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Clinical Investigations

Effects of Exercise During Radiation Therapy on Physical Function and Treatment-Related Side Effects in Men With Prostate Cancer: A Systematic Review and Meta-Analysis

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Purpose: Radiation therapy is a commonly used treatment for prostate cancer; however, the side effects may negatively affect quality of life and cause patients to be less physically active. Although exercise has been shown to mitigate radiation therapy−related fatigue in men with prostate cancer during radiation therapy, other adverse effects of treatment such as physical deconditioning, urinary symptoms, or sexual dysfunction have not been systematically reviewed in this patient population. Thus, the purpose of this review was to investigate the effect of exercise on physical function and treatment-related side effects in men with prostate cancer undergoing radiation therapy.

Methods: A systematic literature search was conducted in the PubMed, Embase, CINAHL Plus, SPORTDiscus, and Web of Science databases in December 2020. Included studies were randomized controlled trials examining the effects of aerobic and/or resistance exercise interventions on measures of physical function and treatment-related side effects in prostate cancer patients undergoing radiation therapy. Meta-analysis was performed on outcomes that were reported in 2 or more studies.

Results: Seven publications from 6 randomized controlled trials involving 391 prostate cancer patients were included. Patients had stage I to IV cancer with a Gleason score of ≤6 to 10. Exercise resulted in consistent significant benefits for physical function in terms of cardiovascular fitness (standardized mean difference [SMD], 0.83; 95% confidence interval [CI], 0.31-1.36; $P < .01$) and muscle function (SMD, 1.30; 95% CI, 0.53-2.07; $P < .01$). Furthermore, there was a significant positive effect of exercise on urinary toxicity (SMD, −0.71; 95% CI, −1.25 to −0.18; $P < .01$), but not on intestinal ($P = .21$) or hormonal toxicity ($P = .41$), depression ($P = .45$), or sleep symptoms ($P = .88$).

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Conclusion: Based on the current evidence, exercise in men with prostate cancer undergoing radiation therapy improves physical function and mitigates urinary toxicity. The effect of exercise on other treatment-related side effects are less clear and require further investigation. © 2021 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)

Introduction

Radiation therapy has undergone substantial advances over the past century as a result of technological innovations that have continually led to improvements in patient care. Better radiation dose distribution resulting in superior tumor control while reducing treatment toxicity has benefitted patients in terms of treatment outcome as well as quality of life.[1,2] In prostate cancer, radiation therapy is an effective and commonly used treatment modality but, for some patients, treatment may result in sexual dysfunction and can cause bladder as well as bowel symptoms, which have been shown to adversely affect the mental health and quality of life of patients.[3,4]

The benefits of integrating exercise into cancer care, and even directly into treatment centers, are increasingly being recognized.[5,6] Researchers have consistently demonstrated that exercise may improve cancer- and treatment-related health outcomes such as fatigue, quality of life, anxiety, depression, bone health, lymphedema, physical function, and sleep.[7-9] However, in prostate cancer, the vast majority of these studies have either focused on patients before and after radical prostatectomy or to manage the known and extensive side effect profile of patients receiving androgen deprivation therapy (ADT), and very little attention has been given to exploring whether there are potential benefits of exercise in patients during radiation therapy alone.

In a recent meta-analysis examining the effect of exercise training on fatigue and quality of life in prostate cancer patients undergoing radiation therapy, exercise resulted in significant benefits for fatigue but was found to have no significant effect on quality of life.[10] However, measures of global quality of life have been found to not accurately represent the influence of disease or treatment-specific symptoms in prostate cancer patients, with global health status being similar between previously treated prostate cancer patients and a group of men with no history of prostate cancer in spite of greater urinary, bowel, and sexual dysfunction in the prostate cancer group.[11] Thus, closer investigation of more specific health-related outcomes before and after prostate cancer treatment and whether exercise programs can prevent, reduce, or aid the recovery of these problems is warranted. Furthermore, the role of exercise during radiation therapy and the effect on physical function and other domains of health-related outcomes such as depression or sleep quality as well as prostate cancer-specific symptoms have not been systematically reviewed.

Therefore, the purpose of this review was to examine the current evidence resulting from investigations of the effects of exercise on physical function and treatment-related side effects in men with prostate cancer undergoing radiation therapy. In addition, we report on adverse events that occurred in the trials to assess the safety of these exercise interventions.

Methods and Materials

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[12,13] and was registered on PROSPERO (registration no.: CRD42021228764). The search term strategy and study eligibility criteria are based on the Population, Intervention, Comparison, Outcomes, and Study design framework (Table 1).

Search strategy

Systematic literature searches were conducted in the PubMed, Embase, CINAHL Plus, SPORTDiscus, and Web of Science databases in December 2020 using search terms related to "prostate cancer," "exercise," and "radiation therapy." The full electronic search strategy is presented in Table E1. A combination of keywords (search limited to title and abstract) and subject index terms was used to search all listed databases. No other limits such as date of publication or article type were applied to the database search. In addition, reference lists of all included publications and relevant review articles were checked for any additional studies.

Identified records were imported into Covidence (Veritas Health Innovation Ltd, Melbourne, VIC, Australia) where duplicates were automatically removed. To exclude irrelevant records, titles and abstracts were first screened by one reviewer (O.S.). Subsequently, full-text reports were further reviewed independently by 2 researchers (O.S. and H.L.) to assess eligibility. Any disagreements between the 2 reviewers were resolved through consensus.

Table 1 Components of Study Eligibility Criteria (Population, Intervention, Comparison, Outcomes, and Study Design Framework)

Component	Description
Population	Prostate cancer patients during radiation
Intervention	Clinic- and/or home-based exercise
Comparison	Usual care (ie, no formal exercise)
Outcomes	Physical function and treatment toxicity
Study design	Randomized controlled trials

Eligibility criteria

Randomized controlled trials were included if: (1) a clinic- and/or home-based resistance and/or aerobic exercise program was conducted during the course of radiation therapy in men with prostate cancer; and (2) outcomes of objectively measured physical function (eg, cardiorespiratory fitness, upper/lower body strength, or mobility) or treatment-related side effects (eg, urinary and gastrointestinal toxicity, sleep quality, or depression and anxiety) were reported. Treatment-related side effects were defined as radiation therapy toxicity or any patient-reported outcome or symptom assessed by questionnaire response or clinician assessment. However, fatigue and general quality of life were not assessed as they were the subject of a recent meta-analysis.[10]

Studies were excluded if: (1) mixed cancer cohorts were investigated, unless data for prostate cancer patients were reported separately, (2) exercise interventions were not performed concurrently with radiation therapy, (3) not all patients were undergoing radiation therapy at the time of the exercise intervention, (4) study interventions consisted only of holistic training modalities (such as yoga, qigong, or tai chi) or specific rehabilitation techniques (eg, pelvic floor muscle training), (5) no specific data were reported for the outcomes of interest, (6) full-text articles were not available, or (7) studies were reported in languages other than English.

Data extraction

Data extraction was performed independently by 2 review authors (O.S. and H.L.) using a pre-established data extraction form. The form was piloted by O.S. and refined accordingly. Finally, the following data items were extracted: (1) study characteristics such as year of publication, sample size, and study setting; (2) participant characteristics and clinical information, including patient age, disease stage, and treatment plan; (3) exercise intervention descriptors such as program duration, exercise modality, training frequency, intensity and duration; and (4) outcomes of interest (including adverse events) for each group. Any disagreements between the 2 reviewers were resolved by consensus.

Quality assessment

The methodological quality of included studies was assessed using the Physiotherapy Evidence Database (PEDro) scale.[14] The PEDro scale consists of 11 items to assess external (item 1) and internal (items 2-9) validity as well as statistical reporting (items 10 and 11). All but the first item that is satisfied contributes 1 point to the total score, resulting in an overall score of 0 to 10 for each study. However, given the nature of exercise trials, it is not possible to blind patients and research personnel administering the intervention. Thus, a score of 8 on the PEDro scale was considered to be the highest possible score attainable. The score for methodological quality was rated as poor if 3 or lower, fair if 4 to 5, and good if 6 or higher.[15] All studies were included in qualitative and quantitative data synthesis, regardless of their PEDro score. The methodological quality assessment was independently performed by 2 review authors (O.S. and H.L.) and any discrepancies were resolved through consensus.

Statistical analysis

Meta-analysis was performed for outcomes that were reported in 2 or more studies. Pooled effect estimates were obtained from standardized mean differences (SMD) when combining different scales of a comparable outcome, whereas mean differences (MD) were used when combining studies with the same scale for a particular outcome. Where outcomes were assessed at multiple timepoints, values were calculated from first assessment to assessment at or earliest assessment after completion of radiation therapy. “Cardiorespiratory fitness” was created as a composite outcome using peak oxygen consumption ($\dot{V}O_2$peak), metabolic equivalents (METs), and walking distance obtained from either the 6-minute walk test or a modified shuttle test. Time to complete the 5-repetition sit-to-stand test as well as 8-repetition maximum leg and chest press performance were combined to establish a “Muscle function” outcome. “Depressive symptoms” were comprised of the Beck Depression Inventory and Center for Epidemiological Studies Depression Scale. “Sleep problems” was a combination of the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 insomnia scale, the Pittsburgh Sleep Quality Index, the Epworth Sleepiness Scale, and Insomnia Severity Index. The Radiation Therapy Oncology Group (RTOG)/EORTC acute radiation morbidity scale for bladder toxicity, the EORTC QLQ-PR25 urinary symptoms scale, as well as the Expanded Prostate Cancer Index Composite (EPIC) urinary function score and American Urological Association (AUA) Symptom Index were aggregated to form the “Urinary toxicity” outcome. “Intestinal toxicity” was comprised of the same outcome measures as “Urinary toxicity” with the corresponding scales/scores, but instead of the AUA Symptoms Index it incorporated the EORTC QLQ-C30 constipation and diarrhea scales. Finally, the EORTC QLQ-PR25 hormonal treatment-related symptoms scale and EPIC hormonal function score were combined to create “Hormonal toxicity.” For reverse scaled physical function outcomes (ie, where lower values indicate a better outcome) and treatment-related side effects (ie, where higher values indicate a better outcome), the mean values in each group were multiplied by −1, as recommended in the Cochrane Handbook for Systematic Reviews of Interventions,[16] to ensure same direction of measuring effects.

