the 400-m walk (i.e., time in seconds to walk a distance of 400 m; a measure of cardiorespiratory fitness and endurance) [8–10,12–14], chair rise (i.e., time in seconds to rise from the chair five times; a measure of lower-limb power and strength) [8–11,13,14], 6-m fast walk (i.e., time in seconds to walk as fast as possible a distance of 6 m; a measure of gait speed) [8,10,12–14] and 6-m backwards tandem walk (i.e., time in seconds to walk backwards a distance of 6 m placing one foot directly behind the heel of the other with the shoes touching; a measure of dynamic balance) [8–10,13,14] and followed standard procedures.

2.5. Moderators of Exercise Response

Potential moderators of exercise response included age (continuous, and groups based on ≤70 and > 70 yrs) as patients older than 70 yrs. seem to present a more accelerated decline in lean mass during ADT [6], baseline values of outcomes (continuous, and groups based on 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})], low skeletal muscle index (defined as skeletal muscle index of ≤7.26 kg.m^{-2}, i.e., pre-sarcopenia) [28,31,32], time since diagnosis (continuous and based on tertiles), ADT duration [groups based on acute (< 6 months) and chronic ADT exposure (≥ 6 months)] [33,34], exercise type (groups based on combined resistance and aerobic exercise, resistance training plus impact-loading and multimodal exercise program) and total number of exercise sessions (defined as the product of intervention duration and exercise frequency; continuous, and groups based on median value). Categorical analyses were undertaken when there were significant interactions of potential moderators in order to perform stratified analysis. Sub-analyses on treatment with chemotherapy (n = 14), and presence of metastatic disease (n = 41) were not undertaken given the small number of participants with data available (i.e., fewer than 50 participants).

2.6. Statistical Analysis

One-step complete-case IPD meta-analyses were conducted to examine the effects and moderators of resistance-based exercise programs response on whole-body and appendicular lean mass, skeletal muscle index, upper- and lower-limb relative muscle strength, 400-m walk, chair rise, 6-m fast walk, and 6-m backwards tandem walk tests. Linear mixed model analyses with a two-level structure were undertaken to consider the clustering of patients within studies by using a random

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 (%)		
≤70 yrs	171 (53.6%)	124 (51.5%)
>70 yrs	146 (45.8%)	113 (46.9%)
Married, n (%) [a]	249 (78.1%)	191 (79.3%)
Tertiary education, n (%) [a]	88 (27.6%)	52 (21.6%)
Currently 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%)
Pre-Sarcopenic, n (%) [a]	50 (15.7%)	29 (12.0%)
Time since diagnosis, median (IQR), mo [a]	7.0 (4.0 to 58)	7.0 (4.0 to 39.0)
Number of medications, median (IQR) [a]	3.0 (1.0 to 5.0)	3.0 (2.0 to 5.0)
Number of comorbidities, median (IQR) [a, b]	0.0 (0.0 to 1.0)	1.0 (0.0 to 1.0)
PSA, median (IQR), ng.ml^{-1} [a]	0.6 (0.1 to 3.1)	0.8 (0.1 to 4.2)
Testosterone level, median (IQR), nmol.l^{-1} [a]	1.7 (0.8 to 9.3)	3.3 (0.8 to 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 to 6.0)	3.0 (2.0 to 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%)

ADT, Androgen deprivation therapy; BMI, body mass index; IQR, interquartile range; 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; Pre-sarcopenic, n = 51; 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; ADT duration, n = 9; treatment regimen, n = 33; chemotherapy, n = 64; [b], cardiovascular disease, diabetes, dyslipidaemia, hypertension, and osteoporosis.

Table 2
Effects and moderators of exercise on whole-body and appendicular lean mass and skeletal muscle index in men with prostate cancer.

	Lean mass, kg		Appendicular lean mass, kg		Skeletal muscle index, kg.m^{-2}	
	χ^2 (df), P-value [a]	β (95% CI) [b]	χ^2 (df), *P*-value [a]	β (95% CI) [b]	χ^2 (df), P-value [a]	β (95% CI) [b]
Overall exercise effect	Reference	0.4 (0.1 to 0.7) [c]	Reference	0.4 (0.2 to 0.6) [c]	Reference	0.12 (0.06 to 0.19) [c]
Moderators of exercise response						
Age continuous	0.3 (1), 0.567	–	0.5 (1), 0.492	–	0.5 (1), 0.502	–
Baseline levels	0.8 (1), 0.388	–	1.4 (1), 0.231	–	–	–
BMI continuous	0.8 (1), 0.369	–	0.2 (1), 0.653	–	0.2 (1), 0.647	–
Low skeletal muscle index	0.9 (1), 0.333	–	0.3 (1), 0.563	–	0.4 (1), 0.552	–
Time since diagnosis	1.0 (1), 0.322	–	2.2 (1), 0.137	–	2.0 (1), 0.160	–
ADT duration	0.8 (1), 0.368	–	1.1 (1), 0.294	–	1.0 (1), 0.307	–
Exercise type	5.7 (3), 0.127	–	2.3 (3), 0.511	–	2.2 (3), 0.536	–
Number of sessions	2.0 (1), 0.151	–	0.4 (1), 0.532	–	0.5 (1), 0.493	–

ADT, Androgen deprivation therapy; BMI, body mass index; [a], results of the likelihood ratio test comparing models with and without interaction term; [b], stratified analyses, regression coefficients and 95% confidence intervals were only provided if the interaction terms were statistically significant (P ≤ 0.05) or approaching statistical significance to examine potential moderators; [c], P-value ≤0.05 derived from overall effect.

intercept on the study level. Effects were evaluated by regressing the study group (intervention vs. control group) on the post-intervention value of the outcome adjusted for the baseline value. Potential 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 [35]. The likelihood ratio test was used to compare models with and without interaction terms, with χ^2 values, degrees of freedom (df) and *P*-values reported. Stratified analyses were undertaken if the interaction terms were statistically 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' [36].

3. Results

Seven RCTs examining resistance-based exercise program effects on the outcome measures in men diagnosed with prostate cancer were included [8–14]. After screening, data from 27 men who did not receive any form of ADT were excluded from the analyses, resulting in 560 men with prostate cancer included for analysis.

