Title

Exercise for men with prostate cancer: a systematic review and meta-analysis.

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Abstract

Context: Exercise for prostate cancer survivors could be beneficial. However, no systematic review across cancer stages and treatment types addressing potential benefits and harms exists to date.

Objectives: Primarily, to assess the effects of exercise on cancer specific quality of life and adverse events in prostate cancer trials.

Evidence acquisition: We searched the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, AMED, CINAHL, PsycINFO, SPORTDiscus and PEDro. We also searched grey literature databases, including trials registers. Searches were from database inception to March 2015. Standardised mean differences (SMD) were calculated for meta-analysis.

Evidence synthesis: We included 16 RCTs involving 1574 men with prostate cancer. Follow-up varied from just eight weeks to 12months. RCTs involved men with stages I-IV cancers. High risk of bias was frequently due to attrition and intervention adherence. Seven trials involving 912 men measured cancer specific quality of life. No significant effect on this outcome was found from pooling the data from these seven trials (SMD = 0.13, 95% CI = -0.08, 0.34, median follow-up 12 weeks). Sensitivity analysis of studies that were judged to be of high quality indicated a moderate positive effect estimate (SMD = 0.33, 95% CI = 0.08, 0.58, median follow-up 12 weeks). Similar beneficial effects were seen in cancer specific fatigue, submaximal fitness and lower body strength. We found no evidence of benefit for disease progression, cardiovascular health or sexual function. There were no deaths attributable to exercise interventions. Other serious adverse events (e.g. myocardial infarction) were equivalent to those seen in controls.

Conclusions: These results support exercise interventions for improving cancer specific quality of life, cancer specific fatigue, submaximal fitness and lower body strength.

Patient summary: This review shows that exercise or physical activity interventions can improve quality of life, fatigue, fitness and function for men with prostate cancer.

1. Background

Prostate cancer is the primary cause of years lived with cancer disability in the Americas, North-western European, Australia and New Zealand and much of sub-Saharan Africa.[1] Management of prostate cancer, ranges from no intervention (active surveillance or watchful waiting) to radical local treatment (prostatectomy and radiation therapy) with or without combined androgen deprivation therapy (ADT), ADT alone, to taxane-based chemotherapy for progressive castration-resistant disease [2] and second line hormone agents. [3, 4] First-line radical treatment for prostate cancer can negatively impact quality of life (e.g. erectile dysfunction, incontinence, radiation proctitis), as can ADT (e.g. loss of muscle mass, fatigue, psychological morbidity, increased cardiovascular and bone fracture risk). [5, 6] Direct symptoms from advanced or metastatic cancer (e.g. pain, hypercalcaemia, spinal cord compression, pathological fractures) can also adversely affect health. [7, 8]

Several recent systematic reviews have examined the effects of exercise in cancer survivors, in terms of quality of life outcome [9, 10], exercise behaviour [11] and effects on fatigue. [12] These reviews are an amalgamation of heterogeneous primary cancers. Indeed, most evidence comes from trials in breast cancer and as such cannot be generalised to men with prostate cancer. Further, exercise therapy appears beneficial in the short term, but little is known about dose, duration and longer-term effects of such therapy, including adverse effects over an extended follow-up. Finally, despite the potential health benefits for men with prostate cancer, few clinicians are aware of the role of exercise, and in many cases it goes un-prescribed. The aim of this review was primarily to evaluate the effect of exercise interventions on cancer specific quality of life after prostate cancer diagnosis and assess adverse effects.

2. Evidence acquisition

Methods for this systematic review have been described in detail elsewhere.[13] Briefly, the primary review outcomes were quality of life and adverse events. Secondary outcomes include the effect on fatigue, disease progression, cardiovascular health, physical fitness/function and sexual function. We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, AMED, CINAHL, PsycINFO, SPORTDiscus and PEDro databases from inception to March 31st 2015. We expanded the database search by attempting to identify unpublished studies and references in the grey literature (i.e. via the OpenGrey database). We also searched the WHO trials page and the ISRCTN meta-Register of Controlled Trials and ClinicalTrials.gov.

2.1 Inclusion / exclusion criteria

We included only randomised controlled trials (RCTs) involving adults. Participants in these trials must have been diagnosed with prostate cancer. Only interventions that included a component targeted at increasing aerobic exercise and/or resistance exercise behaviour compared with a usual care or 'waiting list' control group with at least six weeks of follow-up (from trial baseline assessment) were included in this review. We excluded trials that address recovery of continence only. Investigators must have reported frequency, duration and intensity of aerobic exercise behaviour, or frequency, intensity, type, sets and repetitions of resistance exercise behaviour as prescribed in the intervention.

2.2 Data extraction

After extraction piloting, three review authors worked independently (LB, DS and AC) to screen all titles and abstracts identifying records that met the inclusion criteria, or that could not be safely excluded without assessment of the full text (e.g. when no abstract was available). Disagreements at this stage were resolved by discussion with another review author (DJR). Full-text articles for these records were retrieved. After training to ensure a consistent approach to study assessment and data

abstraction, three review authors worked independently (LB, DS and AC) to assess the retrieved full-text articles. We documented the selection process in a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) study flow diagram.[14]

Review authors did not conduct data extraction from any primary studies for which they have been listed as an author. Data were entered into the statistical software of The Cochrane Collaboration, Review Manager (RevMan 5) for calculation of meta-analyses. We contacted study authors to request information that was missing from reports of included studies (where appropriate).
Risks of bias was assessed using The Cochrane Collaboration tool. [15] Two of three review authors (LB, DS and AC) applied the risk of bias tool independently to each study. Differences were resolved by discussion or by appeal to a third review author (DJR). Review authors who were authors of included studies did not perform risk of bias assessment for studies that they had authored. We summarised results in a risk of bias summary figure.

2.3 Data synthesis

If data were sufficient and if it was appropriate to do so, we performed a meta-analysis. Meta-analysis was performed by LB using Review Manager software. RH performed I^2 calculations in STATA. If statistical heterogeneity was noted, meta-analysis were performed using a random-effects model. Fixed-effect models were used only if no significant statistical heterogeneity were present. We noted the time points at which outcomes were collected and reported. If adverse effects data were insufficient, or if meta-analysis were determined not to be appropriate, we provided a narrative synthesis.

For continuous outcomes (e.g. cancer-specific quality of life), we extracted the point estimate for the measure of central tendency for the final value of the outcome of interest and the number of

participants assessed at stated follow-up in each treatment arm to estimate the standardised mean difference (SMD) between treatment arms and its 95% confidence interval (CI).

2.4 Unit of analysis issues

We did not include cross-over trials in this review because of the difficulty involved in 'washing out' behaviour change interventions. For trials with multiple intervention groups, we first eliminated groups for which the intervention did not meet the criteria for inclusion in the review; we then combined all relevant intervention groups to create a single pair-wise comparison with the control group.

2.5 Assessment of heterogeneity

We used clinical expertise to judge whether it was appropriate to combine trials in a meta-analysis. Consistency of results was assessed using the I^2 statistic and, its 95% confidence limits. Data were analysed using RevMan and Stata 12 (RevMan; Stata).

2.6 Sensitivity analysis

Results of meta-analyses were interpreted in light of the findings with respect to risk of bias. Risk of bias is assessed for each follow-up, and for the sensitivity analysis we used the longest follow-up for which there is low risk of bias. We contacted study authors for additional information or for further clarification of study methods if any doubt arose regarding sources of bias (where appropriate).

2.7 Sub-group analysis

If a sufficient number of studies were identified, and if resolution of reporting is adequate, we performed subgroup analyses. These were: anticancer treatment received, cancer stage, obesity , previously physically active participants at baseline, explanatory (efficacy) versus pragmatic (effectiveness) trial designs. We categorised interventions according to theoretical basis; behaviour

change techniques and categorisation using the Coventry, Aberdeen & London-Refined (CALO-RE) taxonomy.[14]

3. Results

3.1 Results of the search

Figure 1 illustrates the results of the literature searches and screening process for the review. We identified 4356 unique records from database searches and 22 manuscripts through grey literature and hand checking of references from included studies and related systematic reviews[16, 17]. After reviewing by title and abstract we further evaluated 91 records by full text, after which, 67 studies were excluded from the review. All full text manuscripts were available in English. We sent 31 emails requesting further information to published manuscripts, we received 4 responses (only one of which provided new data).

3.2 Included studies

We included 16 RCTs (please see Table 1 for descriptions) [18-33] including 1574 men with prostate cancer (sample size range 423 to 20). We also found eight linked secondary analysis manuscripts.[34-41] All studies were randomised at the patient level. Follow-up varied from just eight weeks to 12 months. RCTs involved men with stages I-IV cancers but no trials were found in men exclusively undergoing chemotherapy (two trials included a small proportion of men who had chemotherapy) [26, 33]. Exercise interventions were either supervised [22, 27, 29-31], home-based [21, 24, 32], a mix of supervised and home-based [18, 23, 25, 33], supervised with suggested home-based activity [19, 20] and two were unclear.[26, 28] Exercise behaviour (dose) was monitored using objective [22, 29-32], subjective [24, 26], a mixture of objective or subjective methods[18, 23, 25, 33], was not monitored [21] or was unclear. [19, 20, 27, 28] All trials included a usual care comparator. Two trials supplemented usual care with standard exercise advice for cancer survivors.[23, 26] As our previous

Cochrane review[11] has demonstrated that simple advice is highly unlikely to improve exercise behaviour, we judged these studies were eligible for inclusion.

The behaviour change techniques used primarily focused on instruction on how to perform behaviour with practice and goals set by trainers. Three trials[18, 21, 26] reported a more psychological approach to changing behaviours by incorporating techniques such as problem solving, social support and client set goals. Of interest in comparison to our previous review, significantly more studies reported that they taught generalisation of behaviour, however, association with outcome was not possible in this review due to small numbers of studies per outcome. All studies were conducted in countries categorised as 'high income' by the WHO.

3.3 Risk of bias and quality of included studies

Figure 2 illustrates risk of bias judgements made for included studies. Online supplement 1 describes the detail of risk of bias judgements. All trials were judged to have a high risk of bias for blinding of participants given that it is not possible to blind the participant in an exercise intervention. We did not, however, judge that this necessarily compromised study quality. The most common issues around high risk of bias that would impact on study quality were level of study attrition during at least one follow-up point, poor intervention adherence, lack of investigator blinding and selective reporting bias.