In studies comparing multiple exercise interventions to a single control group, data from exercise groups were combined according to recommendations by Borenstein et al.[17]

Furthermore, where multiple comparable outcomes were assessed in a single study, these outcomes were combined to form a single composite measure of that outcome.[18] Pooled effect estimates were calculated using a random-effects model with the DerSimonian-Laird method and considered statistically significant for P values less than .05.[19] Heterogeneity was assessed using Cochran's Q and quantified with the I^2 statistic. Heterogeneity was considered statistically significant for P values less than .05 and I^2 greater than 50% was considered indicative of high heterogeneity.[20] All data were analyzed using R, version 4.1.0 (The R Foundation) with the packages *meta* (version 4.18-1)[21] and *dmetar* (version 0.0.9000).[22]

Results

Search results

Electronic database searching yielded a total of 1878 records. After removal of duplicates (n = 405) and exclusion of nonrelevant references through title and abstract screening (n=1426), 47 full-text articles were assessed for eligibility. Of these, 8 publications describing 6 trials met the eligibility criteria (Fig. 1). However, one publication[23] from the study by Hojan et al[24] was excluded from the analysis and is not further discussed in this systematic review, as it only reported additional results after the

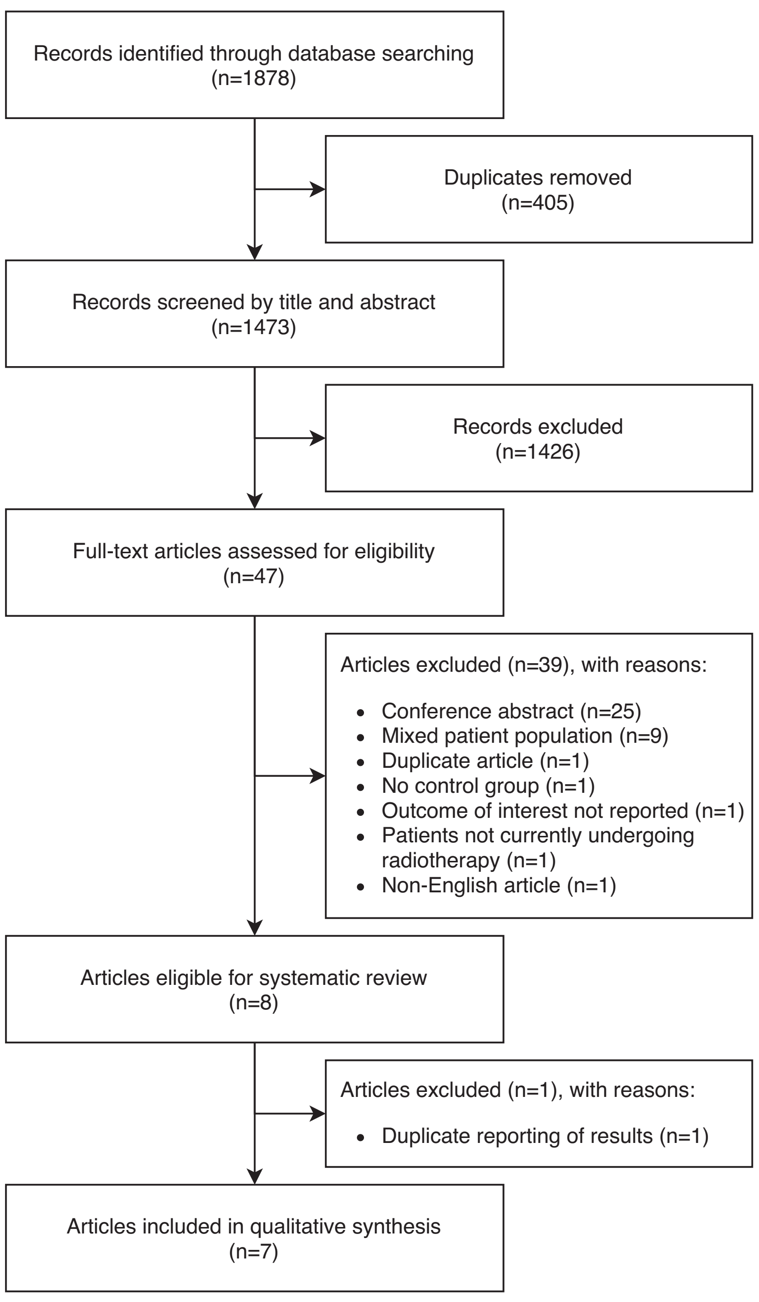


Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

completion of radiation therapy compared with the initial study report.[24] Thus, a total of 7 publications describing 6 trials were ultimately included in this systematic review.

Study characteristics

The characteristics of included studies are presented in Table 2. Reports were published between 2004 and 2020, and trials included a total of 391 prostate cancer patients (range, 21-121 patients). Patients were diagnosed with stage I to IV prostate cancer with Gleason scores ranging from ≤6 to 10. All patients were treated with radiation therapy with or without hormone therapy.

Exercise interventions were either home-based,[25] conducted in a clinic setting,[24,26-28] or a combination of both.[29] A detailed description of individual exercise programs used in each study is presented in Table E2. Exercise programs were 4 to 24 weeks in duration with most being ≤8 weeks and usually depended on duration of radiation therapy received. Programs consisted of either aerobic only exercise such as walking or cycling,[25-28] resistance training only,[27-29] or a combined aerobic and resistance training regimen.[24] Exercise sessions lasted between 25 to 55 minutes with a frequency of 3 to 5 times per week. Aerobic exercise intensity was 60% to 70% of age-predicted maximal heart rate,[24,25] 65% of heart rate reserve,[26] or 50% to 75% of $\dot{V}O_2$peak,[28] and 60% to 75% of 1-repetition maximum[24,28] or 4 to 6 rating of perceived exertion on the 10-point modified Borg scale[27] for resistance training. Furthermore, resistance training was performed for 1 to 3 sets of 8 to 12 repetitions for 5 to 10 different exercises targeting major muscle groups. Patients in one study performed high-intensity interval training at heart rates at and above 85% of age-predicted maximum,[27] and the resistance training group in another study served as an active control group rather than an actual intervention group, thus, the intensity was low.[29]

Quality assessment

The PEDro quality assessment of included randomized controlled trials is shown in Table 3. Methodological quality was rated as "good" overall, with a median PEDro score of 6.5 (range, 4-7). Four[24,25,27,28] out of 6 trials were deemed to have good methodological quality (ie, scores ≥6 on the PEDro scale).

Effects of exercise on physical function

Five studies included assessment of physical function before and after radiation therapy in men with prostate cancer.[24-28] Functional exercise capacity/cardiorespiratory fitness was assessed in all 5 trials by either measuring walking distance,[24,25,27] METs,[24,26] or $\dot{V}O_2$peak.[28] Meta-analysis of pooled outcomes showed a significant effect of exercise (SMD, 0.83; 95% confidence interval [CI], 0.31-1.36; $P < .01$) (Fig. 2A). The study by Windsor et al[25] was considered an outlier and was omitted from the result for the effect of cardiorespiratory fitness. In studies assessing walking distance, test performance was significantly improved in aerobic,[25,27] resistance,[27] and mixed modality[24] training groups compared with usual care. The 2 studies assessing METs reported conflicting results; functional capacity calculated based on a treadmill test using a modified Bruce protocol significantly increased by 2.6 ± 0.9 METs ($P < .001$) with 8 weeks of aerobic exercise (ie, walking) compared with no change in the control group (−0.2 ± 2.5 METs; $P = .77$),[26] whereas 8 weeks of combined aerobic and resistance training showed no significant difference between groups after radiation therapy, nor any within-group changes, in METs derived from the 6-minute walk test.[24] In the study by Segal et al,[28] aerobic exercise as well as resistance training prevented a decline in $\dot{V}O_2$peak. However, a significant difference was only observed between the resistance training and control groups (1.5 mL/kg/min; 95% CI, 0.06-3.0 mL/kg/min; $P = .041$), with the difference between the aerobic exercise and control group being similar in magnitude but statistically not significant (1.4 mL/kg/min; 95% CI, −0.01 to 2.8; $P = .052$).[28]

Lower-body strength was assessed in 2 studies.[26,28] Monga et al[26] found that an 8-week walking program resulted in superior performance on the 5-repetition sit-to-stand test, whereas Segal et al[28] reported that only the resistance training group had increased 8-repetition maximum leg press performance after 24 weeks of training compared with the control group, with no change in the aerobic exercise training group. Segal et al[28] also assessed upper-body strength using 8-repetition maximum chest press performance, which was improved in the resistance training group, unchanged in the aerobic exercise group and declined in the control group. Consequently, between-group differences in upper-body strength were significant for both exercise groups compared with the usual care group. For combined upper- and lower-body muscle function, meta-analysis showed a significant effect of exercise (SMD, 1.3; 95% CI, 0.53-2.07; $P < .01$) (Fig. 2B). Furthermore, Monga et al[26] reported increased flexibility as assessed by a modified sit-and-reach test in the exercise group with no change in the control group.