3.1. Study and Patient Characteristics

Three-hundred nineteen patients were allocated to intervention groups and 241 patients to the control groups (Table 1). The average age was 69.5 ± 7.8 years, with most patients married (79%), without a tertiary education (71%), and no longer employed (72%). The average BMI was 28.6 ± 4.0 kg.m^{-2}, with most patients overweight or obese (83%). Pre-sarcopenia was found in 14% of the sample. The median time since prostate cancer diagnosis was 7.0 months [interquartile range (IQR): 4 to 48 months]. Furthermore, 39% were treated with ADT only, 36% with ADT + radiotherapy, 14% with ADT + prostatectomy, and 11% with ADT + prostatectomy + radiotherapy. During the study intervention, 58% of patients received ADT, while 42% received ADT before the intervention. The median duration of ADT before study commencement was 2.0 months (IQR: 0 to 6 months). Patient characteristics are presented in Table 1. Characteristics of the studies are shown in Supplementary Table S1, and baseline and post-intervention values of the outcomes are presented in Table S2.

3.2. Effects and Moderators of Exercise on Lean Mass and the Skeletal Muscle Index

Resistance-based exercise programs resulted in a significant overall increase in whole-body lean mass (0.4 kg, 95% CI: 0.1 to 0.7 kg, $P = 0.016$), appendicular lean mass (0.4 kg, 95% CI: 0.2 to 0.6 kg, $P < 0.001$), and the skeletal muscle index (0.12 kg.m^{-2}, 95% CI: 0.06 to 0.19 kg.m^{-2}, $P < 0.001$) compared with control groups (Table 2). Other clinical and exercise prescription characteristics such as age, baseline levels, BMI, low muscle mass, time since diagnosis, ADT duration, exercise type (i.e., combined resistance and aerobic exercise, resistance training plus impact-loading, or multimodal exercise programs), and total number of sessions did not significantly moderate the exercise intervention effects on these outcomes ($P = 0.127$–0.653) (Fig. 1 and Table 2).

3.3. Effects and Moderators of Exercise on Physical Function

There was a significant positive overall intervention effect for the time to perform the 400-m walk (−12.9 s, 95% CI: −19.1 to −6.8 s, $P < 0.001$), chair rise test (−0.9 s, 95% CI: −1.2 to −0.5 s, $P < 0.001$), 6-m fast walk (−0.1 s, 95% CI: −0.2 to −0.0, $P = 0.014$), and backwards tandem walk (−1.2 s, 95% CI: −2.4 to −0.1 s, $P = 0.036$) compared to control groups (Table 3). Baseline levels of 400-m walk significantly moderated the resistance-based exercise program effects on this outcome ($P = 0.014$). The effect of resistance-based exercise program was statistically significant for patients presenting with >276.9 s in the 400-m walk test (β = −19.4 s, 95% CI: −36.6 to −2.3 s, $P = 0.027$) and between 243.1 and 276.9 s (β = −13.9 s, 95% CI: −19.0 to −8.9 s, $P < 0.001$), while those presenting with values ≤243.1 s did not experience significant reductions in time to perform the 400-m walk following resistance-based exercise programs (β = −4.2 s, 95% CI: −9.5 to 1.2, $P = 0.128$) (Fig. 2, panel A). Likewise, exercise intervention effects on the 6-m backwards walk were significantly moderated by baseline levels of this outcome ($P < 0.001$). Patients with values >18.9 s in the 6-m backwards tandem walk had significantly greater decreases in this outcome (β = −3.0 s, 95% CI: −5.7 to −0.3 s, $P = 0.031$) (Fig. 2, panel B). Changes were not statistically significant in patients presenting with values ≤13.5 s (β = 0.2 s, 95% CI: −0.9 to 1.4, $P = 0.670$) and values between 13.5 and 18.9 s (β = −0.7 s (95% CI: −2.1 to 0.6 s, $P = 0.291$). Other clinical and exercise prescription characteristics such as age, BMI, low skeletal muscle index, time since diagnosis, ADT duration, exercise type (i.e., combined resistance and aerobic exercise, resistance training plus impact-loading, or multimodal exercise programs), and total number of sessions did not significantly moderate the intervention effects on the 400-m walk, chair rise, 6-m fast walk, or 6-m backwards tandem walk performance ($P = 0.177$–0.987).