3.4 Effects of interventions on primary review objectives

Seven trials involving 912 men measured cancer specific quality of life using a tool that gave an overall/summary score that could be entered into a meta-analysis. [18, 22, 25-27, 29, 30] No significant effect on this outcome was found from pooling the data from these seven trials (SMD = 0.13, 95% CI = -0.08, 0.34). No statistical heterogeneity was observed (I^2 = 46%, 95% CI = 0 to 76). Sensitivity analysis of studies that were judged to be of high quality[18, 22, 30] (NB Bourke 2014

three month follow-up data was used) indicated a moderate positive effect estimate (SMD = 0.33, 95% CI = 0.08, 0.58) with no significant heterogeneity (I^2 = 0%, 95% CI = 0, 73). Please see Figure 3 for forest plot.

Ten studies reported information on adverse events involving 685 men. Four studies reported no adverse events. [20, 22, 28, 33] Two studies reported deaths, one due to lung cancer [23] and one in the control arm of the trial.[18] One incidence of acute MI (no previous cardiac history) was reported requiring hospitalisation and resuscitation after only the third day of the aerobic training protocol.[30] In the Galvão 2014 trial, one participant in the control group with no previous history of cardiac disease had a nonfatal myocardial infarction during the second half of the study but had a full recovery. One study reported three incidences of adverse ECG changes during exercise testing, reflected by significant ST segment depression in 3 patients. [25] One study reported two incidences of fractures of the fibula in the intervention group [31] with one of the occurrences revealing underlying peripheral neuropathy. One study described an incident where one man in the exercise group fell while dressing at home and suffered a fractured rib [19] but was able to complete the final 2 weeks of the intervention with a modified prescription. Three studies reported mixed musculo-skeletal complications from pre-existing back and knee pain [23], training-induced leg cramps or back pain [25] and three incidences of minor tendon/ligament/quadriceps injury [31] with exercise.

3.5 Secondary review outcomes

Positive beneficial effects were seen on cancer specific fatigue, lower body strength and aerobic fitness. Please see online supplement 2 for details of secondary review outcomes meta-analysis. No effect was seen on cardiovascular health or disease progression outcomes. A borderline positive effect was seen on sexual activity (P=0.05) but no effect on sexual function.

3.6 Planned sub-group analysis and CALO-RE behaviour change technique taxonomy.

Please see online supplement 3 for planned sub-group outcomes and the results of the CALO-RE taxonomy data.

4. Discussion

Sixteen trials involving 1574 men with prostate cancer were included in the review. From sensitivity analysis, we found high quality evidence that exercise interventions can improve cancer specific quality of life and cancer specific fatigue in men with prostate cancer at up to six months of follow-up (with moderate beneficial effect estimate). There were no deaths attributable to exercise interventions. Other serious adverse events as a result of exercise (e.g. MI) were equivalent to those seen in controls. In one trial which used a competitive, contact sport as the intervention (football) a high rate of lower limb fracture was seen in the intervention arm. More frequently, soft tissue complications such as minor musculo-skeletal sprains and strains were reported from intervention groups in more controlled settings. No effect was seen on cardiovascular health or disease progression outcomes. Positive beneficial effects were seen on lower body strength alongside positive effects on aerobic fitness. A borderline positive effect was seen on sexual activity, but this should be viewed with caution as these data are taken from two small trials.

We specifically only selected trials for this review which report key metrics of exercise prescription in order to support reproducibility. In doing so we have synthesised 11 more RCTs than a recent systematic review. [17] Further, to the authors knowledge, this is the first review to have been able to report quantified meta-analysis of effect estimates around key patient related outcomes such as cancer specific quality of life and fatigue. Our review offers the most up to date evidence on adverse effects systematically gathered from an exhaustive review of RCTs. Our meta-analysis of improvements in sexual activity is unique but should be interpreted with caution as data are taken from just two available trials.

Much of the uncertainty in judging trial bias came from poor reporting around randomisation procedures, both sequence generation and allocation concealment: however no trials were judged to be at high risk of bias. As with other systematic reviews our group has undertaken in exercise and cancer populations [11], we have not penalised trials for being at high risk of performance bias for blinding of participants. Further, bias is not likely as trials with poor adherence to the exercise intervention, commonly produce no effect on clinical outcomes.[24, 26] It is not possible to blind participants to taking part in an exercise intervention. Some trials have suggested this should be addressed by "sham" exercise conditions. However, given that aerobic exercise recommendation guidelines for survivors are not only freely available on the web (e.g. from the American Cancer Society) but are also often positively promoted by care providers and cancer support charities (e.g.Macmillan), the legitimacy of any "sham" condition seems dubious.

Like any behaviour change intervention, requiring participants to maintain exercise behaviour can be very challenging and lead to issues with retention and adequate 'dose' of the intervention, actually being received. The majority of the reasons trials were judged to have a high risk of bias was due to attrition and adherence biases, which we judged would have a substantial impact on the quality of evidence. Selective reporting biases - particularly with regards to adverse events - was the other most prevalent issue.

Three studies reported data on up to 12months of follow-up [23, 25, 33], however all were judged to be at high risk of bias. As such to harmonise where possible with other high quality evidence, we only extracted six month data for use in meta-analyses. As such, long term durability of some of the key findings of this review, are uncertain. The studies reported here are very often a mixture of T stage cancers, with some studies e.g. [29, 30] including T 1-4 men. This limits the certainty to which we are able to make recommendations, stratified by disease stage (indeed we were not able to conduct planned sub-group analysis). This is also true in regards to treatment type, although, several

meta-analyses of high quality studies are largely representative of men on ADT. High quality studies of men with earlier stages of disease undergoing radical treatment are required. No evidence was found for men undergoing chemotherapy (apart from a very small minority of the cohort in two trials)[26, 33] and further, it is not clear what value exercise interventions have in men on newer hormone treatments e.g. Enzalutamide. Also, we did not find any evidence of men undergoing more recent radical innovations such as HIFU.

All studies were taken from peer reviewed journals as we were unable to locate any unpublished results, despite contacting internationally recognised experts in the field. We found some evidence that exercise might have a beneficial impact on sexual activity, but in the absence of concurrent improvements in sexual function, the value of this finding to patients is uncertain. It should also be noted that the majority of these interventions took place in a controlled environment.

All studies were conducted in countries classified as high income by the WHO taxonomy. No evidence was derived from developing countries, and it is uncertain whether the resources and/or infrastructure required for some of the interventions included in this review would be available in these other parts of the world. Very few trials reported baseline ethnicity data, but what was available seems to indicate the large majority of studies involve Caucasian men. Given prostate cancer disproportionally effects other ethnic groups e.g. black men, it should be noted that these men are underrepresented in these trials. We were not able to identify any trials that satisfied our pragmatic design criteria, and as such these data should be considered to address efficacy of these interventions rather than effectiveness in health services. Our review objective to assess the effect of exercise interventions on disease progression was difficult to achieve. We were only able to undertake a synthesis of PSA data measured as a secondary outcome in underpowered trials. This finding should be viewed with much caution. Trials that evaluate the impact of exercise on dichotomous outcomes such as progression-free survival or overall mortality would be an excellent addition to the field.

The mechanisms whereby exercise interventions improve cancer specific quality of life remain speculative. It was beyond the scope of this review to undertake any formal analysis of mechanisms. Improvements in fatigue, lower limb function and exercise capacity are potentially occurring due to well established adaptations associated with exercise training, such as improvements in cardiac output, metabolic adaptations, skeletal muscle motor unit recruitment etc. Exercise has also been linked to improving negative physiological changes associated with advanced cancer such as cachexia. [42] To what extent this contributes to improved physical functioning and QoL is uncertain. A substantive psychological benefit related to empowerment and self-efficacy could be a factor. Formal mediator and moderator studies would be useful to address this uncertainty. A number of studies included dietary interventions as part of a lifestyle intervention. Although not formally analysed, most studies reported minimal impact on dietary outcomes, thus suggesting the predominant effector in the intervention was the exercise component.

The key recommendations from this review are that treating clinicians and guidelines bodies should be cognisant that there is level 1 evidence that exercise interventions are efficacious for improving cancer specific quality of life, fatigue, and exercise capacity in men with prostate cancer. Much of the high quality evidence comes from trials involving men on ADT. There is very early evidence (which should be interpreted with caution, owing to limited number of trials) that exercise could also be useful for improving sexual activity. Trials are ongoing to look at these outcomes.[43] Any exercise programme should be individually tailored and work with the individuals physical capabilities and limitations.[11] The treating clinician should play a role in directly advocating the benefits of exercise to men with prostate cancer and leading the multidisciplinary team in the referral process. Where possible, men should be sign-posted to relevant exercise referral schemes e.g. in the community. Ideally, behavioural change support should also be offered to maximise adherence and also include periodic re-evaluation of exercise prescription, either in terms of

tapering or progression. Effectiveness and cost-effectiveness data for these interventions when integrated into health care services would be informative.

5. Conclusions

There is level 1 evidence that exercise interventions are efficacious for improving cancer specific quality of life, fatigue, and exercise capacity in men with prostate cancer. The high quality evidence comes mainly from men on ADT with advanced disease. Adverse events such as minor soft tissue injuries (sprains and strains) can be expected in a minority of men but can also be mitigated by properly tailored exercise prescription and progression around individual capabilities / existing co-morbidities. We found no evidence that exercise improved cardiovascular health but we were limited to synthesising evidence around blood pressure only. Effectiveness and cost-effectiveness data for these interventions when integrated into health care services would be informative.

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Author contributions

Liam Bourke had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Bourke, Rosario.

Acquisition of data: Bourke, Amed

Analysis and interpretation of data: Bourke, Smith, Steed, Hooper, Rosario.

Drafting of the manuscript: Bourke

Critical revision of the manuscript for important intellectual content: Bourke, Smith, Steed, Hooper, Carter, Catto, Albertsen, Tombal, Payne, Rosario

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Figure legends:

Figure 1: PRISMA flow diagram of results

Figure 2: Risk of bias graph for included trials.