Effects of exercise on treatment toxicity

Treatment-related side effects before and after radiation therapy in men with prostate cancer were investigated in 6 studies.[24,26-30] An overview of the studies, including when which outcomes were assessed in relation to radiation therapy, is presented in Figures 3 to 5. Prostate cancer-specific symptoms were assessed in 5 studies by a variety of measures (Fig. 3); 2 studies used the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire,[26,28] 1 study used the EORTC QLQ-C30 in combination with the EORTC QLQ-PR25,[24] another study used the EPIC and

Table 2 Characteristics of Included Studies and Overview of Results

Study	Sample size	Patient characteristics	Treatment details	Exercise intervention and prescription*	Exercise adherence/ attendance and patient dropout	Key findings (exercise vs control)†
Windsor et al[25]	n=66 Ex: 33; Con: 33	Mean age: 68.8 years (range, 52-82 y) Localized prostate cancer	50 or 52 Gy in 20 fractions over 4 weeks 28.8% receiving adjuvant hormone therapy	Home-based aerobic exercise program (4 wk): ≥3 times/wk at 60%-70% HR_{max} for 30 minutes	100% adherence n = 1 (1.5%) dropout Ex: 1; Con: 0	↑ Modified shuttle test walk distance
Monga et al[26]	n = 21 Ex: 11; Con: 10	Mean age: 69.2 ± 4.8 years (range, 62-80 y) Localized prostate cancer Gleason score: 5.3 ± 1.1	68-70 Gy in 34-38 fractions over 7-8 weeks	Clinic-based aerobic exercise program (8 wk): 3 times/wk at 65% $HR_{reserve}$ for 30 minutes	Adherence and/or attendance not reported n = 9 (30%) dropout‡	**Physical function:** ↑ METs ↑ Flexibility ↑ Lower-limb strength **Treatment-related side effects:** ↔ Prostate cancer-specific symptoms ↔ Depressive symptoms
Segal et al[28]	n = 121 RT: 40; AE: 40; Con: 41	Mean age: 66.3 ± 7.0 years Stage I-IV prostate cancer Gleason score: 6.7 ± 0.9	Radiation therapy regimen not reported 61.2% receiving adjuvant hormone therapy	Clinic-based aerobic exercise or resistance training program (24 wk): 3 times/wk at 50%-75% $\dot{V}O_2$peak for 15-45 minutes or 60%-70% 1RM for 2 sets of 8-12 repetitions	88% attendance in RT group and 83% attendance in AE group n = 11 (9.1%) dropout RT: 7; AE: 3; Con: 1	**Physical function:** *Resistance training:* ↑ $\dot{V}O_2$peak ↑ Upper-body strength ↑ Lower-body strength *Aerobic exercise:* ↔ $\dot{V}O_2$peak ↑ Upper-body strength ↔ Lower-body strength **Treatment-related side effects:** ↔ Prostate cancer-specific symptoms
Kapur et al[30]	See Windsor et al[25] above					*Rectal toxicity:* ↓ Mean rectal toxicity over 4 weeks of radiation therapy ↔ Rectal toxicity at weekly treatment review ↔ Rectal toxicity at 4 weeks postradiation therapy *Bladder toxicity:* ↔ Mean bladder toxicity over 4 weeks of radiation therapy§ ↔ Bladder toxicity at weekly treatment review§

(*Continued*)

Table 2 (*Continued*)

Study	Sample size	Patient characteristics	Treatment details	Exercise intervention and prescription[*]	Exercise adherence/ attendance and patient dropout	Key findings (exercise vs control)[†]
						↓ Bladder toxicity at 4 weeks postradiation therapy[§]
Hojan et al[24]	n = 55 Ex: 27; Con: 28	Mean age: 68.5±6.1 years High-risk prostate cancer Gleason score: 6.63± 0.38	76 Gy in 38 fractions over 8 weeks 100% receiving hormone therapy 3-5 months before, during and after completion of radiation therapy	Clinic-based aerobic and resistance training program (8 wk): 5 times/wk at 65%-70% HR_{max} for 30 minutes and 70%-75% 1RM for 2 sets of 8 repetitions	95% attendance n = 1 (1.8%) dropout Ex: 0; Con: 1	**Physical function:** ↑ 6-minute walk test distance ↔ METs **Treatment-related side effects:** ↔ General cancer- and treatment-related symptoms[‖] ↔ Sexual activity ↑ Sexual functioning ↓ Urinary symptoms ↔ Bowel symptoms ↔ Hormonal treatment-related symptoms ↓ Problems with wearing an incontinence aid
McQuade et al[29]	n = 50[¶] Ex: 26; Con: 24	Mean age: 65.5 ± 7.3 years Stage I-III prostate cancer Gleason score: ≤6-9	75-76 Gy in 36-42 fractions over 6-8 weeks 73.3% receiving adjuvant hormone therapy	Clinic-based (and encouraged home-based practice) light resistance training and stretching exercise program (6-8 wk): 3 times/wk for 8-12 repetitions per set	100% attendance in 63.5% of patients and >50% attendance in 80.8% of patients n = 9 (18%) dropout Ex: 7; Con: 2	↔ Sleep quality ↔ Urinary function ↔ Bowel function ↔ Hormonal function ↔ Prostate symptom score
Piraux et al[27]	n = 78 HIIT: 27; RT: 25; Con: 26	Mean age: 69.1 ± 8.2 years Intermediate- to high-risk prostate cancer Gleason score: 7.8 ± 0.9 (range, 7-10)	62-78 Gy in 26-39 fractions over 5-8 weeks 81% receiving neoadjuvant and adjuvant hormone therapy 19% had a previous prostatectomy	Clinic-based aerobic exercise (HIIT) or resistance training program (5-8 wk): 3 times/wk at 65% to ≥85% HR_{max} for 16-30 minutes (8-15 intervals) or 4-6 RPE for 1-3 sets of 8-12 repetitions	93.5% attendance in HIIT group and 91.4% attendance in RT group n = 6 (7.7%) dropout HIIT: 3; RT: 1; Con: 2	**Physical function:** ↑ 6-minute walk test distance **Treatment-related side effects:** ↔ Depressive symptoms ↔ Daytime sleepiness ↔ Insomnia ↔ Sleep quality

Abbreviations: 1RM = one-repetition maximum; AE = aerobic exercise; Con = control group; EORTC = European Organisation for Research and Treatment of Cancer; Ex = exercise group; HIIT = high-intensity interval training; HR_{max} = maximal heart rate; $HR_{reserve}$ = heart rate reserve; MET = metabolic equivalent of task; RPE = rating of perceived exertion; RT = resistance training; QLQ-C30 = Quality of Life Questionnaire; QoL = quality of life; $\dot{V}O_2$peak = peak oxygen uptake.

* Detailed exercise prescriptions are presented in Table E2.

† Results are presented for between-group differences (P<.05): ↑, significant increase with exercise vs control; ↓, significant decrease with exercise vs control; ↔, no significant difference between exercise and control.

‡ Out of 30 patients randomized.

§ Three patients in the exercise group had indwelling urinary catheters during the course of their treatment and were excluded from the analysis for bladder toxicity.

‖ As assessed by the EORTC QLQ-C30: nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties.

¶ This study is a 3-arm randomized controlled trial; only the results from the exercise (active control) and waiting list control group are presented.

Table 3 Quality Assessment of Included Randomized Controlled Trials

Study	Assessment criteria* 1	2	3	4	5	6	7	8	9	10	11	Total score†
Windsor et al[25]	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	7
Monga et al[26]	Y	Y	N	Y	N	N	N	N	Y	Y	Y	5
Segal et al[28]	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	7
Hojan et al[24]	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	7
McQuade et al[29]	Y	Y	N	N	N	N	N	N	Y	Y	Y	4
Piraux et al[27]	Y	Y	N	Y	N	N	N	Y	Y	Y	Y	6

Abbreviations: N = no; Y = yes.

* Assessment criteria of the PEDro scale: (1) eligibility criteria were specified; (2) particpants were randomly allocated to groups; (3) allocation was concealed; (4) groups were similar at baseline; (5) participants were blinded; (6) therapists who administered the therapy were blinded; (7) assessors were blinded; (8) measures of at least 1 key outcome were obtained from >85% of participants; (9) participants received treatment or control condition as allocated or data was analyzed by intention to treat; 10) statistical comparisons between groups were reported; and 11) point measures and measures of variability were provided.

† Criterion 1 (ie, "eligibility criteria were specified") relates to external validity and is not used to calculate the total PEDro score.[14]

AUA Symptom Index,[29] and 1 study assessed clinician-graded bladder and rectal toxicity using the RTOG/EORTC acute radiation morbidity scale.[30]

Monga et al[26] found that the total FACT-P score increased after the exercise intervention, indicating improved quality of life, compared with the control group. However, there was no significant difference in this study for the prostate cancer subscale that assesses prostate cancer-specific symptoms.[26] Furthermore, prostate cancer-specific symptoms as assessed by the corresponding subscale on the FACT-P questionnaire decreased (ie, worsened) by −1.91 to −4.17 points (mean change across all groups; $P = .047$ to $P < .001$) after 12 weeks of the intervention in the study by Segal et al,[28] regardless of group allocation but recovered again to baseline levels after 24 weeks. Pooled results of meta-analysis showed a borderline significant effect of exercise (MD, 2.15; 95% CI, −0.06 to 4.35; $P = .06$) (Fig. 6A).