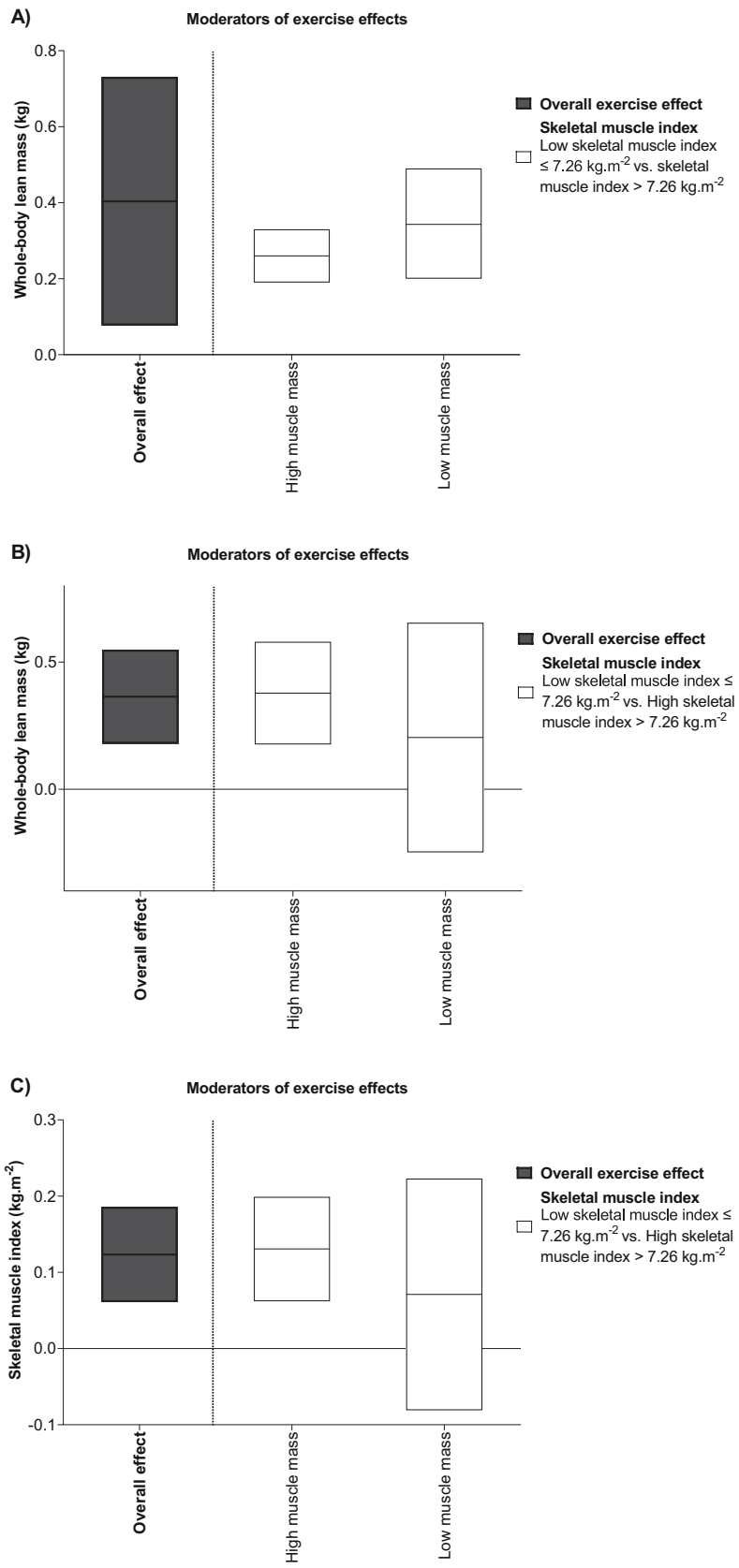

Fig. 1. Exercise intervention effects on whole-body lean mass (panel A), appendicular lean mass (panel B) and skeletal muscle index (panel C) stratified for subgroups based on low skeletal muscle index. Data are presented in mean difference and 95% confidence intervals.

Table 3
Effects and moderators of exercise on 400-m walk, chair rise, 6-m fast walk and 6-m backward tandem walk tests in men with prostate cancer.

	400-m walk test, sec		Chair rise test, sec	6-m fast walk, sec		6-m backward walk, *sec*		
	χ^2 (df), P-value [a]	β (95% CI) [b]	χ^2 (df), P-value [a]	β (95% CI) [b]	χ^2 (df), P-value [a]	β (95% CI) [b]	χ^2 (df), P-value [a]	β (95% CI) [b]
Overall exercise effect	Reference	−12.9 (−19.1 to −6.8) [c]	Reference	−0.9 (−1.2 to −0.5) [c]	Reference	−0.1 (−0.2 to −0.0) [c]	Reference	−1.2 (−2.4 to −0.1) [c]
Moderators of exercise response								
Age continuous	0.9 (1), 0.340	–	0.4 (1), 0.524	–	0.6 (1), 0.435	–	0.3 (1), 0.602	–
Baseline levels	6.0 (1), 0.014[d]		0.5 (1), 0.488	–	0.2 (1), 0.676	–	44.8 (1), <0.001[d]	
*Tertile 1**		−4.2 (−9.5 to 1.2)		–		–		0.2 (−0.9 to 1.4)
*Tertile 2**		−13.9 (−19.0 to −8.9) [e]		–		–		−0.7 (−2.1 to 0.6)
*Tertile 3**		−19.4 (−36.6 to −2.3) [e]		–		–		−3.0 (−5.7 to −0.3) [e]
BMI continuous	0.4 (1), 0.533	–	0.5 (1), 0.471	–	0.1 (1), 0.788	–	0.3 (1), 0.599	–
Low skeletal muscle index	0.5 (1), 0.467	–	0.2 (1), 0.643	–	1.8 (1), 0.181	–	0.0 (1), 0.891	–
Time since diagnosis	0.0 (1), 0.981	–	0.7 (1), 0.389	–	0.1 (1), 0.797	–	0.3 (1), 0.592	–
ADT duration	0.5 (1), 0.499	–	0.0 (1), 0.879	–	0.7 (1), 0.408	–	0.4 (1), 0.509	–
Exercise type	1.0 (3), 0.800	–	4.3 (3), 0.230	–	1.1 (3), 0.774	–	3.2 (3), 0.358	–
Number of sessions	0.0 (1), 0.946	–	0.0 (1), 0.987	–	1.7 (1), 0.193	–	1.8 (1), 0.177	–

ADT, Androgen deprivation therapy; BMI, body mass index; *, Tertile 1, 400-m walk test: ≤243.1 s, 6-m backward walk: ≤13.5 s; Tertile 2, 400-m walk test: 243.1 to ≤276.9 s, 6-m backward walk: 13.5 to ≤18.9 s; Tertile 3, 400-m walk test: >276.9 s, 6-m backward walk: >18.9 s; [a], results of the likelihood ratio test comparing models with and without interaction term; [b], stratified analyses, regression coefficients and 95% confidence intervals were only provided if the interaction terms were statistically significant (P ≤ 0.05) or approaching statistical significance to examine potential moderators; [c], P-value ≤0.05 derived from overall effect; [d], *P*-value ≤0.05 derived from interaction terms with the likelihood ratio test; [e], P-value ≤0.05 derived from within-subgroup effect.

3.4. Effects and Moderators of Exercise on Muscle Strength

Resistance-based exercise programs resulted in a significant increase of 0.05 $kg.kg^{-1}$ (95% CI: 0.03 to 0.06 $kg.kg^{-1}$, $P < 0.001$) in upper-limb and 0.26 $kg.kg^{-1}$ (95% CI: 0.20 to 0.32 $kg.kg^{-1}$, $P < 0.001$) in lower-limb relative muscle strength compared to control groups (Table 4). Exercise type ($P = 0.046$) significantly moderated the intervention effects on upper-limb muscle strength. However, effects were very similar between different exercise types compared to controls (combined resistance and aerobic exercise, β = 0.05; resistance training plus impact-loading, β = 0.05; multimodal exercise program, β = 0.06), and the difference may not be clinically relevant. Other clinical and exercise prescription characteristics such as age, baseline levels of strength, BMI, low skeletal muscle index, time since diagnosis, ADT duration, and total number of sessions did not significantly moderate the intervention effects on upper-limb muscle strength ($P = 0.162–0.840$).

Regarding lower-limb muscle strength, age potentially moderated the resistance-based exercise program effects on this outcome ($P = 0.078$). Although both age groups presented significant improvements in lower-limb muscle strength following intervention, younger patients experienced greater effects (≤70 yrs.: β = 0.35 $kg.kg^{-1}$, 95% CI: 0.22 to 0.48 $kg.kg^{-1}$, $P < 0.001$) compared to older patients (>70 yrs.: β = 0.20 $kg.kg^{-1}$, 95% CI: 0.10 to 0.29 $kg.kg^{-1}$) (Fig. 3). Other clinical and exercise prescription characteristics such as baseline levels of strength, BMI, low skeletal muscle index, time since diagnosis, ADT duration, exercise type and total number of sessions did not significantly moderate the exercise intervention effects on lower-limb muscle strength ($P = 0.173–0.941$).