Figure 3: Figure 3. Forrest plot of quality of life outcomes from included trials (A) and sensitivity analysis (B)

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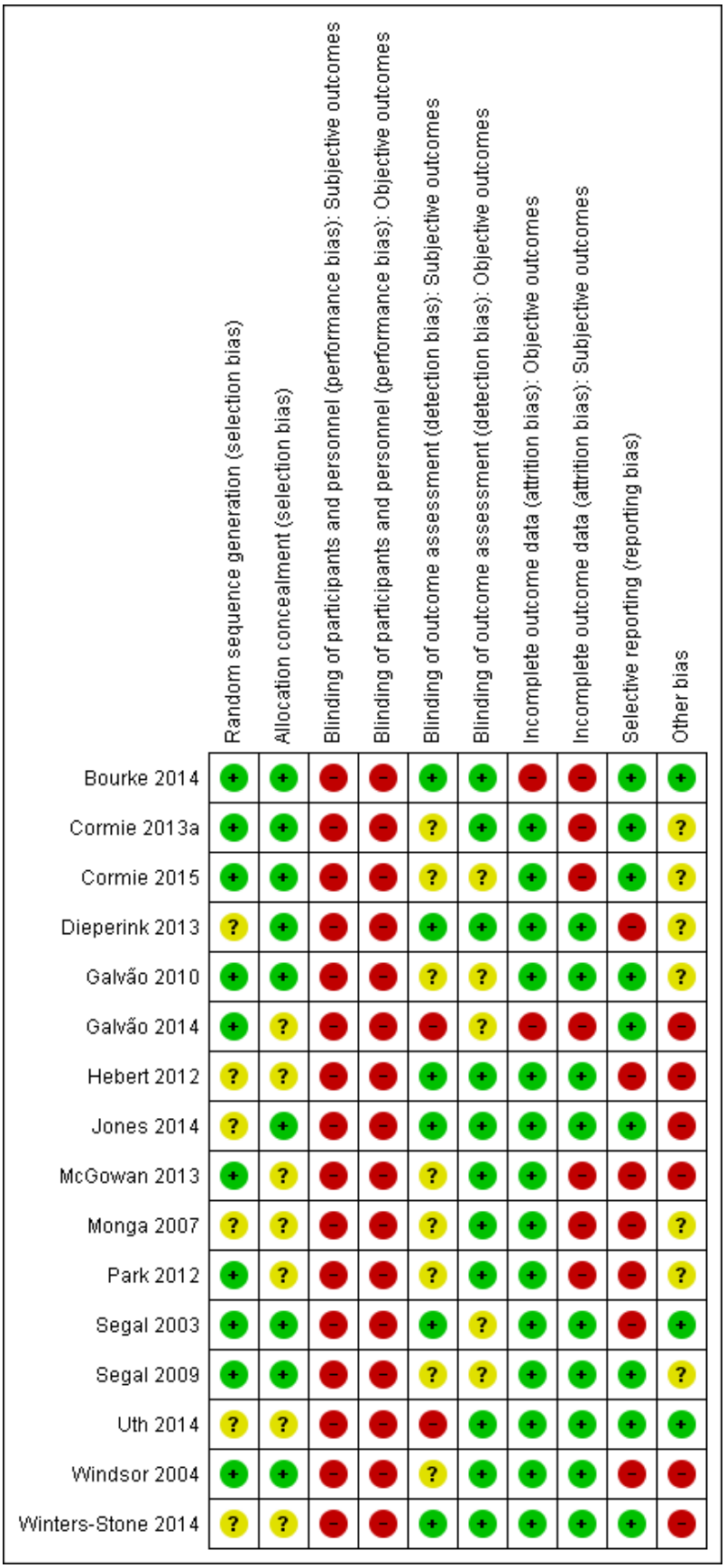
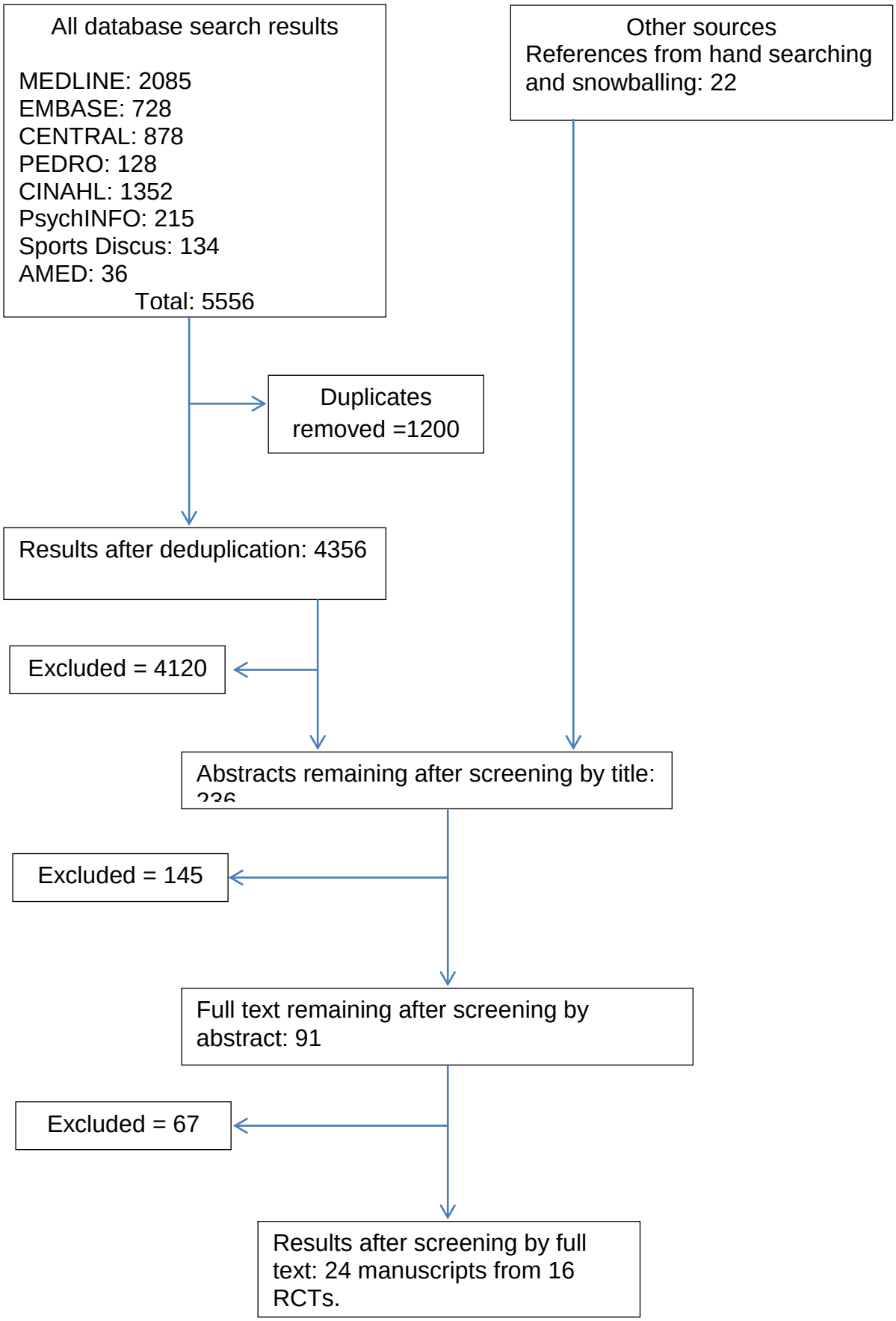


Figure 2: Assessment of risk of bias from included RCTs.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EMBASE: 728
CENTRAL: 878
PEDRO: 128
CINAHL: 1352
PsychINFO: 215
Sports Discus: 134
AMED: 36
Total: 5556
Other sources
References from hand searching and snowballing: 22
Duplicates removed =1200
Results after deduplication: 4356
Excluded = 4120
Abstracts remaining after screening by title:
Excluded = 145
Full text remaining after screening by abstract: 91
Excluded = 67
Results after screening by full text: 24 manuscripts from 16 RCTs.

ONLINE SUPPLEMENT 1: RISK OF BIAS JUDGEMENTS

Allocation

Random sequence generation

Ten studies reported enough information for a judgement of low risk regarding randomisation sequence generation (Bourke 2014; Cormie 2013; Cormie 2015; Galvão 2010; Galvão 2014 McGowan 2013; Park 2012; Segal 2003; Segal 2009; Windsor 2004). In all other trials, insufficient information was present to permit judgement.

Allocation concealment

Nine studies reported enough information for a judgement of low risk allocation concealment (Bourke 2014; Cormie 2013; Cormie 2015; Dieperink 2013; Galvão 2010; Jones 2014, Segal 2003; Segal 2009; Windsor 2004). In all other trials, insufficient information was present to permit judgement.

Blinding

Blinding of participants and personnel

All studies were judged to have a high risk of performance bias, as it would not be possible to blind participants or personnel in an exercise intervention.

Blinding of outcome assessment

We assessed risk of bias for blinding of outcome assessment on an outcome specific basis, i.e. objective vs. subjective outcomes.

<u>Objective outcomes (cardiovascular health and disease progression)</u>

Eight studies reported objective outcome data. Only three studies used any form of blinding for assessment of objective outcomes. Bourke 2014 and Jones 2014 used blinded trials staff to assess blood pressure, whilst Hebert 2012 sent PSA to external laboratories. Five other studies collecting objective outcomes (Cormie 2015; Galvão 2010; Galvão 2014; Segal 2003; Segal 2009) reported insufficient information to permit a judgment on bias.

<u>Subjective outcomes (cancer specific quality of life, cancer specific fatigue, physical function, sexual function)</u>

Fifteen trials reported subjective outcomes data. Five studies reported blinding techniques for subjective outcomes. Jones 2014 and Segal 2003 reported blinding for all trial subjective

assessments. Bourke 2014 and Dieperink 2013 ensured that questionnaires (assessing quality of life, atigue and sexual function) were completed independently by participants. Windsor 2004 also ensured that questionnaires were completed independently by participants but blinding for shuttle tests in not clear. Bourke 2014 used blinding for assessment of physical function test (i.e. submaximal fitness). Winters-stone 2014 reported that tests were administered by trained technicians blinded to group assignment. Seven trials were judged to have an unclear risk of bias due to insufficient reporting (Cormie 2013; Cormie 2015; Galvão 2010; McGowan 2013; Monga 2007; Park 2012; Segal 2009). Two trials were judged to have a high risk of bias, as they reported using unblinded assessors for physical function tests (Galvão 2014; Uth 2014). Hebert 2012 did not report any subjective outcomes.

Incomplete outcome data

We assessed risk of bias for incomplete outcome data on an outcome specific basis, i.e. objective vs. subjective outcomes.