Moreover, no significant differences between exercise and control were reported by McQuade et al[29] for any of the EPIC domains, including urinary, bowel, and hormonal function, or the AUA prostate symptoms score. These

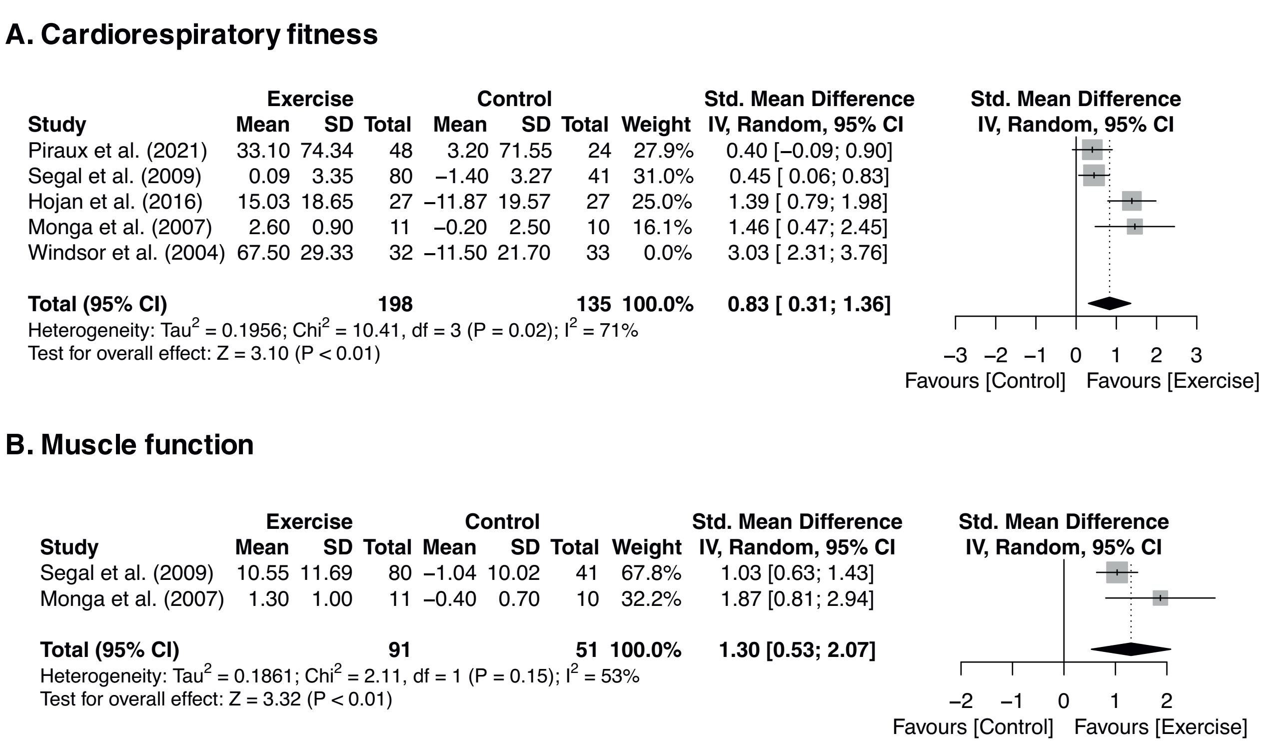


Fig. 2. Effects of exercise compared with usual care on cardiorespiratory fitness (A) and muscle function (B).

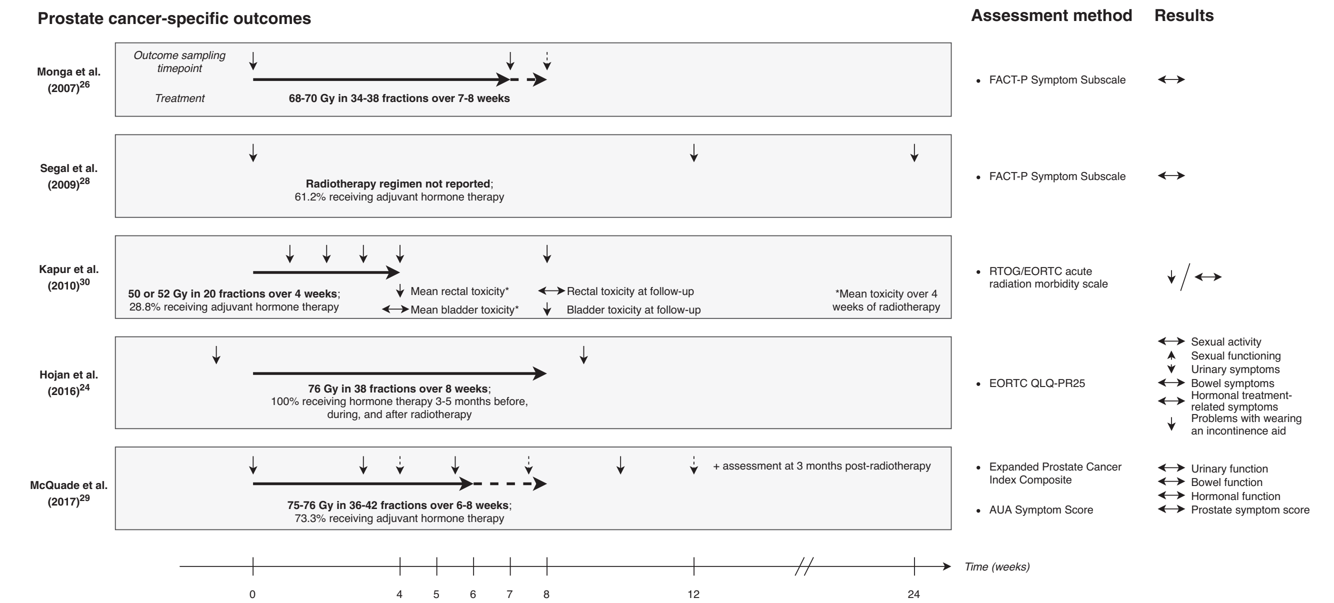


Fig. 3. Overview of studies with assessment of prostate cancer-specific outcomes. Results are presented for between-group differences ($P < .05$): ↑, significant increase with exercise vs control; ↓, significant decrease with exercise vs control; ↔, no significant difference between exercise and control. Continuous lines with arrows indicate the duration of radiation therapy. Where variable durations of radiation therapy were reported, continuous lines represent the shortest and dashed lines represent the longest duration of radiation therapy reported. Vertical arrows represent timepoints of outcome assessments (dashed vertical arrows correspond with the assessment timepoints for the longest duration of radiation therapy reported). If specific intervals for assessment timepoints before/after the start/end of radiation therapy were indicated, these are shown accordingly (eg, in the study by Hojan et al,[24] it was reported that outcomes were assessed 1 week before/after the start/end of radiation therapy, respectively). Where no precise assessment timepoints were reported (ie, at baseline before radiation therapy and after the end of radiation therapy, or similar), we assumed that assessments were performed shortly before/after the start/end of radiation therapy. Hence, for these studies, assessment timepoints are shown at the start/end or radiation therapy. *Abbreviations:* AUA, American Urologic Association; EORTC, European Organisation for Research and Treatment of Cancer; FACT-P, Functional Assessment of Cancer Therapy-Prostate; RTOG, Radiation Therapy Oncology Group; QLQ, Quality of Life Questionnaire.

results are consistent with outcomes from the meta-analysis, except for the urinary domain (Fig. 6B-D). For urinary toxicity, there was a significant benefit of engaging in exercise compared with the usual care control group when pooling study outcomes (SMD, −0.71; 95% CI, −1.25 to −0.18; $P < .01$) (Fig. 6B).

The EORTC QLQ-C30 is a questionnaire that is not prostate cancer-specific but includes symptom subscales such as pain or diarrhea that are nevertheless relevant to prostate cancer. In the study by Hojan et al,[24] however, there were no significant differences for any of these symptoms, except for a significant within-group change in diarrhea. In the control group, diarrhea significantly increased by 11.5 ± 32.7 points ($P \leq .05$) after treatment compared with pretreatment levels, and, although not statistically significant, there was a similar magnitude of increase regarding symptoms of diarrhea (10.8 ± 18.9 points) in the exercise group.[24] Similarly, problems associated with wearing an incontinence aid increased in both groups after 8 weeks of radiation therapy and exercise or usual care (9.1 ± 24.3 and 12.2 ± 38.5 points, respectively; $P \leq .05$), but to a significantly lesser extent in the group doing combined aerobic and resistance training throughout treatment (between-group mean change, −3.1 points in favor of exercise; $P < .05$).[24] Urinary symptoms, however, were significantly lower in the exercise group after radiation therapy compared with the control population (31.8 ± 16.2 vs 48.9 ± 20.7 points; $P \leq .01$), in that exercise prevented an increase in symptom burden (1.9 ± 18.5 points; $P > .05$) that was seen in the control group (16.4 ± 16.0 points; $P \leq .01$).[24] As observed with urinary symptoms, there was also a decrease in sexual functioning in the nonexercise control group after treatment (−9.7 ± 36.4 points; $P \leq .05$) that was not seen in the intervention group (0.6 ± 41.4 points; $P > .05$).[24]

In contrast to other studies included in this systematic‘ review, Kapur et al[30] did not use self-administered questionnaires to assess prostate cancer treatment−related side effects, but rather analyzed acute radiation morbidity scoring for bladder and rectal toxicity, which were prospectively recorded but retrospectively extracted from patient records at weekly treatment reviews. Although rectal toxicity was comparable between groups at these weekly assessments during the 4 weeks of radiation therapy as well as at