4. Discussion

The present IPD meta-analysis examined the effects of resistance-based exercise programs on sarcopenia-related outcomes in patients previously or currently treated with ADT for prostate cancer. There were three main findings. First, resistance-based exercise programs significantly improved whole-body and appendicular lean mass and the skeletal muscle index, with benefits observed across different demographic, clinical, and treatment characteristics. Second, resistance-based exercise programs resulted in significant improvements in physical function outcomes, and these were greater in patients presenting with lower baseline values of 400-m walk and 6-m backwards walk. Third, a significant increase in muscle strength was observed following intervention and this was potentially greater in younger than older men.

Sarcopenia has become a marker of substantial interest in oncology [32]. We have recently demonstrated that men with prostate cancer presenting with low levels of muscle mass are at ~50% greater mortality risk than those presenting with high levels [21]. In the present study, our findings are that supervised resistance-based exercise programs can significantly improve lean mass and the skeletal muscle index, with benefits achieved regardless of age, BMI, baseline values, and ADT-related treatment as well as exercise prescription characteristics. These results are in agreement with previous meta-analyses [15,16] and are of clinical importance as ADT is associated with an accelerated shift towards sarcopenia in older men with prostate cancer [4,6,32]. For example, while a decrease of ~1 kg per year in lean mass occurs with healthy aging [37], ADT is associated with substantial declines of ~2.0 kg within the first nine months of treatment [4,6]. The ADT-related reductions in lean mass as well as bone mineral density may also explain the increased risk of accidental falls and fractures in this group [38]. Our findings are that resistance-based exercise programs are effective in counteracting reductions in lean mass, which, in turn, may decrease the risk of physical disability and adverse events such as falls and fractures in older men with prostate cancer. In addition, it is important to note that benefits in maintaining lean mass may be achieved even with shorter interventions (i.e., ≤24 weeks, twice a week, 24 to 36 exercise sessions), which may be important for this population considering the effects of ADT on the musculoskeletal system [4,6,32]. Despite the lack of moderation from ADT duration on lean mass or the skeletal muscle index, we recommend commencing exercise at the onset of ADT treatment for preventing side effects while maintaining lean mass of older men with prostate cancer [10,13,14].

Impairments in muscle strength and physical function are

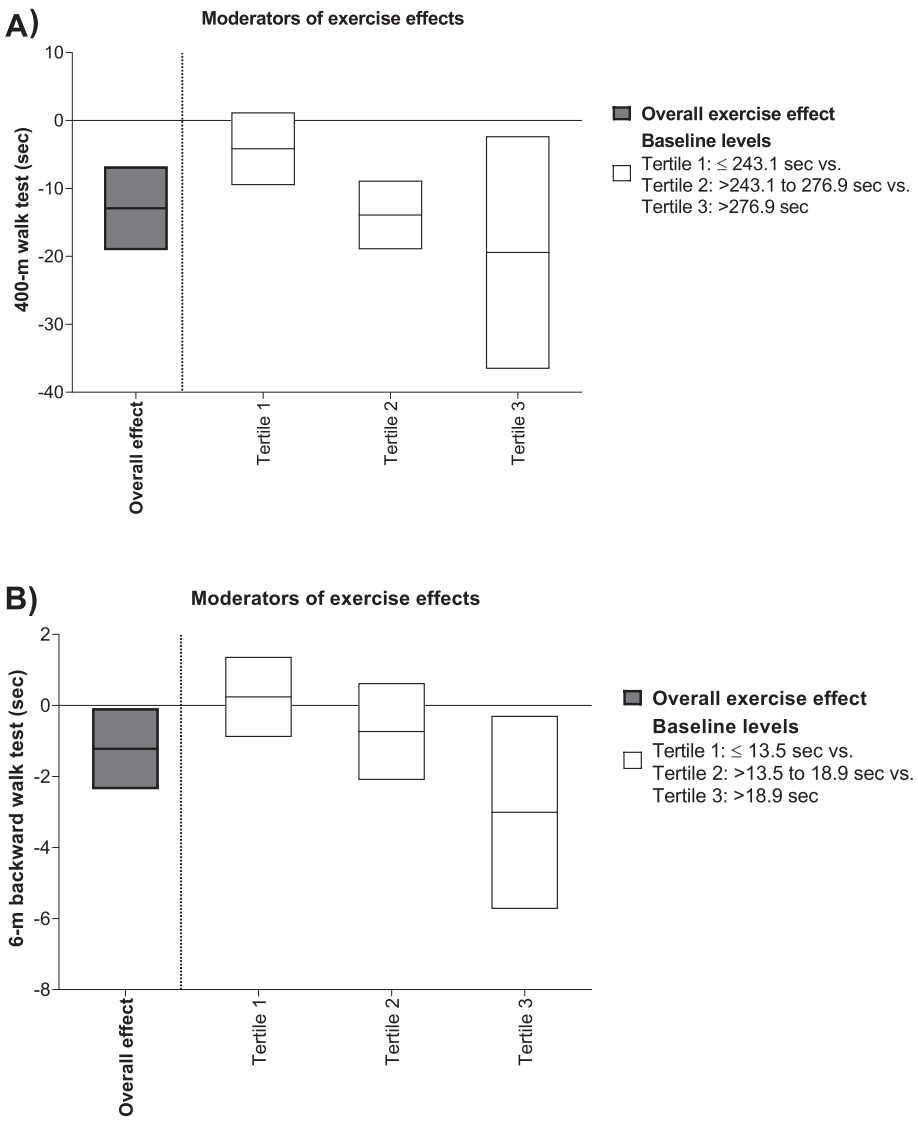

Fig. 2. Exercise intervention effects on 400-m walk (panel A) and 6-m backwards tandem walk (panel B) stratified for subgroups based on baseline values. Data are presented in mean difference and 95% confidence intervals.

extensively documented following ADT, compromising physical function and independent living of older patients with prostate cancer [5]. Although previous studies have demonstrated the benefits of exercise on physical function in men with prostate cancer during or following ADT [8–15,17,18], our findings are that patients presenting with lower baseline levels derived greater exercise benefits as measured by the 400-m walk and 6-m backwards tandem walk. These results followed the principle of *window of adaptation* and are promising for those approaching thresholds for physical disabilities such as older patients with cancer. For example, in older community-dwelling adults, low levels of physical function are associated with physical disabilities and limitations, cardiovascular disease, hospitalisation, and mortality [39], and, likewise, older patients with lower physical functioning may also be at an increased risk for treatment-related complications and poorer survival [20]. Therefore, for most men with prostate cancer [19] and specifically those who may present with little reserve capacity for the performance of daily physical activities, resistance-based exercise may be effective in improving physical function and activities of daily living, reducing the risk of falls, and potentially improving disease prognosis of patients most in need [20]. This result is clinically important as it can enhance recommendations for older men with prostate cancer, one of the subgroups most affected by toxicities and poorer treatment outcomes [40]. For example, while cancer treatment goals for older adults may include living longer even with cancer, having fewer symptoms and side effects from cancer and treatment, and maintaining physical and emotional strength and quality of life [41], exercise is not considered part of standard of care for cancer survivors. Therefore, future exercise recommendations for patients with cancer, specifically for older patients, should include resistance-based exercise programs, as this exercise modality can alleviate side effects, maintain physical strength, and improve prognostic markers in those patients most in need.