Objective outcomes (cardiovascular health and disease progression)

Of the eight studies reporting objective outcome data, six were judged to have a low risk of attrition bias (<20%), five reporting PSA (Cormie 2015; Galvão 2010;Hebert 2012; Segal 2003; Segal 2009) and two reporting blood pressure data (Cormie 2015; Jones 2014). Two studies were judged to have high risk of attrition bias. For blood pressure data, Bourke 2014 reported 32% study attrition at six months of follow-up (three months after the end of the intervention) and Galvão 2014 reported 22% study attrition at 12months of follow-up for blood pressure and PSA data.

Subjective outcomes (cancer specific quality of life, cancer specific fatigue, physical function, sexual function)

Five studies reported low attrition bias (<20%) for quality of life (Dieperink 2013; Galvão 2010; Jones 2014; Segal 2003; Segal 2009). Three trials reported high attrition bias for quality of life at one study assessment point. McGowan 2013 and Monga 2007 reported 28 and 30% study attrition (respectively) at the single study follow-up point, whereas Bourke 2014 reported 32% attrition at six months of follow-up only (three months after the end of the intervention).

Seven studies reported low attrition bias for fatigue (Cormie 2015; Galvão 2010; Jones 2014; Segal 2003; Segal 2009; Windsor 2004; Winters-Stone 2014). Four trials reported high attrition bias for fatigue. Cormie 2013;McGowan 2013 and Monga 2007 reported 25, 28 and 30% study attrition

(respectively) at the single study follow-up point, whereas Bourke 2014 reported 32% attrition at six months of follow-up only (three months after the end of the intervention).

Seven studies reported low attrition bias for physical function tests (Cormie 2015; Galvão 2010; Jones 2014; Segal 2003; Segal 2009; Uth 2014; Winters-Stone 2014). Five trials reported high attrition bias for physical function data. Cormie 2013; Monga 2007; Park 2012 reported 25, 30 and 23% study attrition (respectively) at the post-intervention follow-up point. Bourke 2014 reported 32%attrition at six months of follow-up only (three months after the end of the intervention). Galvão 2014 reported only 57 data points from 100 men randomised for the study dynamic strength tests.

Three studies reported low attrition bias for sexual function outcomes (Dieperink 2013; Galvão 2010; Jones 2014). Cormie 2015 was judged to have a high risk of bias as only 17 data points were reported from 63 men randomised for sexual function for domain of the QLQ-PR25 questionnaire.

Ten studies reported conforming to intention-to-treat analysis (Cormie 2013; Cormie 2015; Dieperink 2013; Galvão 2010; Galvão 2014; Hebert 2012; Jones 2014; Segal 2003; Segal 2009; Winters-Stone 2014). Five trials were unclear in their reporting of this analysis method (McGowan 2013; Monga 2007; Park 2012;Uth 2014;Windsor 2004). Bourke 2014 analysed data from men according the groups to which were randomised, but did not impute data. Further, a sensitivity analysis of outcomes was performed to ensure confidence of results.

Selective reporting

Nine trials reported all specified outcomes of interest in the review (Bourke 2014; Cormie 2013; Cormie 2015; Galvão 2010; Galvão 2014; Jones 2014; Segal 2009; Uth 2014; Winters-Stone 2014). Ten studies reported adverse events (Bourke 2014; Cormie 2013; Cormie 2015; Galvão 2010; Galvão 2014; Jones 2014; Park 2012; Segal 2009; Uth 2014; Winters-Stone 2014). We judged the six trials which failed to report adverse events or reported them incompletely (Dieperink 2013; Hebert 2012; McGowan 2013; Monga 2007; Segal 2003; Windsor 2004) as having a high risk of bias, given that this information should be reported as standard in any interventional clinical trial. Further, three trials (Park 2012; Segal 2003; Windsor 2004) reported outcomes incompletely (physical function, PSA and fatigue, respectively) preventing them from being entered into a meta-analysis.

Other potential sources of bias

Three trials were judged to have low risk of other biases (Bourke 2014; Segal 2003; Uth 2014). Six trials were judged to have a high risk of other biases. Galvão 2014; and Windsor 2004 reported that there was no significant difference in exercise behaviour between intervention and control groups over the study follow-up points. Also, Hebert 2012 reported exercise behaviour at six months which was lower than at baseline in the intervention arm. Jones 2014 reported a substantial contamination in the control arm at six months of follow-up. Low adherence to the intervention was reported in the McGowan 2013 (13.6%) and Winters-Stone 2014 (43% adherence to the home-only component). Winters-Stone 2014 failed to recruit target trial sample.

Other sources of bias were judged to be unclear in seven studies. Exercise adherence data was missing for the suggested home-based component of the prescription in Cormie 2013; Cormie 2015 and Galvão 2010. No exercise adherence data was reported from the Dieperink 2013; Monga 2007 and Park 2012 trials. Segal 2009 did not report assumptions for the imputation of missing data.

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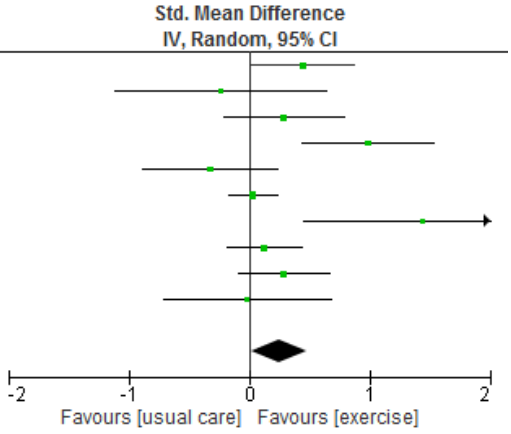
ONLINE SUPPLEMENT 2: REVIEW SECONDARY OUTCOMES

Cancer specific fatigue (up to six months follow-up)

Ten trials involving 1031 men measured cancer specific (Bourke 2014; Cormie 2013A; Cormie 2015; Galvão 2010; Jones 2014; McGowan 2013; Monga 2007; Segal 2003; Segal 2009; Winters-Stone 2014). Data from Cormie 2013A; Galvão 2010; Monga 2007 and Winters-Stone 2014 was reversed (multiplied by -1) to allow for combination with other outcomes tools with directional differences. Windsor 2004 measured fatigue but did not report data in a format that was possible to enter into a meta-analysis. A mild positive effect on this outcome was found from combining these studies (SMD= 0.25, 95%CI = 0.02, 0.49) with substantial heterogeneity (I^2 = 61, 95% CI =0, 79). Sensitivity analysis of studies that were judged to be of high quality (Bourke 2014; Cormie 2015; Galvão 2010; Segal 2009: NB Bourke 2014 three month follow-up data was used) indicated a moderate positive effect estimate (SMD = 0.45, 95% CI = 0.22, 0.67) with no significant heterogeneity (I^2 = 37%, 95% CI = 0, 78).

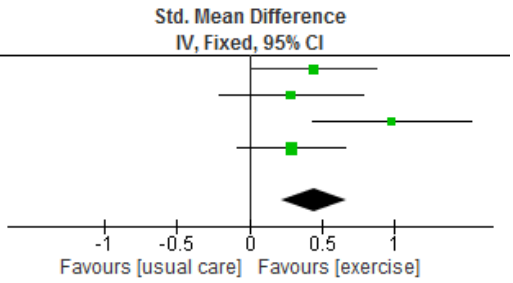
	Exercise			Usual care				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Bourke 2014	45.8	5.3	43	42.4	9.3	42	11.5%	0.45 [0.02, 0.88]
Cormie 2013a	-8.8	24.9	10	-3.8	13.7	10	5.1%	-0.24 [-1.12, 0.64]
Cormie 2015	43.8	6.8	32	41.4	9.5	31	10.2%	0.29 [-0.21, 0.78]
Galvão 2010	-14.8	13.8	29	-30.6	17.6	28	9.2%	0.99 [0.44, 1.54]
Jones 2014	39	7	25	41	5	25	9.1%	-0.32 [-0.88, 0.23]
McGowan 2013	39.5	10.3	282	39.2	10.2	141	16.6%	0.03 [-0.17, 0.23]
Monga 2007	-0.8	1.8	11	-3.8	2.2	10	4.4%	1.44 [0.46, 2.42]
Segal 2003	41.6	10.5	82	40.3	9.4	73	14.1%	0.13 [-0.19, 0.45]
Segal 2009	44.7	8.9	80	42.1	8.8	41	12.7%	0.29 [-0.09, 0.67]
Winters-Stone 2014	-9.22	3.46	24	-9.17	2.98	12	7.1%	-0.01 [-0.71, 0.68]
Total (95% CI)			**618**			**413**	**100.0%**	**0.25 [0.02, 0.49]**

Heterogeneity: Tau² = 0.08; Chi² = 23.04, df = 9 (P = 0.006); I² = 61%
Test for overall effect: Z = 2.11 (P = 0.03)



	Exercise			Usual care				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Bourke 2014	45.8	5.3	43	42.4	9.3	42	27.3%	0.45 [0.02, 0.88]
Cormie 2015	43.8	6.8	32	41.4	9.5	31	20.6%	0.29 [-0.21, 0.78]
Galvão 2010	-14.8	13.8	29	-30.6	17.6	28	16.6%	0.99 [0.44, 1.54]
Segal 2009	44.7	8.9	80	42.1	8.8	41	35.5%	0.29 [-0.09, 0.67]
Total (95% CI)			**184**			**142**	**100.0%**	**0.45 [0.22, 0.67]**

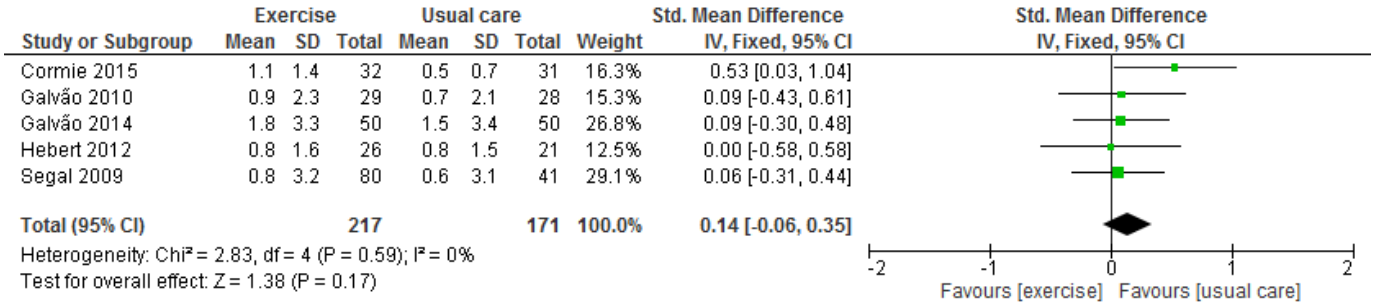
Heterogeneity: Chi² = 4.73, df = 3 (P = 0.19); I² = 37%
Test for overall effect: Z = 3.91 (P < 0.0001)