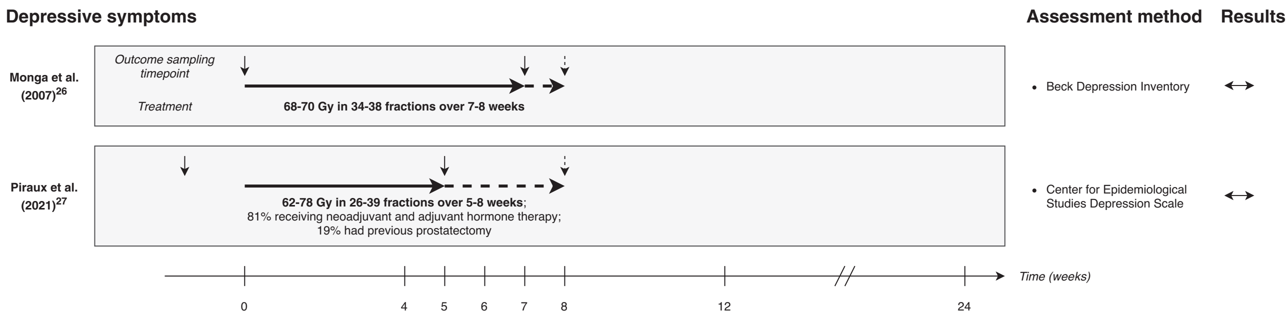


Fig. 4. Overview of studies with assessment of depressive symptoms. Results are presented for between-group differences ($P < .05$): ↑, significant increase with exercise vs control; ↓, significant decrease with exercise vs control; ↔, no significant difference between exercise and control. Continuous lines with arrows indicate the duration of radiation therapy. Where variable durations of radiation therapy were reported, continuous lines represent the shortest and dashed lines represent the longest duration of radiation therapy reported. Vertical arrows represent timepoints of outcome assessments (dashed vertical arrows correspond with the assessment timepoints for the longest duration of radiation therapy reported). If specific intervals for assessment timepoints before/after the start/end of radiation therapy were indicated, these are shown accordingly (eg, in the study by Piraux et al,[27] it was reported that outcomes were assessed 10 days before the start of radiation therapy). Where no precise assessment timepoints were reported (ie, at baseline before radiation therapy and after the end of radiation therapy, or similar), we assumed that assessments were performed shortly before/after the start/end of radiation therapy. Hence, for these studies, assessment timepoints are shown at the start/end or radiation therapy.

follow-up 4 weeks after treatment, the mean rectal toxicity scores over the 4 weeks of treatment were significantly lower in the exercise group, who were provided with a home-based walking program, compared with the usual care control group (0.91 ± 0.52 vs 1.27 ± 0.46; mean difference, −0.36; 95% CI, −0.61 to −0.12; P = .004).[30] In addition, bladder toxicity was also significantly lower in the exercise group at the follow-up assessment 4 weeks post radiation therapy (1.17 ± 0.38 vs 1.73 ± 0.84; mean difference, −0.56; 95% CI, −0.89 to −0.27; P = .001).[30]

Depressive symptoms were assessed in 2 studies using either the Beck Depression Inventory or the Center for Epidemiological Studies Depression Scale (Fig. 4).[26,27] No significant difference between the usual care and exercise groups, which consisted of either walking on a treadmill[26]; high-intensity interval training on a cycle ergometer[27]; or resistance training using body weight, resistance bands, and dumbbells was reported.[27] Moreover, there were no significant within-group changes in either study.[26,27] Meta-analysis of pooled studies also revealed no significant benefit of exercise on depressive symptoms (SMD, −0.16; 95% CI, −0.59 to 0.26; P = .45) (Fig. 7A).

Sleep quality (Pittsburgh Sleep Quality Index), daytime sleepiness (Epworth Sleepiness Scale), and the severity of insomnia (Insomnia Severity Index) were assessed in 2 studies (Fig. 5).[27,29] No significant differences or within-group changes were observed for any of the sleep domains with either resistance[27,29] or high-intensity interval training[27] compared with usual care. Pooled meta-analysis of all 3 outcome measures also indicated no significant effect of exercise on sleep (SMD, 0.02; 95% CI, −0.29 to 0.34; P = .88) (Fig. 7B).

Adverse events

For 3 of the 6 trials,[24,27,28] information about adverse events was reported. One study[27] recorded no exercise-related adverse events, whereas the other 2 studies[24,28] reported a total of 4 adverse events. In the study by Hojan et al,[24] 1 patient in the control group experienced a stroke and was excluded from the analysis. In the study by Segal et al,[28] 3 adverse events occurred in the 2 exercise groups. One patient in the aerobic exercise group experienced an acute myocardial infarction shortly after completing the third exercise session. The patient was resuscitated and fully recovered but did not complete the study. The patient who experienced the myocardial infarction had no previous cardiac history. A second patient in the aerobic exercise group had syncope before treadmill exercise testing, and 1 patient in the resistance training group experienced chest pain during exercise. For both patients with syncope and chest pain, no underlying causes were identified.

Discussion

In this systematic review, we provide a comprehensive assessment of the current literature with regard to exercise training during radiation therapy treatment in men diagnosed with prostate cancer and the effect on physical function and treatment-related adverse effects. The studies indicate that exercise may be beneficial to improve multiple aspects of physical function such as cardiorespiratory fitness and muscle strength, as well as mitigate urinary

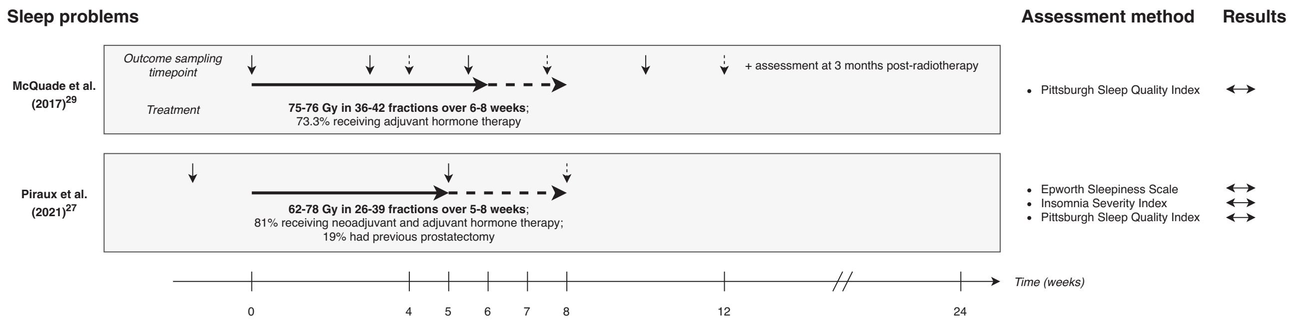


Fig. 5. Overview of studies with assessment of sleep problems. Results are presented for between-group differences ($P < .05$): ↑, significant increase with exercise vs control; ↓, significant decrease with exercise vs control; ↔, no significant difference between exercise and control. Continuous lines with arrows indicate the duration of radiation therapy. Where variable durations of radiation therapy were reported, continuous lines represent the shortest and dashed lines the longest duration of radiation therapy reported. Vertical arrows represent timepoints of outcome assessments (dashed vertical arrows correspond with the assessment timepoints for the longest duration of radiation therapy reported). If specific intervals for assessment timepoints before/after the start/end of radiation therapy were indicated, these are shown accordingly (eg, in the study by McQuade et al,[29] it was reported that outcomes were assessed during the last week of radiation therapy). Where no precise assessment timepoints were reported (ie, at baseline before radiation therapy and after the end of radiation therapy, or similar), we assumed that assessments were performed shortly before/after the start/end of radiation therapy. Hence, for these studies, assessment timepoints are shown at the start/end or radiation therapy.

toxicity. In contrast, there is no evidence of an effect of exercise on other side effects commonly associated with prostate cancer treatments that include radiation therapy such as intestinal toxicity, depressive symptoms, or sleep problems.

The most evident benefits of exercise were improvements in physical function. All included studies and exercise modalities resulted in increased performance of at least 1 domain of physical function, including cardiorespiratory fitness, upper- and lower-body muscle strength, and flexibility. Although not assessed in the majority of included studies, these improvements are likely to translate into increased performance of functional tasks or at least enhance patients' physical reserve capacity. This is important as it may allow patients to remain independent and perform activities of daily living without any significant restrictions. In particular, a decline in musculoskeletal fitness secondary to loss of lean mass with ageing and accelerated by ADT is believed to contribute to a reduced physical reserve capacity that may be prevented or even reversed by targeted resistance training.[31] Moreover, exercise has been shown to reduce the rate of falls in older people[32] and is an important strategy in osteoporosis management,[33] thus reducing the risk of fractures, a concern particularly relevant for men treated with ADT.[34] In addition, worse outcomes on physical performance tests have been associated with treatment-related complications and reduced survival in cancer patients.[35] Hence, improving or maintaining physical function via structured exercise is of high clinical importance in this patient population.

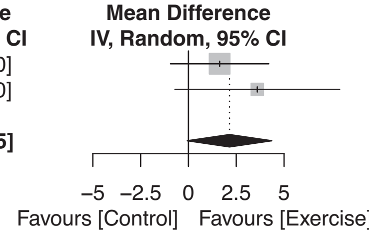
Declining neuromuscular efficiency and mitochondrial dysfunction have also been implicated with fatigue,[36,37] a major debilitating side effect of radiation therapy that can persist for some time after treatment.[36] This highlights the importance of improving or at least maintaining current aerobic capacity and muscular strength through exercise to potentially mitigate the onset and/or severity of fatigue. However, fatigue may be the result of various other potential causes[36,38] and has also been correlated with late urinary and rectal toxicity in men with prostate cancer after radiation therapy, possibly owing to their negative effect on sleep,[39] thus emphasizing the need to address fatigue as a multietiological problem.