Improvements in muscle strength following resistance-based training programs were expected due to the principle of *specificity* and consistently observed across a previous meta-analysis [15]. Nevertheless, the fact that older patients derived smaller effects on muscle strength (i.e., 40% less than younger patients) is novel and has not been previously reported in men with prostate cancer. In fact, this result may be considered relevant for older patients with cancer as higher muscle strength is significantly associated with improved overall survival in older patients with advanced cancer [42]. Although it was expected that older patients would benefit most from exercise due to reduced physical activity levels and a potential larger window for adaptations, our findings show the opposite, in contrast to our findings on physical function.

Table 4
Effects and moderators of exercise on upper-limb and lower-limb strength in men with prostate cancer.

	Upper-limb strength, kg.kg^{-1}		Lower-limb strength, kg.kg^{-1}	
	χ^2 (df), P-value [a]	β (95% CI) [b]	χ^2 (df), P-value [a]	β (95% CI) [b]
Overall exercise effect	Reference	0.05 (0.03 to 0.06) [c]	Reference	0.26 (0.20 to 0.32) [c]
Moderators of exercise response				
Age continuous	0.0 (1), 0.840	–	3.1 (1), 0.078 [e]	
≤70 yrs		–		0.35 (0.22 to 0.48) [f]
>70 yrs		–		0.20 (0.10 to 0.29) [f]
Baseline levels	2.0 (1), 0.162	–	0.0 (1), 0.872	–
BMI continuous	1.0 (1), 0.329	–	0.4 (1), 0.546	
Low skeletal muscle index	0.5 (1), 0.504	–	0.7 (1), 0.411	
Time since diagnosis	0.1 (1), 0.720	–	0.2 (1), 0.633	
ADT duration	0.8 (1), 0.371	–	0.0 (1), 0.941	–
Exercise type	8.0 (3), 0.046[d]		5.0 (3), 0.173	–
Combined resistance and aerobic exercise		0.05 (0.03 to 0.06) [e]		–
Resistance training plus impact-loading		0.05 (0.00 to 0.10) [e]		–
Multimodal exercise program		0.06 (0.03 to 0.08) [e]		–
Number of sessions	0.2 (1), 0.643		0.3 (1), 0.572	–

ADT, Androgen deprivation therapy; BMI, body mass index; [a], results of the likelihood ratio test comparing models with and without interaction term; [b], stratified analyses, regression coefficients and 95% confidence intervals were only provided if the interaction terms were statistically significant (P ≤ 0.05) or approaching statistical significance to examine potential moderators; [c], P-value ≤0.05 derived from overall effect; [d], P-value ≤0.05 derived from interaction terms with the likelihood ratio test; [e], P-value ranging from 0.05 to 0.10 derived from interaction terms with the likelihood ratio test; [f], P-value ≤0.05 derived from within-subgroup effect.

The reasons for that are unlikely to be explained by resistance-based exercise programs attendance between older and younger patients (83% vs. 88%) as previously suggested [43], although it may be related to treatment-related adverse events and fatigue experienced by older patients during treatment [44]. Furthermore, whether age impacts the adaptive response to exercise or the effort exerted during exercise sessions remains to be determined in men with prostate cancer. Altogether, this finding is important to guide clinicians in terms exercise prescription for older patients with cancer. It is essential to individualise exercise programs to achieve greater gains in strength and, as a result, potentially improve survival rates. For example, while younger patients with prostate cancer benefit from resistance-based exercise programs, older patients may need additional supportive care strategies. The utilisation of resistance training plus protein supplementation may be a potential strategy to overcome this barrier in older patients [45], although more studies are necessary to explore the impact of such intervention in older men with prostate cancer.

To the best of our knowledge, this is the first IPD meta-analysis examining the effects of resistance-based exercise programs on sarcopenia-related outcomes in men with prostate cancer. The strengths of the present study are the large number of patients on ADT ($n = 560$) and examination of potential moderators of resistance-based exercise program effects. However, some limitations are worthy of comment. First, analyses on those undergoing chemotherapy or with metastatic disease were not undertaken due to the small number of participants with those characteristics. Second, most patients volunteering to participate in the exercise trials included were relatively healthy, presenting with high levels of physical function. Therefore, only the examination of low skeletal muscle index was undertaken [28,31], and future studies are necessary to validate methods and elucidate sarcopenia as well as aspects of frailty such as weakness, slowness, low levels of physical activity, low energy, and unintentional weight loss in men with prostate cancer. Third, the literature search used in the POLARIS study [22] was not specifically focused on lean mass and physical function outcomes but on quality of life, and authors of eligible studies were not all able or willing to share data of exercise trials in men with prostate cancer. Fourth, the exercise programs investigated featured the combination of resistance training with other exercise components such as aerobic exercise and impact-loading exercise programs, and this affected our ability to explore the effects of resistance training alone in this population. Fifth, we have not tested for interactions between the potential moderators investigated given the necessity of larger sample

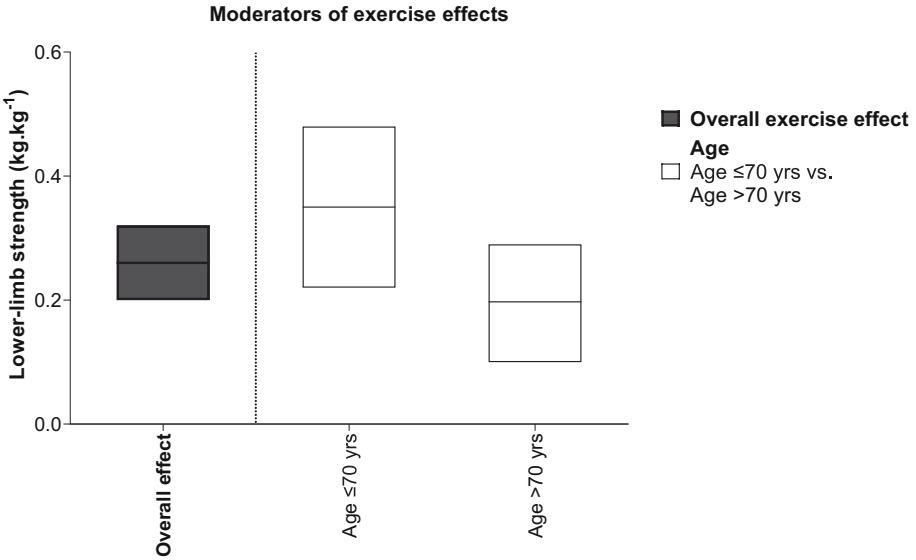

Fig. 3. Exercise intervention effects on lower-limb relative muscle strength stratified for subgroups based on age. Data are presented in mean difference and 95% confidence intervals.