Disease progression (up to six months follow-up)

Five trials involving 388 men measured PSA (Cormie 2015; Galvão 2010; Galvão 2014; Hebert 2012; Segal 2003: NB Galvão 2014 six month follow-up data was used). Segal 2003 reported PSA data

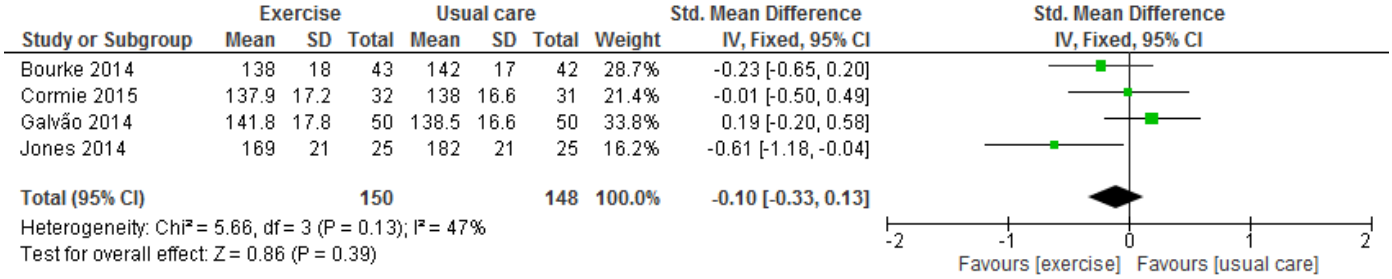
incompletely so that it cannot be entered in a meta-analysis. No significant effect on PSA was found (SMD = 0.14, 95% CI = -0.06, 0.35) with no significant heterogeneity (I^2 = 0, 95% CI = 0, 64).

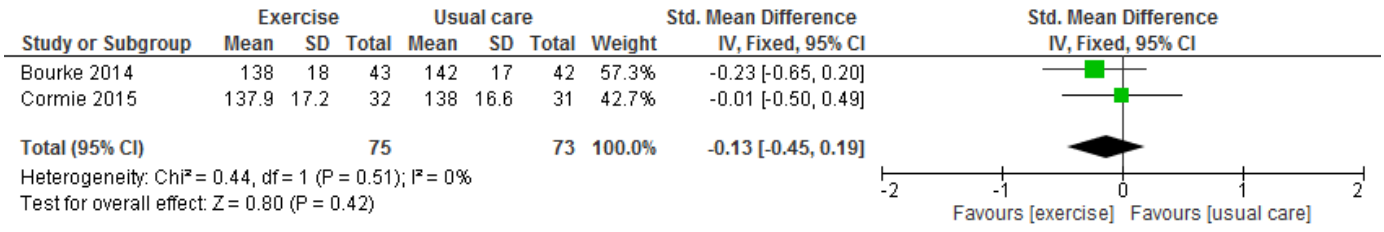


Cardiovascular health (up to six months follow-up)

Systolic blood pressure

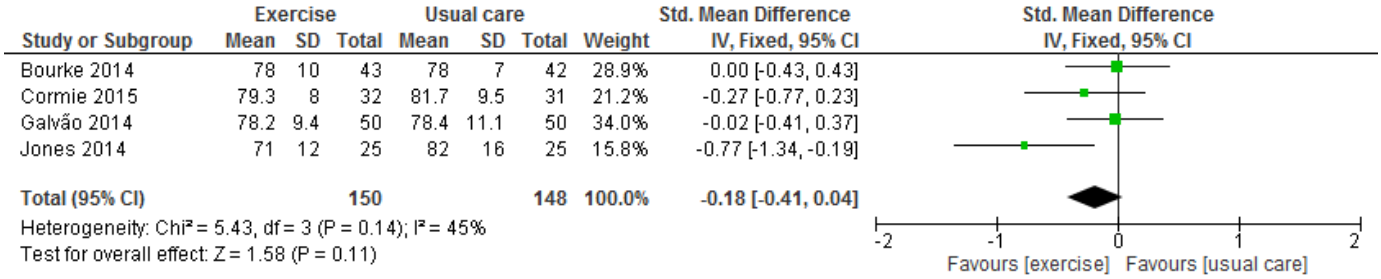
Four trials involving 298 men measured systolic blood pressure (Bourke 2014; Cormie 2015;Galvão 2014; Jones 2014:NB Galvão 2014 six month and Bourke 2014 three month follow-up data was used). No significant effect on systolic blood pressure was found (SMD = -0.10, 95% CI = 0.33, 0.13) and no statistical heterogeneity (I^2 = 47%, 95% CI = 0, 81). This finding was supported (SMD = -0.13, 95% CI = -0.45, 0.19) by including only high quality studies (Bourke 2014; Cormie 2015).

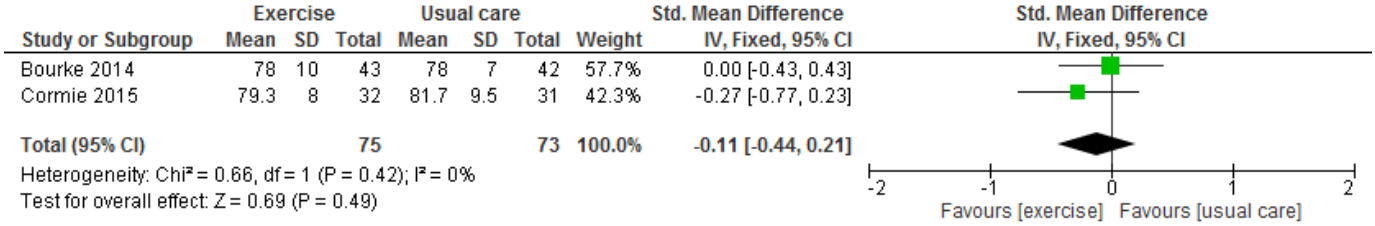




Diastolic blood pressure (up to six months follow-up)

Four trials involving 298 men measured systolic blood pressure (Bourke 2014; Cormie 2015; Galvão 2014; Jones 2014: NB Galvão 2014 six month and Bourke 2014 three month follow-up data was used). No significant effect on systolic blood pressure was found (SMD = -0.18, 95% CI = -0.41, 0.04) and no statistical heterogeneity (I^2 = 45%, 95% CI = 0, 80).This finding was supported (SMD = -0.11, 95% CI = -0.44, 0.21) by including only high quality studies (Bourke 2014; Cormie 2015).





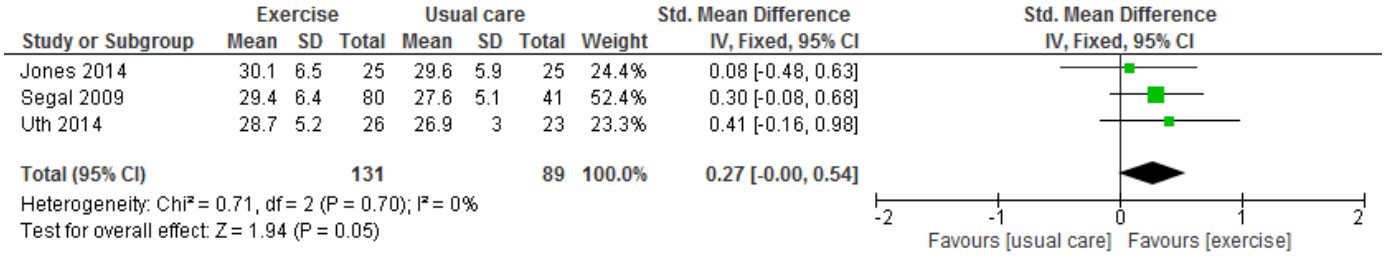
Physical fitness/function (up to six months follow-up)

VO_2 peak

Three trials involving 220 men measured VO_2 peak (Jones 2014; Segal 2009; Uth 2014). A borderline significant positive effect was observed for this outcome (SMD = 0.27, 95% CI = 0.00, 0.54) with no significant heterogeneity (I^2 = 0%, 95% CI = 0, 73). No sensitivity analysis of high quality trials was possible as only one of these three studies is judged to be of high quality (Segal 2009).

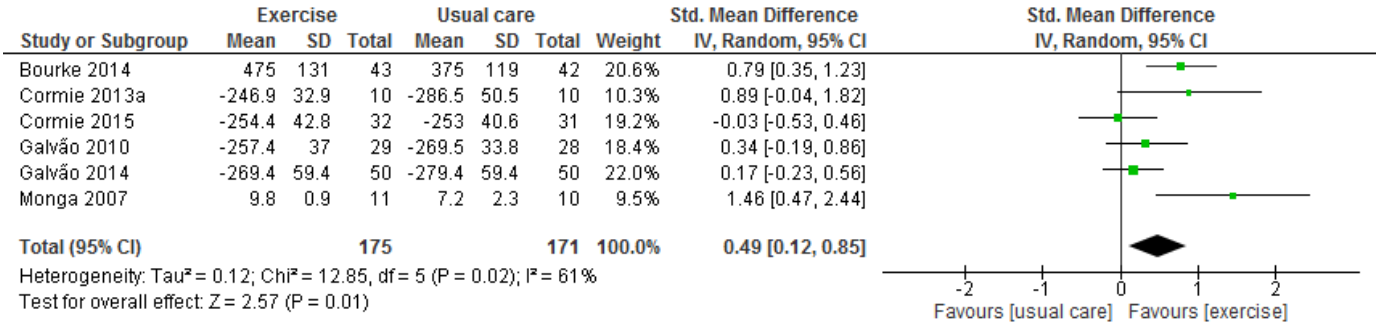
Sub-maximal aerobic fitness

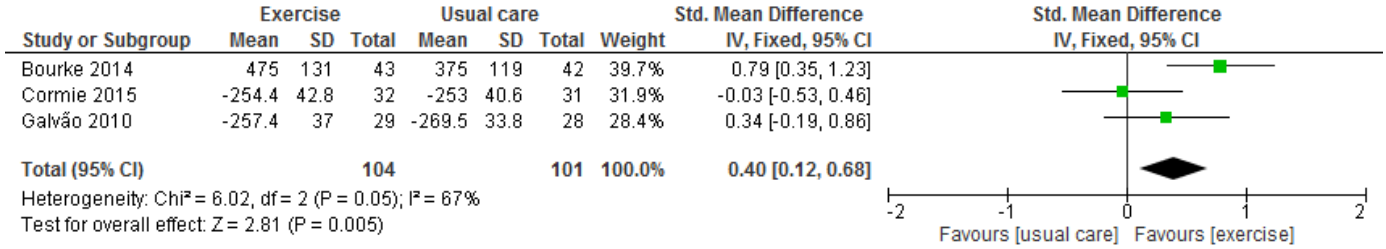
Six studies involving 346 men measured sub-maximal fitness (Bourke 2014; Cormie 2013A; Cormie 2015; Galvão 2010; Galvão 2014; Monga 2007: NB Galvão 2014 six month and Bourke 2014 three month follow-up data was used). Data from Cormie 2013A; Cormie 2015; Galvão 2010; Galvão 2014