Findings regarding the effects of exercise on gastrointestinal and genitourinary toxicity in our review are conflicting, however, and allow only limited comparability because of the various assessment methods and timepoints used to investigate these symptoms, the heterogeneity of the patient population, and the different radiation doses and treatment combinations used. Although no significant effects of exercise were observed in the study by McQuade et al,[29] the correlation between physical symptoms (ie, urinary, bowel, and hormonal toxicity) and fatigue, as well as sleep quality, was also demonstrated for acute symptoms in exploratory analyses. In addition, bowel symptoms and urinary function have been shown to negatively affect physical activity levels in men with prostate cancer.[40,41] The resulting sedentary lifestyle may lead to development or aggravation of other chronic comorbidities that may further affect quality of life. On the other hand, physician-graded bladder and rectal toxicity, an arguably more objective measure than patient-reported outcomes,[42] was significantly lower in the exercise group in 1 study comparing home-based exercise to usual care.[30] Furthermore, despite significantly worse prostate cancer-specific symptoms in all groups at 12 weeks in the study by Segal et al,[28] the scores in the resistance training group did not constitute a clinically meaningful change,[43] highlighting a further potential benefit of this exercise

A. FACT-P Prostate Cancer Subscale

Study	Exercise Mean	Exercise SD	Exercise Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Segal et al. (2009)	−2.54	8.40	80	−4.17	5.86	41	73.7%	1.63 [−0.94; 4.20]
Monga et al. (2007)	1.80	5.80	11	−1.80	4.20	10	26.3%	3.60 [−0.70; 7.90]
Total (95% CI)			**91**			**51**	**100.0%**	**2.15 [−0.06; 4.35]**

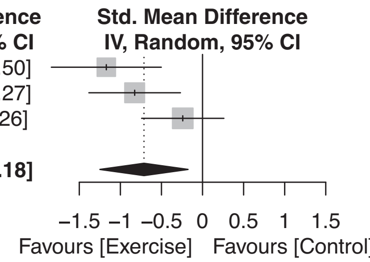
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.59$, df = 1 (P = 0.44); $I^2 = 0\%$
Test for overall effect: Z = 1.91 (P = 0.06)



B. Urinary toxicity

Study	Exercise Mean	Exercise SD	Exercise Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
McQuade et al. (2017)	1.51	7.63	19	10.33	7.17	22	29.3%	−1.17 [−1.84; −0.50]
Hojan et al. (2016)	1.90	18.50	27	16.40	16.00	27	34.1%	−0.83 [−1.38; −0.27]
Kapur et al. (2010)	0.68	0.64	29	0.86	0.81	33	36.7%	−0.24 [−0.74; 0.26]
Total (95% CI)			**75**			**82**	**100.0%**	**−0.71 [−1.25; −0.18]**

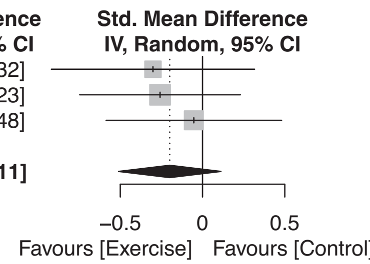
Heterogeneity: $Tau^2 = 0.1392$; $Chi^2 = 5.28$, df = 2 (P = 0.07); $I^2 = 62\%$
Test for overall effect: Z = −2.60 (P < 0.01)



C. Intestinal toxicity

Study	Exercise Mean	Exercise SD	Exercise Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
McQuade et al. (2017)	4.16	11.06	19	7.44	10.34	22	25.4%	−0.30 [−0.92; 0.32]
Kapur et al. (2010)	1.48	0.83	32	1.66	0.52	33	40.6%	−0.26 [−0.75; 0.23]
Hojan et al. (2016)	8.83	13.67	27	9.67	17.23	27	34.0%	−0.05 [−0.59; 0.48]
Total (95% CI)			**78**			**82**	**100.0%**	**−0.20 [−0.51; 0.11]**

Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.45$, df = 2 (P = 0.80); $I^2 = 0\%$
Test for overall effect: Z = −1.25 (P = 0.21)



D. Hormonal toxicity

Study	Exercise Mean	Exercise SD	Exercise Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Hojan et al. (2016)	4.50	9.70	27	7.40	16.90	27	56.9%	−0.21 [−0.74; 0.33]
McQuade et al. (2017)	−1.25	14.46	19	0.43	13.51	22	43.1%	−0.12 [−0.73; 0.50]
Total (95% CI)			**46**			**49**	**100.0%**	**−0.17 [−0.57; 0.23]**

Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.05$, df = 1 (P = 0.83); $I^2 = 0\%$
Test for overall effect: Z = −0.82 (P = 0.41)

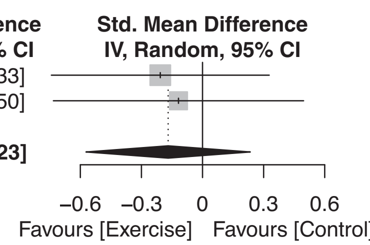


Fig. 6. Effects of exercise compared with usual care on prostate cancer-specific symptoms (A), urinary toxicity (B), intestinal toxicity (C), and hormonal treatment-related toxicity (D). *Abbreviation:* FACT-P = Functional Assessment of Cancer Therapy-Prostate.

modality that warrants further investigation. One caveat is that the radiation therapy regimen was not reported in this study. Thus, radiation for higher stage prostate cancer may have been for metastatic disease, which would have possibly not affected bladder, bowel, or sexual function as radiation was not directed to the pelvis. However, only 1 patient had stage IV prostate cancer, and that patient was allocated to the control group; the proportion of stage III

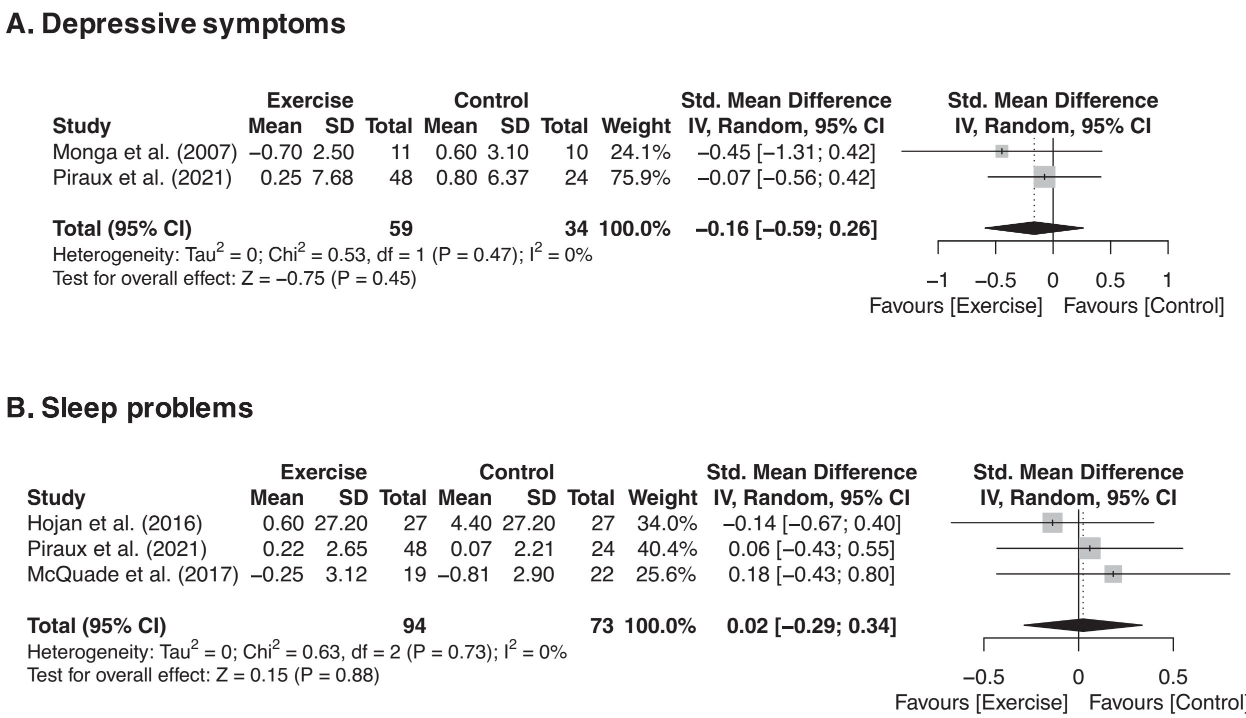


Fig. 7. Effects of exercise compared with usual care on depressive symptoms (A) and sleep problems (B).

prostate cancer patients was actually higher in the aerobic exercise (22.5%) and resistance training (20.0%) groups compared with the usual care group (9.8%).[28]

Based on the included studies, it was not possible to make any conclusions about long-term or late side effects of radiation therapy as study outcomes were only assessed immediately pre- and postradiation therapy or a couple of weeks after radiation therapy. However, Dieperink et al[44] conducted a multidisciplinary rehabilitation study assessing prostate cancer-specific outcomes after patients had completed radiation therapy and recently published 3-year follow-up data of this trial.[45] Initial results 6 months post radiation therapy demonstrated improved urinary symptoms compared with usual care, although these were not sustained at later follow-up. However, the beneficial effect of the intervention was maintained at 3 years for the urinary irritative subscale score in patients with moderate-to-severe problems at baseline (ie, after radiation therapy). Furthermore, moderate-to-severe bowel problems were more prevalent in the control group than in the intervention group after 3 years. As the intervention included pelvic floor training, incorporating exercises to strengthen pelvic floor muscles alongside aerobic and resistance training may be required to maintain adequate function in this population.