sizes and prior evidence in this population. Future studies are required to further explore the interaction between different moderators of exercise response in men with prostate cancer. Finally, the POLARIS study was not specifically designed to investigate exercise effects on the outcomes of the present study. As a result, the data available in the POLARIS database may not reflect the whole body of evidence on the efficacy of exercise on sarcopenia-related outcomes (i.e., data availability bias).

5. Conclusion

In conclusion, supervised resistance-based exercise can effectively improve well-known markers of sarcopenia in men with prostate cancer. Our results indicate that resistance-based exercise programs can improve lean mass in patients regardless of demographic and clinical characteristics while specific subgroups of patients such as those younger and presenting with lower baseline levels of physical function respond more favourably than others to resistance-based exercise. These results are clinically relevant and indicate that these patients with prostate cancer undergoing treatment may present a reduced risk of physical disabilities and falls and potentially improved overall survival when specifically targeted with resistance-based exercise therapy.

Role of Funding Source

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

Funding

The POLARIS project is supported by the Alpe d'HuZes foundation/ Dutch Cancer Society (VU2011–5045) via the Bas Mulder Award to Laurien M. Buffart. No financial support was received to conduct the present study, or for the preparation or publication of this manuscript.

Author Contributions

Pedro Lopez and Laurien M. Buffart had full access to all of the data in the study and takes responsibility for the for the integrity of the data and the accuracy of the data analysis; Conception and design: Pedro Lopez, Robert U. Newton, Dennis R. Taaffe, Daniel A. Galvão, and Laurien M. Buffart; Acquisition, analysis, or interpretation of data: Pedro Lopez and Laurien M. Buffart; Critical revision of the manuscript for important intellectual content: Pedro Lopez, Robert U. Newton, Dennis R. Taaffe, Kerri Winters-Stone, Daniel A. Galvão, and Laurien M. Buffart; Statistical analysis: Pedro Lopez.

Declaration of Competing Interest

None to declare.

Acknowledgment

Pedro Lopez is supported by the National Health and Medical Research Council (NHMRC) Centre of Research Excellence (CRE) in Prostate Cancer Survivorship Scholarship. Daniel A. Galvão and Robert U. Newton are funded by a NHMRC CRE in Prostate Cancer Survivorship. The results of the study are presented clearly, honestly, without fabrication, falsification, or inappropriate data manipulation.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jgo.2023.101535.

References

[1] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021. https://doi.org/10.3322/caac.21660. Epub 2021/02/05. PubMed PMID: 33538338.

[2] D'Amico AV, Chen MH, Renshaw AA, Loffredo M, Kantoff PW. Androgen suppression and radiation vs radiation alone for prostate cancer: a randomized trial. JAMA. 2008;299(3):289–95. Epub 2008/01/24, https://doi.org/10.1001/jama.299.3.289. 18212313.

[3] Gunner C, Gulamhusein A, Rosario DJ. The modern role of androgen deprivation therapy in the management of localised and locally advanced prostate cancer. J Clin Urol 2016;9(2 Suppl):24–9. Epub 2017/03/28, https://doi.org/10.1177/2051415816654048. PubMed PMID: 28344813; PubMed Central PMCID: PMCPMC5356175.

[4] Galvao DA, Spry NA, Taaffe DR, Newton RU, Stanley J, Shannon T, et al. Changes in muscle, fat and bone mass after 36 weeks of maximal androgen blockade for prostate cancer. BJU Int 2008;102(1):44–7. Epub 2008/03/14, https://doi.org/10.1111/j.1464-410X.2008.07539.x. 18336606.

[5] Galvao DA, Taaffe DR, Spry N, Joseph D, Turner D, Newton RU. Reduced muscle strength and functional performance in men with prostate cancer undergoing androgen suppression: a comprehensive cross-sectional investigation. Prostate Cancer Prostatic Dis 2009;12(2):198–203. Epub 2008/10/15, https://doi.org/10.1038/pcan.2008.51. 18852703.

[6] Smith MR, Saad F, Egerdie B, Sieber PR, Tammela TL, Ke C, et al. Sarcopenia during androgen-deprivation therapy for prostate cancer. J Clin Oncol 2012;30(26):3271–6. Epub 2012/06/01, https://doi.org/10.1200/JCO.2011.38.8850. PubMed PMID: 22649143; PubMed Central PMCID: PMCPMC3434987.

[7] Shahinian VB, Kuo YF, Freeman JL, Goodwin JS. Risk of fracture after androgen deprivation for prostate cancer. N Engl J Med 2005;352(2):154–64. Epub 2005/01/14, https://doi.org/10.1056/NEJMoa041943. 15647578.

[8] Galvao DA, Taaffe DR, Spry N, Joseph D, Newton RU. Combined resistance and aerobic exercise program reverses muscle loss in men undergoing androgen suppression therapy for prostate cancer without bone metastases: a randomized controlled trial. J Clin Oncol 2010;28(2):340–7. Epub 2009/12/02, https://doi.org/10.1200/JCO.2009.23.2488. 19949016.

[9] Galvao DA, Spry N, Denham J, Taaffe DR, Cormie P, Joseph D, et al. A multicentre year-long randomised controlled trial of exercise training targeting physical functioning in men with prostate cancer previously treated with androgen suppression and radiation from TROG 03.04 RADAR. Eur Urol 2014;65(5):856–64. Epub 2013/10/12, https://doi.org/10.1016/j.eururo.2013.09.041. 24113319.

[10] Cormie P, Galvão DA, Spry N, Joseph D, Chee R, Taaffe DR, et al. Can supervised exercise prevent treatment toxicity in patients with prostate cancer initiating androgen-deprivation therapy: a randomised controlled trial. BJU Int 2015;115(2):256–66. Epub 2014/01/29, https://doi.org/10.1111/bju.12646. 24467669.