was reversed (multiplied by -1) to allow for directional differences with outcome assessment methods. A significant positive effect estimate was observed for this outcome (SMD = 0.49, 95% CI = 0.12, 0.85) with no significant heterogeneity (I^2 = 61%, 95% CI =0, 82). Sensitivity analysis of studies that were judged to be of high quality (Bourke 2014; Cormie 2015; Galvão 2010 NB Bourke 2014 three month follow-up data was used) indicated a moderate positive effect estimate (SMD = 0.40, 95% CI = 0.12, 0.68) with no significant heterogeneity (I^2 = 67%, 95% CI = 0, 88).

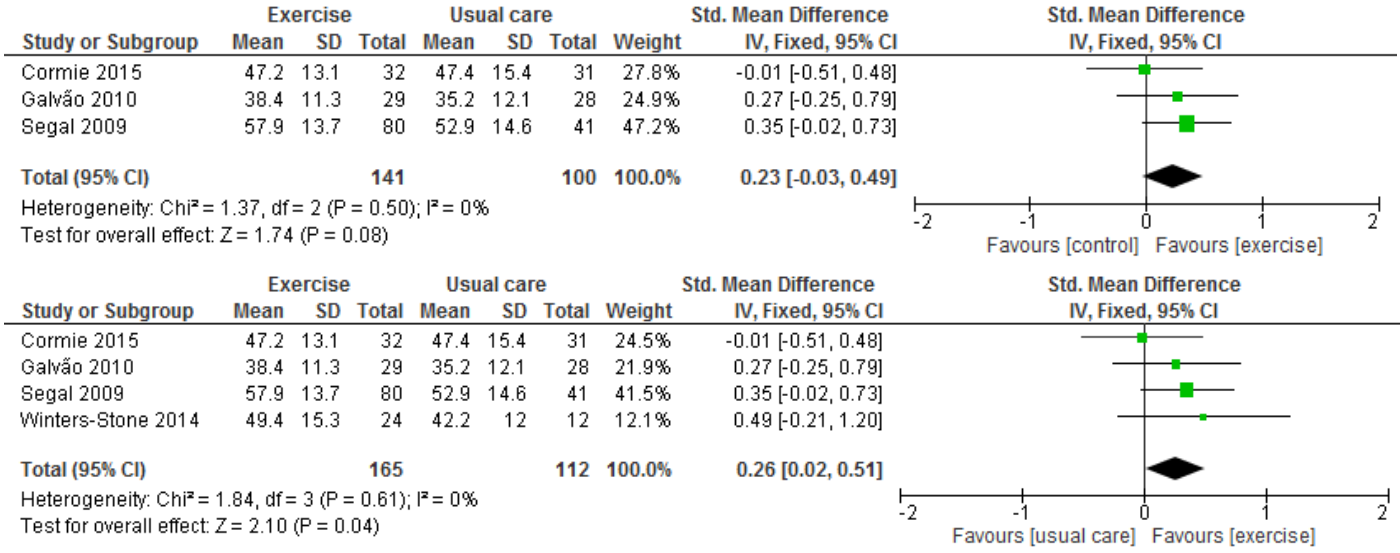
Park 2012 and Segal 2003 reported data that was of insufficient clarity to allow it to be entered into this meta-analysis. However, these studies were judged to be at high risk of bias and as such would not alter the sensitivity analysis results.





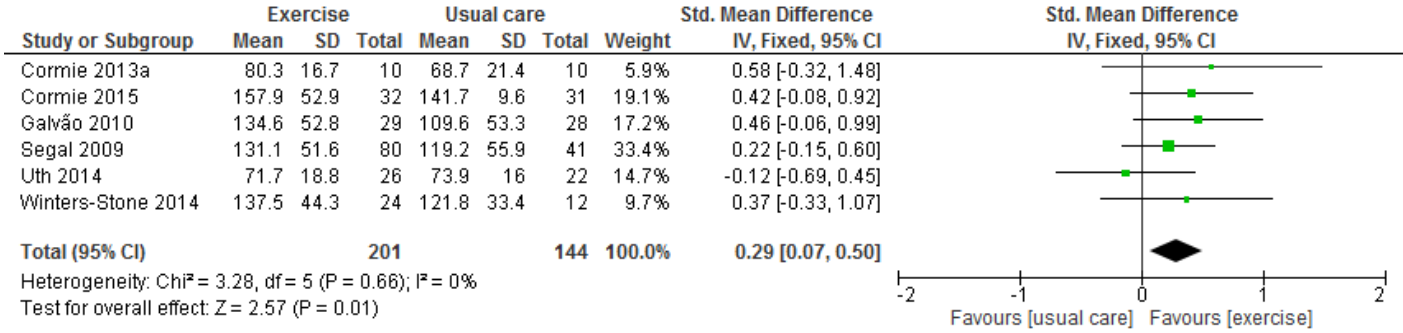
Upper body strength

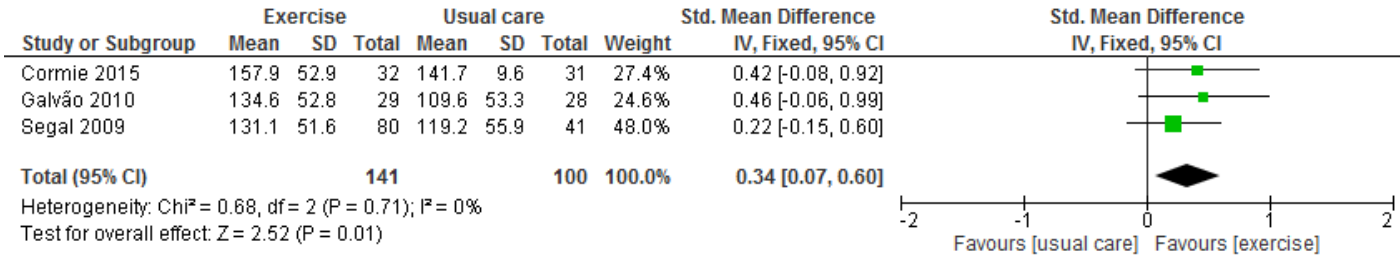
Four studies involving 277 men assessed upper body strength (Cormie 2015; Galvão 2010; Segal 2009 and Winters-Stone 2014). A significant improvement in upper body strength was observed (SMD = 0.26, 95% CI = 0.02, 0.51) with no significant heterogeneity (I^2 = 0%, 95% CI =0, 68). Sensitivity analysis of high quality trials indicates no effect (SMD = 0.23, 95% CI = -0.03, 0.49) with no significant heterogeneity (I^2 = 0%, 95% CI =0, 73).



Lower body strength

Six studies involving 245 men assessed lower body strength (Cormie 2013A; Cormie 2015; Galvão 2010; Segal 2009; Uth 2014; Winters-Stone 2014). A significant positive effect estimate was observed for this outcome (SMD = 0.29, 95% CI = 0.07, 0.50) with no significant heterogeneity (I^2 = 0%, 95% CI =0, 75). Sensitivity analysis of studies that were judged to be of high quality (Cormie 2015; Galvão 2010; Segal 2009) confirmed this (SMD = 0.34, 95% CI = 0.07, 0.60) with no significant heterogeneity (I^2 = 0, 95% CI = 0, 73).

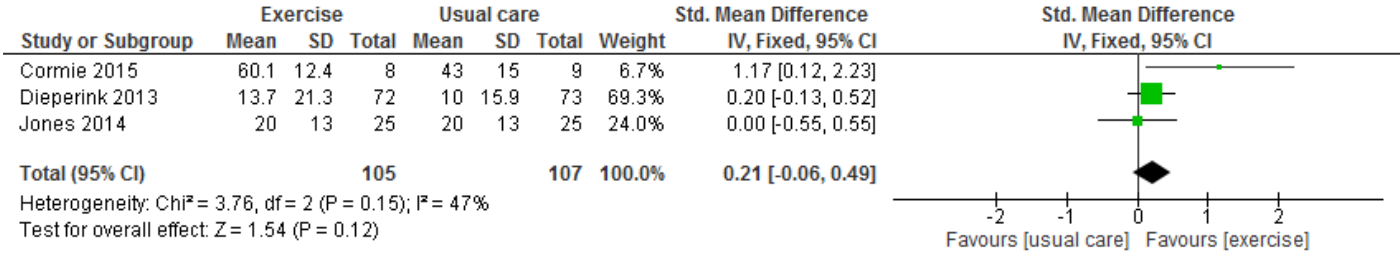




Sexual function

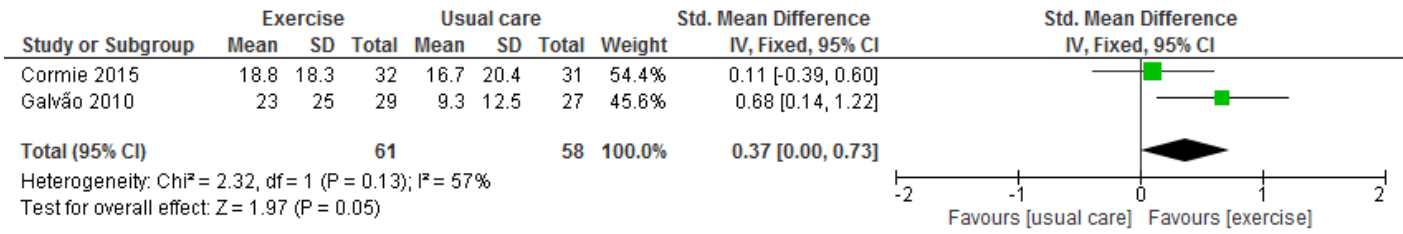
Function (up to six months follow-up)

Three studies involving 212 men assessed sexual function (Cormie 2015; Dieperink 2013; Jones 2014). No significant effect on sexual function was observed (SMD = 0.21, 95% CI = -0.06, 0.49) with no significant heterogeneity (I^2 = 47%, 95% CI = 0, 84). Sensitivity analysis was not possible as two out of these three trials are judged as having a high risk of bias.