Cardiometabolic dysfunction and related diseases are a common occurrence in men with prostate cancer and are linked to a host of other complications.[46-49] For example, prostate cancer patients with unmanaged type 2 diabetes and patients receiving insulin for treatment have been identified as having an increased risk of both early and late gastrointestinal and genitourinary toxicity after radiation therapy compared with those patients not diagnosed with diabetes.[50] Prescribing exercise as medicine is an effective therapy for the management of diabetes, for which exercise has been shown to increase insulin sensitivity and improve glycemic control.[51,52] It may well be that exercise medicine could reduce gastrointestinal and genitourinary toxicity after radiation therapy in prostate cancer patients with diabetes. However, more research is required to investigate these relationships.

Reports of the effects of exercise on sexual activity and function are conflicting. In the study by Hojan et al,[24] the only research to assess sexual health included in this systematic review, there was a decrease in sexual function with usual care that was not observed in the exercise intervention group, whereas there was no significant effect on sexual activity. This finding is in line with observational data showing that more physical activity was positively associated with better sexual function,[53] including active men having better erectile function than inactive men.[41] However, recent contrasting reports indicate that a structured exercise program had no significant beneficial effect on sexual function in men with prostate cancer undergoing treatment,[54,55] although exercise resulted in maintenance of sexual activity levels.[56] Nevertheless, exercise may appear to be a potentially promising intervention to address sexual dysfunction in prostate cancer patients via protective or restorative effects on vascular function.[57]

Psychological distress is also a significant issue in men with prostate cancer and related treatment side effects.[58,59] Furthermore, higher levels of depressive symptoms have been associated with decreased physical activity and a lower likelihood of meeting the recommendations of national physical activity guidelines.[60] Among the studies assessed in this systematic review, depressive symptoms and sleep variables such as daytime sleepiness, insomnia, and sleep quality were not affected by the exercise interventions. However, treatment of patients with radiation therapy only has been associated with a lower risk of depression compared with ADT in men treated for recurrent prostate cancer,[61] thus the potential benefit of exercise may have been too small to detect in the investigated patient population, given the presumably relatively low level of depressive symptoms present. Indeed, symptoms of psychological distress improved the most after exercise in patients with prostate cancer receiving ADT who experienced the highest level of anxiety, depression, and somatization.[62] Moreover, a reduction in psychological distress was achieved with various supervised exercise modalities, including aerobic exercise, resistance training, and impact loading.[62]

Based on the analysis from this systematic review, it was not possible to provide specific exercise recommendations for prostate cancer patients during radiation therapy regarding select outcomes; however, general exercise guidelines for patients affected by cancer include evidence-based recommendations and specific exercise prescriptions for a number of outcomes such as fatigue, depressive symptoms, or physical function.[8,9] Nevertheless, it is recommended that an individualized assessment and exercise prescription process be adopted.[9] In general, a multimodal, moderate to high intensity exercise program will be appropriate, although individual patient circumstances, including any accompanying health issues and exercise-related patient preferences and goals, should be considered and exercise prescriptions adapted accordingly.[9]

This review has some limitations that are worthy of comment. Owing to the small number of studies assessing specific domains of physical function as well as the heterogeneity of assessment tools used for patient-reported outcomes, there is considerable heterogeneity in the quantitative analysis of the results, thus reducing the robustness of the findings. We also acknowledge that some treatment-related side effects could be due to either radiation therapy, ADT, or both, thus prohibiting an analysis of how exercise may affect side effects purely arising as a consequence of radiation. Furthermore, considerable variability existed regarding the exercise prescription across studies, preventing recommendations of a specific intervention for select outcomes. However, the strength of this review is the comprehensive assessment of current evidence regarding the effects of exercise on unfavorable physical, psychological, and psychophysical outcomes commonly experienced by men with prostate cancer currently receiving radiation therapy that may affect their quality of life and wellbeing.

The lack of conclusive evidence for patient-reported outcomes may partially result from severe side effects of treatment being rare and population summary statistics therefore not reflecting any changes in subgroups with significant toxicity. Even small reductions of these significant toxicities by exercise would be valuable and worthwhile to investigate in exploratory analyses of future trials. We suggest that investigators consider including toxicity outcomes of subgroups with moderate-to-severe or significant side effects in their reports (eg, as supplementary material) in addition to reporting summary scores for the entire study population or individual intervention groups. Given that minor toxicity is irrelevant and moderate-to-severe toxicity is uncommon, a classification like this may provide valuable insight into the data, and investigators should use this philosophy when they design their studies. A classification like this may also allow comparability of endpoints between different assessment tools to some degree, as they are now "normalized" on a categorical level. Furthermore, reporting of prostate cancer-specific endpoints such as bladder and bowel problems or potency issues is heavily influenced by the timepoints at which they are collected. Given that these side effects get worse and may then improve again, it is paramount that researchers sample them at the correct and equivalent timepoints to prevent the collection of potentially misleading data that does not allow meaningful conclusions about a potential benefit of exercise.

In conclusion, exercise during radiation therapy was safe for prostate cancer patients in the included studies as evident by low rates of adverse events and resulted in significant improvements in physical function and mitigation of urinary symptoms, while not negatively affecting other treatment toxicity outcomes such as intestinal symptoms, depression, and sleep. On this basis, prostate cancer patients should be informed about existing exercise programs and should be encouraged to participate in regular structured exercise training as part of supportive care during treatment. However, further high-quality studies are required to expand this field of enquiry and better understand the potential benefits of exercise during radiation therapy and how it may counter treatment-related adverse effects. One such example is the currently ongoing EXERT trial for men with metastatic prostate cancer receiving palliative radiation therapy (ClinicalTrials.gov: NCT04556045). Future research may also investigate how the timing of exercise (ie, during vs after radiation therapy) or different exercise prescriptions (eg, comparing different exercise modalities and intensities) may affect treatment toxicity, including assessment of long-term follow-up of side effects as well as potential mechanisms of action for exercise as an adjunct therapy during radiation therapy in patients with prostate cancer.[63]