[11] Winters-Stone KM, Dieckmann N, Maddalozzo GF, Bennett JA, Ryan CW, Beer TM. Resistance exercise reduces body fat and insulin during androgen-deprivation therapy for prostate cancer. Oncol Nurs Forum 2015;42(4):348–56. Epub 2015/07/07, https://doi.org/10.1188/15.Onf.348-356. 26148314.

[12] Galvao DA, Taaffe DR, Spry N, Cormie P, Joseph D, Chambers SK, et al. Exercise preserves physical function in prostate cancer patients with bone metastases. Med Sci Sports Exerc 2018;50(3):393–9. Epub 2017/10/17, https://doi.org/10.1249/MSS.0000000000001454. PubMed PMID: 29036016; PubMed Central PMCID: PMCPMC5828380.

[13] Newton RU, Galvao DA, Spry N, Joseph D, Chambers SK, Gardiner RA, et al. Exercise mode specificity for preserving spine and hip bone mineral density in prostate cancer patients. Med Sci Sports Exerc 2019;51(4):607–14. Epub 2018/11/06, https://doi.org/10.1249/MSS.0000000000001831. 30395051.

[14] Taaffe DR, Galvao DA, Spry N, Joseph D, Chambers SK, Gardiner RA, et al. Immediate versus delayed exercise in men initiating androgen deprivation: effects on bone density and soft tissue composition. BJU Int 2019;123(2):261–9. Epub 2018/09/22, https://doi.org/10.1111/bju.14505. PubMed PMID: 30239116; PubMed Central PMCID: PMCPMC6635752.

[15] Lopez P, Taaffe DR, Newton RU, Galvao DA. Resistance exercise dosage in men with prostate cancer: systematic review, meta-analysis, and meta-regression. Med Sci Sports Exerc 2021;53(3):459–69. Epub 2020/09/06, https://doi.org/10.1249/MSS.0000000000002503. 32890199.

[16] Lopez P, Newton RU, Taaffe DR, Singh F, Lyons-Wall P, Buffart LM, et al. Interventions for improving body composition in men with prostate cancer: a systematic review and network meta-analysis. Med Sci Sports Exerc 2021. https://doi.org/10.1249/mss.0000000000002843. Epub 2021/12/23. PubMed PMID: 34935706.

[17] Segal RJ, Reid RD, Courneya KS, Sigal RJ, Kenny GP, Prud'Homme DG, et al. Randomized controlled trial of resistance or aerobic exercise in men receiving radiation therapy for prostate cancer. J Clin Oncol 2009;27(3):344–51. Epub 2008/12/10, https://doi.org/10.1200/jco.2007.15.4963. 19064985.

[18] Bourke L, Gilbert S, Hooper R, Steed LA, Joshi M, Catto JW, et al. Lifestyle changes for improving disease-specific quality of life in sedentary men on long-term androgen-deprivation therapy for advanced prostate cancer: a randomised controlled trial. Eur Urol 2014;65(5):865–72. Epub 2013/10/15, https://doi.org/10.1016/j.eururo.2013.09.040. 24119318.

[19] Taaffe DR, Newton RU, Spry N, Joseph DJ, Galvão DA. Responsiveness to resistance-based multimodal exercise among men with prostate cancer receiving androgen deprivation therapy. J Natl Compr Canc Netw 2019;17(10):1211–20. Epub 2019/10/08, https://doi.org/10.6004/jnccn.2019.7311. 31590154.

[20] Ezzatvar Y, Ramírez-Vélez R, Sáez de Asteasu ML, Martínez-Velilla N, Zambom-Ferraresi F, Izquierdo M, et al. Physical function and all-cause mortality in older adults diagnosed with cancer: a systematic review and meta-analysis. J Gerontol A Biol Sci Med Sci 2020. https://doi.org/10.1093/gerona/glaa305. Epub 2021/01/10. PubMed PMID: 33421059.

[21] Lopez P, Newton RU, Taaffe DR, Singh F, Buffart LM, Spry N, et al. Associations of fat and muscle mass with overall survival in men with prostate cancer: a systematic review with meta-analysis. Prostate Cancer Prostatic Dis 2021. https://doi.org/10.1038/s41391-021-00442-0. Epub 2021/08/23. [PubMed PMID: 34420038].

[22] Buffart LM, Kalter J, Chinapaw MJ, Heymans MW, Aaronson NK, Courneya KS, et al. Predicting OptimaL cAncer RehabIlitation and Supportive care (POLARIS): rationale and design for meta-analyses of individual patient data of randomized controlled trials that evaluate the effect of physical activity and psychosocial interventions on health-related quality of life in cancer survivors. Syst Rev 2013;2:75. Epub 2013/09/17, https://doi.org/10.1186/2046-4053-2-75. PubMed PMID: 24034173; PubMed Central PMCID: PMCPMC3848838.

[23] Stewart LA, Clarke M, Rovers M, Riley RD, Simmonds M, Stewart G, et al. Preferred reporting items for systematic review and meta-analyses of individual participant data: the PRISMA-IPD statement. JAMA. 2015;313(16):1657–65. Epub 2015/04/29, https://doi.org/10.1001/jama.2015.3656. 25919529.

[24] Buffart LM, Kalter J, Sweegers MG, Courneya KS, Newton RU, Aaronson NK, et al. Effects and moderators of exercise on quality of life and physical function in patients with cancer: an individual patient data meta-analysis of 34 RCTs. Cancer Treat Rev 2017;52:91–104. Epub 2016/12/23, https://doi.org/10.1016/j.ctrv.2016.11.010. 28006694.

[25] Galvão DA, Spry N, Denham J, Taaffe DR, Cormie P, Joseph D, et al. A multicentre year-long randomised controlled trial of exercise training targeting physical functioning in men with prostate cancer previously treated with androgen suppression and radiation from TROG 03.04 RADAR. Eur Urol 2014;65(5):856–64. Epub 2013/10/12, https://doi.org/10.1016/j.eururo.2013.09.041. 24113319.

[26] Newton RU, Galvão DA, Spry N, Joseph D, Chambers SK, Gardiner RA, et al. Exercise mode specificity for preserving spine and hip bone mineral density in prostate cancer patients. Med Sci Sports Exerc 2019;51(4):607–14. Epub 2018/11/06, https://doi.org/10.1249/mss.0000000000001831. 30395051.

[27] Taaffe DR, Galvão DA, Spry N, Joseph D, Chambers SK, Gardiner RA, et al. Immediate versus delayed exercise in men initiating androgen deprivation: effects on bone density and soft tissue composition. BJU Int 2019;123(2):261–9. Epub 2018/09/22, https://doi.org/10.1111/bju.14505. PubMed PMID: 30239116; PubMed Central PMCID: PMCPMC6635752.