Sexual activity (up to three months follow-up)

Two trials involving 119 men assessed sexual activity (Cormie 2015; Galvão 2010). A borderline positive effect estimate was observed (SMD = 0.37, 95% CI = 0.00, 0.73) with no significant heterogeneity (I^2 = 57%, P = 0.13. NB 95% CI are not calculable with only 1 degree of freedom).



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ONLINE SUPPLEMENT 3

Planned subgroup analysis

Our planned subgroup analysis was not possible due to the following reasons:

• Anti-cancer treatment received: trials involved a mixture of different anti-cancer treatments in their study sample, or studies of high quality were all conducted in men on the same treatment e.g. see Analysis 1.2 where in the three high quality studies, all men were on ADT in Bourke 2014; Galvão 2010 and the majority of men were on ADT (61%) in Segal 2009.

• Cancer stage: studies rarely reported full TNM data for their cohorts. Where T stage data was available, this always involved multiple T stages making specific comparisons not possible.

• Obese cohorts: where BMI data was available, no obese cohorts were reported.

• Previously physically active participants at baseline: in the majority of studies, reporting of baseline physical activity was either not reported or was reported as a proportion of the cohort at baseline that was sedentary vs those that were active.

Further, definitions of what constitutes previously physically active was also variable (e.g. currently meeting physical activity guidelines of 150 minutes per week [Cormie 2015] or not moderately active for more than 90 minutes per week [Bourke 2014]). In four trials that could be interpreted as having participants not regularly active at baseline, two trials were judged as having a high risk of bias (Galvão 2014; Jones 2014) and one did not report any review outcomes of interest (Winters-Stone 2014).

• Explanatory (efficacy) versus pragmatic (effectiveness) trial designs: we had planned to designate studies as pragmatic if they met the following criteria: an exclusively non physically active cohort at baseline, a clinically meaningful primary outcome, a multi-centre study, usual care comparators, no restrictions on exercise behaviour in comparator, a co-morbidity profile representative of the prostate cancer population being tested and use of intent-to-treat analysis. This was based on previously published criteria for pragmatic trials (Thorpe 2009). No studies met these criteria.

CALO-RE taxonomy analysis

AE – Aerobic Exercise, RE – Resistance Exercise, UC- Usual care, NR – None reported

BCT	Segal (2009)			Segal (2003)		Cormie (2013a)		Cormie (2015)		Dieperink (2013)		Galvao (2010)	
	AE	RE	UC (NR)	RE	C	AE/ RE	UC	AE/ RE	UC	I	UC	AE/ RE	UC
1. Provide info on consequences in general													
2. Provide info on consequences of behaviour to the individuals													
3. Provide information about others approval													
4. Provide normative information about others behaviour													
5. Goal Setting (behaviour) - with client										X			
5b. Goal Setting (behaviour) - by PT	X	X		X		X		X		X		X	
6. Goal Setting (outcome)													
7. Action Planning	X	X		X		X		X		X		X	
8. Barrier identification/problem solving										X			
9. Set graded tasks	X	X		X		X		X				X	
10. Prompt review of behavioural goals										X			
11. Prompt review of outcome goals													
12. Prompt rewards contingent on effort or progress towards behaviour													
13. Provide rewards contingent on successful behaviour													
14. Shaping													
15. Prompting generalisation of a target behaviour						X		X		X		?	

16. Prompt self-monitoring of behaviour													
17. Prompt self-monitoring of behavioural outcome													
18. Prompting focus on past success													
19. Provide feedback on performance													
20. Provide information on where and when to perform the behaviour	X	X		X				X		X			
21. Provide instruction on how to perform the behaviour	X	X		X		X		X		X		X	
22. Model/Demonstrate the behaviour													
23. Teach to use prompts/cues													
24. Environmental restructuring													
25. Agree behavioural contract													
26. Prompt practice	X	X		X		X		X		X		X	
27. Use of follow-up prompts													
28. Facilitate social comparison													
29. Plan social support/social change										X			
30. Prompt identification as role model/position advocate													
31. Prompt anticipated regret													
32. Fear arousal													
33. Prompt self-talk													
34. Prompt use of imagery													
35. Relapse prevention/coping planning													
36. Stress management/emotional control training													
37. Motivational interviewing										X			
38. Time-management													
39. General communication skills training													
Stimulate anticipation of													

future rewards													

AE – Aerobic Exercise, RE – Resistance Exercise, UC- Usual care, NR – None reported, PII – Personal implementation intention, TII- telephone Implementation intention, FB – Football, SE- Stretching Exercise

BCT	Galvao 2014			Jones 2014			McGowan 2013		Monga 2007		Park 2012		Uth 2014		Wint Ston
	RE & AE	C	-	AE	UC	-	PII	TII	AE	UC	AE & RE	UC	FB	UC	RE
1. Provide info on consequences in general							X	X							
2. Provide info on consequences of behaviour to the individuals															
3. Provide information about others approval															
4. Provide normative information about others behaviour															
5. Goal Setting (behaviour) - with client							X	X							
5b. Goal Setting (behaviour) - by PT	X	X		X			X	X	X		X		X		X
6. Goal Setting (outcome)															
7. Action Planning	X			X			X	X	X		X		X		X
8. Barrier identification/problem solving							X	X							
9. Set graded tasks	X			X									X		X
10. Prompt review of behavioural goals															
11. Prompt review of outcome goals															
12. Prompt rewards contingent on effort or progress towards behaviour															
13. Provide rewards contingent on successful behaviour															
14. Shaping															
15. Prompting generalisation of a target behaviour	X			X											X
16. Prompt self-monitoring of behaviour	X														

17. Prompt self-monitoring of behavioural outcome	X								X						
18. Prompting focus on past success															
19. Provide feedback on performance	X														
20. Provide information on where and when to perform the behaviour	X								X				X		
21. Provide instruction on how to perform the behaviour	X			X			X	X	X		X		X		X
22. Model/Demonstrate the behaviour															
23. Teach to use prompts/cues							X	X							
24. Environmental restructuring															
25. Agree behavioural contract															
26. Prompt practice	X			X					X		X				X
27. Use of follow-up prompts	X														
28. Facilitate social comparison															
29. Plan social support/social change															
30. Prompt identification as role model/position advocate															
31. Prompt anticipated regret															
32. Fear arousal															
33. Prompt self-talk															
34. Prompt use of imagery															
35. Relapse prevention/coping planning															
36. Stress management/emotional control training															
37. Motivational interviewing															
38. Time-management															
39. General communication skills training															
Stimulate anticipation of future rewards															

AE – Aerobic Exercise, RE – Resistance Exercise, UC- Usual care, NR – None reported, PII – Personal implementation intention, TII- telephone Implementation intention, FB – Football, SE- Stretching Exercise

BCT	Windsor 2004			Hebert 2012		
	AE	UC	-	AE		
1. Provide info on consequences in general						
2. Provide info on consequences of behaviour to the individuals						
3. Provide information about others approval						
4. Provide normative information about others behaviour						
5. Goal Setting (behaviour) - with client						
5b. Goal Setting (behaviour) - by PT	X			X		
6. Goal Setting (outcome)						
7. Action Planning	X			X		
8. Barrier identification/problem solving						
9. Set graded tasks				X		
10. Prompt review of behavioural goals						
11. Prompt review of outcome goals						
12. Prompt rewards contingent on effort or progress towards behaviour						
13. Provide rewards contingent on successful behaviour						
14. Shaping						
15. Prompting generalisation of a target behaviour				X		
16. Prompt self-monitoring of behaviour	X					
17. Prompt self-monitoring of behavioural outcome	X					
18. Prompting focus on past success						

19. Provide feedback on performance						
20. Provide information on where and when to perform the behaviour						
21. Provide instruction on how to perform the behaviour	X			X		
22. Model/Demonstrate the behaviour						
23. Teach to use prompts/cues						
24. Environmental restructuring						
25. Agree behavioural contract						
26. Prompt practice	X			X		
27. Use of follow-up prompts				X		
28. Facilitate social comparison						
29. Plan social support/social change	X			X		
30. Prompt identification as role model/position advocate						
31. Prompt anticipated regret						
32. Fear arousal						
33. Prompt self-talk						
34. Prompt use of imagery						
35. Relapse prevention/coping planning						
36. Stress management/emotional control training				X		
37. Motivational interviewing						
38. Time-management						
39. General communication skills training						
Stimulate anticipation of future rewards						

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Winters-Stone KM, Dobek JC, Bennett JA, Maddalozzo GF, Ryan CW, Beer TM. Skeletal response to resistance and impact training in prostate cancer survivors. Med Sci Sport Exer. 2014;46:1482-8.