References

1. De Ruysscher D, Niedermann G, Burnet NG, Siva S, Lee AWM, Hegi-Johnson F. Radiotherapy toxicity. *Nat Rev Dis Primers* 2019;5:13.
2. Thariat J, Hannoun-Levi JM, Sun Myint A, Vuong T, Gerard JP. Past, present, and future of radiotherapy for the benefit of patients. *Nat Rev Clin Oncol* 2013;10:52–60.
3. Fosså SD, Woehre H, Kurth KH, et al. Influence of urological morbidity on quality of life in patients with prostate cancer. *Eur Urol* 1997;31(suppl 3):3–8.
4. Orom H, Biddle C, Underwood 3rd W, Nelson CJ. Worse urinary, sexual and bowel function cause emotional distress and vice versa in men treated for prostate cancer. *J Urol* 2018;199:1464–1469.
5. Kennedy MA, Bayes S, Galvão DA, et al. If you build it, will they come? Evaluation of a co-located exercise clinic and cancer treatment centre using the RE-AIM framework. *Eur J Cancer Care* 2020;29:e13251.
6. Newton RU, Kennedy MA, Singh F, et al. Safety, effectiveness, and uptake of exercise medicine integrated within a cancer care center. *Semin Oncol Nurs* 2020;36 151073.
7. Fuller JT, Hartland MC, Maloney LT, Davison K. Therapeutic effects of aerobic and resistance exercises for cancer survivors: A systematic review of meta-analyses of clinical trials. *Br J Sports Med* 2018; 52:1311.
8. Campbell KL, Winters-Stone KM, Wiskemann J, et al. Exercise guidelines for cancer survivors: Consensus statement from international multidisciplinary roundtable. *Med Sci Sports Exerc* 2019;51: 2375–2390.
9. Hayes SC, Newton RU, Spence RR, Galvão DA. The Exercise and Sports Science Australia position statement: Exercise medicine in cancer management. *J Sci Med Sport* 2019;22:1175–1199.
10. Horgan S, O'Donovan A. The impact of exercise during radiation therapy for prostate cancer on fatigue and quality of life: A systematic review and meta-analysis. *J Med Imaging Radiat Sci* 2018;49:207–219.
11. Clark JA, Inui TS, Silliman RA, et al. Patients' perceptions of quality of life after treatment for early prostate cancer. *J Clin Oncol* 2003;21:3777–3784.
12. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. *PLoS Med* 2009;6 e1000100.
13. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6 e1000097.
14. Maher CG, Sherrington C, Herbert RD, Moseley AM, Elkins M. Reliability of the PEDro scale for rating quality of randomized controlled trials. *Phys Ther* 2003;83:713–721.
15. Cashin AG, McAuley JH. Clinimetrics: Physiotherapy Evidence Database (PEDro) scale. *J Physiother* 2020;66:59.
16. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. Cochrane Handbook for Systematic Reviews of Interventions, version 6.2 (updated February 2021). Available at: www.training.cochrane.org/handbook. Accessed June 3, 2021.
17. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. Independent subgroups within a study. In: Borenstein M, Hedges LV, Higgins JPT, Rothstein HR, eds. *Introduction to Meta-Analysis*. Hoboken, NJ: Wiley; 2009:217–223.
18. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. Multiple outcomes or time-points within a study. In: Borenstein M, Hedges LV, Higgins JPT, Rothstein HR, eds. *Introduction to Meta-Analysis*. Hoboken, NJ: Wiley; 2009:225–238.
19. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177–188.
20. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–560.
21. Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: A practical tutorial. *Evid Based Ment Health* 2019;22:153–160.
22. Harrer M, Cuijpers P, Furukawa T, Ebert DD. dmetar: companion R package for the guide 'Doing Meta-Analysis in R'. Available at: http://dmetar.protectlab.org/. Accessed June 3, 2021.
23. Hojan K, Kwiatkowska-Borowczyk E, Leporowska E, Milecki P. Inflammation, cardiometabolic markers, and functional changes in men with prostate cancer: A randomized controlled trial of a 12-month exercise program. *Pol Arch Intern Med* 2017;127:25–35.
24. Hojan K, Kwiatkowska-Borowczyk E, Leporowska E, et al. Physical exercise for functional capacity, blood immune function, fatigue, and quality of life in high-risk prostate cancer patients during radiotherapy: A prospective, randomized clinical study. *Eur J Phys Rehabil Med* 2016;52:489–501.
25. Windsor PM, Nicol KF, Potter J. A randomized, controlled trial of aerobic exercise for treatment-related fatigue in men receiving radical external beam radiotherapy for localized prostate carcinoma. *Cancer* 2004;101:550–557.
26. Monga U, Garber SL, Thornby J, et al. Exercise prevents fatigue and improves quality of life in prostate cancer patients undergoing radiotherapy. *Arch Phys Med Rehabil* 2007;88:1416–1422.
27. Piraux E, Caty G, Renard L, et al. Effects of high-intensity interval training compared with resistance training in prostate cancer patients undergoing radiotherapy: A randomized controlled trial. *Prostate Cancer Prostatic Dis* 2021;24:156–165.
28. Segal RJ, Reid RD, Courneya KS, et al. Randomized controlled trial of resistance or aerobic exercise in men receiving radiation therapy for prostate cancer. *J Clin Oncol* 2009;27:344–351.
29. McQuade JL, Prinsloo S, Chang DZ, et al. Qigong/tai chi for sleep and fatigue in prostate cancer patients undergoing radiotherapy: A randomized controlled trial. *Psychooncology* 2017;26:1936–1943.
30. Kapur G, Windsor PM, McCowan C. The effect of aerobic exercise on treatment-related acute toxicity in men receiving radical external beam radiotherapy for localised prostate cancer. *Eur J Cancer Care* 2010;19:643–647.
31. Galvão DA, Taaffe DR, Spry N, Newton RU. Exercise can prevent and even reverse adverse effects of androgen suppression treatment in men with prostate cancer. *Prostate Cancer Prostatic Dis* 2007;10:340–346.
32. Sherrington C, Whitney JC, Lord SR, Herbert RD, Cumming RG, Close JC. Effective exercise for the prevention of falls: A systematic review and meta-analysis. *J Am Geriatr Soc* 2008;56:2234–2243.
33. Beck BR, Daly RM, Singh MA, Taaffe DR. Exercise and Sports Science Australia (ESSA) position statement on exercise prescription for the prevention and management of osteoporosis. *J Sci Med Sport* 2017;20:438–445.
34. Hussain A, Tripathi A, Pieczonka C, et al. Bone health effects of androgen-deprivation therapy and androgen receptor inhibitors in patients with nonmetastatic castration-resistant prostate cancer. *Prostate Cancer Prostatic Dis* 2021;24:290–300.
35. Verweij NM, Schiphorst AH, Pronk A, van den Bos F, Hamaker ME. Physical performance measures for predicting outcome in cancer patients: A systematic review. *Acta Oncol* 2016;55:1386–1391.
36. Jereczek-Fossa BA, Marsiglia HR, Orecchia R. Radiotherapy-related fatigue. *Crit Rev Oncol Hematol* 2002;41:317–325.
37. Yang S, Chu S, Gao Y, et al. A narrative review of cancer-related fatigue (CRF) and its possible pathogenesis. *Cells* 2019;8:738.
38. Jacobsen PB, Thors CL. Fatigue in the radiation therapy patient: Current management and investigations. *Semin Radiat Oncol* 2003;13:372–380.
39. Vordermark D, Schwab M, Flentje M, Sailer M, Kölbl O. Chronic fatigue after radiotherapy for carcinoma of the prostate: correlation with anorectal and genitourinary function. *Radiother Oncol* 2002;62:293–297.
40. Bøhn SH, Fosså SD, Wisløff T, Thorsen L. Physical activity and associations with treatment-induced adverse effects among prostate cancer patients. *Support Care Cancer* 2019;27:1001–1011.

41. Thomas RJ, Holm M, Williams M, et al. Lifestyle factors correlate with the risk of late pelvic symptoms after prostatic radiotherapy. *Clin Oncol* 2013;25:246–251.
42. Gross MD, Al Hussein Al Awamlh B, Hu JC. Assessing treatment-related toxicity using administrative data, patient-reported outcomes, or physician-graded toxicity: Where is the truth? *Semin Radiat Oncol* 2019;29:333–337.
43. Cella D, Nichol MB, Eton D, Nelson JB, Mulani P. Estimating clinically meaningful changes for the Functional Assessment of Cancer Therapy-Prostate: Results from a clinical trial of patients with metastatic hormone-refractory prostate cancer. *Value Health* 2009;12:124–129.
44. Dieperink KB, Johansen C, Hansen S, et al. The effects of multidisciplinary rehabilitation: RePCa-a randomised study among primary prostate cancer patients. *Br J Cancer* 2013;109:3005–3013.
45. Dieperink KB, Hansen S, Wagner L, Minet LR, Hansen O. Long-term follow-up 3 years after a randomized rehabilitation study among radiated prostate cancer survivors [e-pub ahead of print]. J Cancer Surviv. doi: 10.1007/s11764-020-00958-9, accessed February 4, 2021.
46. Braga-Basaria M, Dobs AS, Muller DC, et al. Metabolic syndrome in men with prostate cancer undergoing long-term androgen-deprivation therapy. *J Clin Oncol* 2006;24:3979–3983.
47. Gacci M, Russo GI, De Nunzio C, et al. Meta-analysis of metabolic syndrome and prostate cancer. *Prostate Cancer Prostatic Dis* 2017; 20:146–155.
48. Holmes JA, Anderson RF, Hoffman LG, et al. Cardiovascular preventive care and coordination of care in prostate cancer survivors: A multi-institutional prospective study. *Int J Radiat Oncol Biol Phys* 2019;103:112–115.
49. Leong DP, Fradet V, Shayegan B, et al. Cardiovascular risk in men with prostate cancer: insights from the RADICAL PC study. *J Urol* 2020;203:1109–1116.
50. Zaorsky NG, Shaikh T, Ruth K, et al. Prostate cancer patients with unmanaged diabetes or receiving insulin experience inferior outcomes and toxicities after treatment with radiation therapy. *Clin Genitourin Cancer* 2017;15:326–335 e3.
51. Pedersen BK, Saltin B. Evidence for prescribing exercise as therapy in chronic disease. *Scand J Med Sci Sports* 2006;16(suppl 1):3–63.
52. Pedersen BK, Saltin B. Exercise as medicine - evidence for prescribing exercise as therapy in 26 different chronic diseases. *Scand J Med Sci Sports* 2015;25(suppl 3):1–72.
53. Dahn JR, Penedo FJ, Molton I, Lopez L, Schneiderman N, Antoni MH. Physical activity and sexual functioning after radiotherapy for prostate cancer: Beneficial effects for patients undergoing external beam radiotherapy. *Urology* 2005;65:953–958.
54. Galvão DA, Taaffe DR, Chambers SK, et al. Exercise intervention and sexual function in advanced prostate cancer: A randomised controlled trial [e-pub ahead of print]. BMJ Support Palliat Care. doi:10.1136/bmjspcare-2020-002706, accessed March 9, 2021.
55. Schumacher O, Galvão DA, Taaffe DR, et al. Effect of exercise adjunct to radiation and androgen deprivation therapy on patient-reported treatment toxicity in men with prostate cancer: A secondary analysis of 2 randomized controlled trials. *Pract Radiat Oncol* 2021;11:215–225.
56. Cormie P, Newton RU, Taaffe DR, et al. Exercise maintains sexual activity in men undergoing androgen suppression for prostate cancer: A randomized controlled trial. *Prostate Cancer Prostatic Dis* 2013; 16:170–175.
57. Vear NK, Coombes JS, Bailey TG, Skinner TL. The interplay between vascular function and sexual health in prostate cancer: The potential benefits of exercise training. *Med Sci* 2020;8:11.
58. Couper JW, Love AW, Dunai JV, et al. The psychological aftermath of prostate cancer treatment choices: A comparison of depression, anxiety and quality of life outcomes over the 12 months following diagnosis. *Med J Aust* 2009;190:S86–S89.
59. Saini A, Berruti A, Cracco C, et al. Psychological distress in men with prostate cancer receiving adjuvant androgen-deprivation therapy. *Urol Oncol* 2013;31:352–358.
60. Chipperfield K, Fletcher J, Millar J, et al. Factors associated with adherence to physical activity guidelines in patients with prostate cancer. *Psychooncology* 2013;22:2478–2486.
61. Thomas HR, Chen MH, D'Amico AV, et al. Association between androgen deprivation therapy and patient-reported depression in men with recurrent prostate cancer. *Clin Genitourin Cancer* 2018;16:313–317.
62. Galvão DA, Newton RU, Chambers SK, et al. Psychological distress in men with prostate cancer undertaking androgen deprivation therapy: Modifying effects of exercise from a year-long randomized controlled trial [e-pub ahead of print]. Prostate Cancer Prostatic Dis. doi: 10.1038/s41391-021-00327-2, accessed March 16, 2021.
63. Schumacher O, Galvão DA, Taaffe DR, Chee R, Spry N, Newton RU. Exercise modulation of tumour perfusion and hypoxia to improve radiotherapy response in prostate cancer. *Prostate Cancer Prostatic Dis* 2021;24:1–14.