[28] Baumgartner RN, Koehler KM, Gallagher D, Romero L, Heymsfield SB, Ross RR, et al. Epidemiology of sarcopenia among the elderly in New Mexico. Am J Epidemiol 1998;147(8):755–63. Epub 1998/04/29, https://doi.org/10.1093/oxfordjournals.aje.a009520. 9554417.

[29] Adams SC, Segal RJ, McKenzie DC, Vallerand JR, Morielli AR, Mackey JR, et al. Impact of resistance and aerobic exercise on sarcopenia and dynapenia in breast cancer patients receiving adjuvant chemotherapy: a multicenter randomized controlled trial. Breast Cancer Res Treat 2016;158(3):497–507. Epub 2016/07/11, https://doi.org/10.1007/s10549-016-3900-2. 27394134.

[30] Tracy BL, Ivey FM, Hurlbut D, Martel GF, Lemmer JT, Siegel EL, et al. Muscle quality. II. Effects of strength training in 65- to 75-yr-old men and women. J Appl Physiol 1985;86(1):195–201. 1999. Epub 1999/01/14, https://doi.org/10.1152/jappl.1999.86.1.195. PubMed PMID: 9887131.

[31] Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing 2010;39(4):412–23. Epub 2010/04/16, https://doi.org/10.1093/ageing/afq034. PubMed PMID: 20392703; PubMed Central PMCID: PMCPMC2886201.

[32] Williams GR, Dunne RF, Giri S, Shachar SS, Caan BJ. Sarcopenia in the older adult with cancer. J Clin Oncol 2021;39(19):2068–78. Epub 2021/05/28, https://doi.org/10.1200/jco.21.00102. PubMed PMID: 34043430; PubMed Central PMCID: PMCPMC8260902 DunneConsulting or Advisory Role: Exelixis Smith GiriHonoraria: CareVive, OncLiveResearch Funding: Carevive Systems, Pack Health Shlomit S. ShacharConsulting or Advisory Role: Novartis, Roche, Pfizer, LillyTravel, Accommodations, Expenses: Pfizer, RocheNo other potential conflicts of interest were reported.

[33] Galvão DA, Taaffe DR, Spry N, Joseph D, Newton RU. Acute versus chronic exposure to androgen suppression for prostate cancer: impact on the exercise response. J Urol 2011;186(4):1291–7. Epub 2011/08/19, https://doi.org/10.1016/j.juro.2011.05.055. 21849187.

[34] Taaffe DR, Buffart LM, Newton RU, Spry N, Denham J, Joseph D, et al. Time on androgen deprivation therapy and adaptations to exercise: secondary analysis from a 12-month randomized controlled trial in men with prostate cancer. BJU Int 2018;121(2):194–202. Epub 2017/09/06, https://doi.org/10.1111/bju.14008. 28872752.

[35] Fisher DJ, Copas AJ, Tierney JF, Parmar MK. A critical review of methods for the assessment of patient-level interactions in individual participant data meta-analysis of randomized trials, and guidance for practitioners. J Clin Epidemiol 2011;64(9):949–67. Epub 2011/03/18, https://doi.org/10.1016/j.jclinepi.2010.11.016. 21411280.

[36] Bates D, Mächler M, Bolker B, Walker S. Fitting linear mixed-effects models using lme4. J Stat Softw 2015;67(1):1–48.

[37] Melton 3rd LJ, Khosla S, Crowson CS, O'Connor MK, O'Fallon WM, Riggs BL. Epidemiology of sarcopenia. J Am Geriatr Soc 2000;48(6):625–30. Epub 2000/06/16. PubMed PMID: 10855597.

[38] Winters-Stone KM, Moe E, Graff JN, Dieckmann NF, Stoyles S, Borsch C, et al. Falls and frailty in prostate cancer survivors: current, past, and never users of androgen deprivation therapy. J Am Geriatr Soc 2017;65(7):1414–9. Epub 2017/03/07, https://doi.org/10.1111/jgs.14795. PubMed PMID: 28263373; PubMed Central PMCID: PMCPMC5507739.

[39] Newman AB, Simonsick EM, Naydeck BL, Boudreau RM, Kritchevsky SB, Nevitt MC, et al. Association of long-distance corridor walk performance with mortality, cardiovascular disease, mobility limitation, and disability. Jama. 2006;295(17):2018–26. Epub 2006/05/04, https://doi.org/10.1001/jama.295.17.2018. 16670410.

[40] Guida JL, Agurs-Collins T, Ahles TA, Campisi J, Dale W, Demark-Wahnefried W, et al. Strategies to prevent or remediate cancer and treatment-related aging. J Natl Cancer Inst 2021;113(2):112–22. Epub 2020/04/30, https://doi.org/10.1093/jnci/djaa060. PubMed PMID: 32348501; PubMed Central PMCID: PMCPMC7850536.

[41] Given B, Given CW. Older adults and cancer treatment. Cancer 2008;113(12 Suppl):3505–11. Epub 2008/12/06, https://doi.org/10.1002/cncr.23939. PubMed PMID: 19058145; PubMed Central PMCID: PMCPMC2606910.

[42] Versteeg KS, Blauwhoff-Buskermolen S, Buffart LM, de van der Schueren MAE, Langius JAE, Verheul HMW, et al. Higher muscle strength is associated with prolonged survival in older patients with advanced cancer. Oncologist 2018;23(5):580–5. Epub 2017/12/10, https://doi.org/10.1634/theoncologist.2017-0193. PubMed PMID: 29222198; PubMed Central PMCID: PMCPMC5947445.

[43] Courneya KS, Stevinson C, McNeely ML, Sellar CM, Peddle CJ, Friedenreich CM, et al. Predictors of adherence to supervised exercise in lymphoma patients participating in a randomized controlled trial. Ann Behav Med 2010;40(1):30–9. Epub 2010/06/22, https://doi.org/10.1007/s12160-010-9205-5. 20563764.

[44] Courneya KS, Segal RJ, Gelmon K, Reid RD, Mackey JR, Friedenreich CM, et al. Predictors of supervised exercise adherence during breast cancer chemotherapy. Med Sci Sports Exerc 2008;40(6):1180–7. Epub 2008/05/08, https://doi.org/10.1249/MSS.0b013e318168da45. 18460985.

[45] Houben LHP, Overkamp M, van Kraaij P, Trommelen J, van Roermund JGH, de Vries P, et al. Resistance exercise training increases muscle mass and strength in prostate cancer patients on androgen deprivation therapy. Med Sci Sports Exerc 2022. https://doi.org/10.1249/mss.0000000000003095. Epub 2022/12/20. [PubMed PMID: 36534950].