Study author	N randomised	Follow-up	Participants & Treatment	Intervention	Review outcome measures
Bourke 2014	Exercise n= 50, Usual care n= 50	Baseline, three and six months.	• Tumour stage(s): T3,T4 • Current cancer treatment: ADT • Metastatic disease: 11 men in the intervention group vs 9 in the control group	-Aerobic frequency: three times per week -Aerobic intensity: 55-75% of age predicted maximum heart rate or 11-13 on the Borg Rating of Perceived Exertion scale -Aerobic duration: 30 minutes -Resistance frequency: three times per week -Resistance sets: between two and four -Resistance reps: eight-12 repetitions -Resistance load: 60% of one repetition max	• Cancer specific quality of life: FACT-P questionnaire • Adverse events: reported • Cancer specific fatigue: FACT-F questionnaire • Cardiovascular health: systolic and diastolic blood pressure. • Physical function: aerobic exercise tolerance by sub-maximal treadmill test.
Cormie 2013A	Exercise n=10, Usual care n=10	Baseline and 12 weeks	• Tumour stage(s): not clear • Current cancer treatment: unclear. All men had previous ADT • Metastatic disease: all men had metastatic disease	-Aerobic frequency: unclear -Aerobic intensity: unclear -Aerobic duration: 150 mins of total exercise per week -Resistance frequency: twice weekly -Resistance sets: two to four sets per exercise -Resistance reps: 12-8 repetitions -Resistance load: 12-8 repetition maximum (RM)	• Adverse events: reported • Cancer specific fatigue: the Multidimensional Fatigue Symptom Inventory-Short Form questionnaire • Physical function: (1) one repetition max in leg extension (2) 400-m walk, (3) usual and fast pace 6-m walk, (4) timed 'up and go' test
Cormie 2015	Exercise n= 32, Usual care n= 31	baseline, three months	• Tumour stage(s): not clear • Current cancer treatment: ADT, radiation • Metastatic disease: none	-Aerobic frequency: twice weekly -Aerobic intensity: target intensity was set at approximately 70-85% of estimated maximum heart rate. -Aerobic duration: 20-30 minutes supervised -Resistance frequency: twice weekly -Resistance sets: 1-4 sets per exercise -Resistance reps: 6-12 repetition maximum -Resistance load: 60-85% of one repetition maximum	• Cancer specific quality of life: QLQ-PR25 questionnaire • Adverse events: reported • Cancer specific fatigue: FACT-F questionnaire • Disease progression: PSA • Cardiovascular health: Systolic and diastolic blood pressure • Physical function: 400 m walk (s), leg press (kg), chest press (kg), seated row (kg) • Sexual function: sexual function domain on QLQ-PR25 questionnaire
Dieperink 2013	Intervention n=79, control n= 82	12 weeks before radiotherapy, pre-intervention (4 weeks after	• Tumour stage(s): T1-T3 • Current cancer treatment: radiotherapy and ADT • metastatic disease:	-Aerobic frequency: seven days per week -Aerobic intensity: bottom limit for moderate-intensity physical exercise corresponds to walking at an average speed of 4 km/h (taken from the recommendations from the National Board of Health	• Cancer specific quality of life: EPIC questionnaire • Sexual function: EPIC questionnaire sexual sum score

		radiotherapy), 21-22 weeks from pre-intervention	three patients in each randomisation group received pelvic radiotherapy due to metastatic lymph nodes	in Denmark) -Aerobic duration:30 minutes per day	
Galvão 2010	Exercise n= 29, usual care n= 28	Baseline, 12 weeks	• Tumour stage(s): unclear • Current cancer treatment: radiation & ADT • Nodal metastases: exercise = 2 , UC = 3	-Aerobic frequency: twice per week. -Aerobic Intensity: 65% to 80% maximum heart rate and perceived exertion at 11 to 13 (6 to 20 point, Borg scale) -Aerobic duration: 15 to 20 minutes of cardiovascular exercises. * -Resistance frequency: twice per week. -Resistance sets: two to four sets -Resistance reps: 12 to 6 -Resistance load: 12 to 6 repetition maximum *Participants encouraged to supplement with exercise at home to reach 150 mins/week	• Cancer specific quality of life: assessed using QLQ-C30 and QLQ PR 25 questionnaires • Adverse events: reported • Cancer specific fatigue: assessed with fatigue domain of the QLQ-C30 questionnaire • Disease progression: PSA • Physical function: 400m walk, upper and lower body dynamic strength • Sexual function: sexual activity assessed using the QLQ PR 25 questionnaire
Galvão 2014	Exercise n= 50, Usual care n= 50	Baseline, six and 12 months	• Tumour stage(s): T2, T3,T4 • Current cancer treatment: None. Previous ADT & radiation & bisphosphonate • Metastatic disease: excluded from trial	-Aerobic frequency: 4 times per week -Aerobic intensity: 70-85% maximum heart rate and perceived exertion at 11-13 (6- to 20-point Borg scale) -Aerobic duration: 20-30 min of cardiovascular exercises -Resistance frequency: twice per week -Resistance sets: two to four sets -Resistance reps: 12 to 6 -Resistance load: 12 to 6 repetition maximum	• Adverse events: reported • Disease progression: PSA • Cardiovascular health: blood pressure • Physical function: sub-maximal exercise tolerance, chair rise test
Hebert 2012	Exercise n=29, Control n=25	Baseline, three and six months	• Tumour stage(s): unclear • Current cancer treatment: previously treated with surgery, radiotherapy or both • Metastatic disease:	-Aerobic frequency: five times per week -Aerobic intensity: (3.0-6.0 METs or 4-7 kcal/min) (taken from cited ACSM guidelines on what constitutes moderate intensity exercise) -Aerobic duration: ≥30 minutes	• Adverse events: unclear • Disease progression: PSA

			unclear		
Jones 2014	Exercise n= 25, Usual care n= 25	Baseline and six months.	• Tumour stage(s): T I, T II • Current cancer treatment: Previous bilateral nerve-sparing RP • Metastatic disease: none	-Aerobic frequency: five sessions per week -Aerobic intensity: 55% to 100% of VO2 peak -Aerobic duration: 30 to 45 mins per session	• Cancer specific quality of life: assessed by FACT-G and FACT-P questionnaires • Adverse events: reported • Cancer specific fatigue: assessed by FACT-F questionnaire • Cardiovascular health: blood pressure • Physical function:VO_2peak • Sexual function: International Index of Erectile Function questionnaire
McGowan 2013	Physical activity guidelines n= 141. Self-administered implementation intention n = 141. Telephone assisted implementation intention n =141.	Baseline one and three months.	• Tumour stage(s): unclear • Current cancer treatment: watchful waiting, surgery, radiotherapy, ADT, chemotherapy, 'cancer recurrence' • Metastatic disease: 1.9% of the cohort had metastatic disease.	-Aerobic frequency: unclear -Aerobic intensity: *Taken from citation 22* approximately equivalent to 500 to 1,000 metabolic equivalent (MET) minutes a week -Aerobic duration: 150minutes to 300minutes (5 hours) per week, or to increase physical activity by at least 60 min/week if they were already meeting the guidelines	• Cancer specific quality of life: assessed using the FACT-P questionnaire sub-scale • Cancer specific fatigue: assessed using the FACT-F questionnaire
Monga 2007	Unclear (30 men randomised in total)	Baseline and eight weeks	• Tumour stage(s): unclear • Current cancer treatment: radiotherapy • Metastatic disease: unclear	-Aerobic frequency: three times per week -Aerobic intensity: the following formula was used to calculate target heart rate: (.65) (maximum heart rate resting heart rate) resting heart rate -Aerobic duration: 30-minute aerobic segment consisting of walking on a treadmill	• Cancer specific quality of life: FACT-P questionnaire • Cancer specific fatigue: assessed using the Piper fatigue scale • Physical function: submaximal fitness (Bruce treadmill protocol) and timed five repetition chair sit-to-stand test.
Park 2012	Exercise n= 33, Usual care n= 33	The week before surgery, before exercise (3 weeks postoperatively),	• Tumour stage(s): pT2a - pT3a • Current cancer treatment: post radical	-Aerobic frequency: twice per week -Aerobic intensity: 45%-75%of the heart rate reserve maximum and 9-13 rated perceived exertion -Aerobic duration: 60 minutes	• Adverse events: reported • Physical function: sit-ups, chair stand, dominant grip strength, adduction ability, back lift, and knee lift were performed for 2

		and after exercise (15 weeks postoperatively).	prostatectomy • Metastatic disease: unclear		minutes
Segal 2003	Exercise n= 82, Control n=73	Baseline and 12 weeks	• Tumour stage(s): T stage I-IV • Current cancer treatment: ADT • Metastatic disease: unclear	-Resistance frequency: three times per week -Resistance sets: two -Resistance reps: eight to 12 -Resistance load: 60% to 70% of one-repetition maximum	• Cancer specific quality of life: FACT-P questionnaire • Cancer specific fatigue: FACT-F questionnaire • Disease progression: PSA • Physical function: dynamic upper and lower body muscle endurance
Segal 2009	Resistance exercise n= 40, Aerobic exercise n= 40, control n= 41	Baseline, 12 weeks, 24 weeks	• Tumour stage(s): stage I-IV • Current cancer treatment: radiation and ADT (61% of cohort on ADT) • Metastatic disease: none (excluded from trial)	-Aerobic frequency: three times per week -Aerobic intensity: up to 60% of predetermined peak oxygen consumption (VO_2peak) for weeks 1 to 4 and progressing to 70% to 75% for weeks 5 to 24 -Aerobic duration: exercise duration began at 15 minutes and increased by 5 minutes every 3 weeks until it reached 45 minutes -Resistance frequency: three times per week -Resistance sets: two -Resistance reps: eight to 12 -Resistance load: 60% to 70% of estimated one-repetition maximum (1 RM)	• Cancer specific quality of life: assessed by FACT-P questionnaire • Adverse events: reported • Cancer specific fatigue: assessed by FACT-F questionnaire • Disease progression: assessed by PSA • Physical function: VO_2 peak, upper and lower body dynamic strength
Uth 2014	Exercise n= 29, Usual care n= 28	Baseline and 12 weeks	• Tumour stage(s): unclear • Current cancer treatment: ADT (previous radiotherapy / radiation) • metastatic disease: nodal metastases, exercise = 14%, usual care = 35%. Bone metastases, exercise =	-Aerobic frequency: two to three times per week -Aerobic Intensity: 70-100% HRmax -Aerobic duration: during the first 4 weeks, the football training consisted of two weekly sessions, which started with 15 min of warm-up exercises (running, dribbling, passing, shooting, balance, and muscle strength exercises) followed by 2 × 15 min of 5-7 a-side small-sided games. In weeks 5-8, the duration of each session increased to 3 × 15-min games after the warm-up, and in weeks 9-12,	• Adverse events: reported • Physical function: VO_2peak, knee-extensor maximal strength, chair sit-to-stand test

			24%, usual care = 15%	there were three weekly training sessions of the same duration	
Windsor 2004	Exercise n=33, Control n= 33	Baseline, four and eight weeks	• Tumour stage(s): 51 of 65 patients had tumours that were classified as T1 or T2. • Current cancer treatment: All Radiotherapy and 19 of 66 patients (28.8%) were receiving adjuvant hormone therapy for high-risk tumours, including 10 of 33 patients in the control group and 9 of 33 patients in the exercise group • Metastatic disease: unclear	-Aerobic frequency: at least 3 days of each week of radiotherapy -Aerobic intensity: 60-70% of calculated maximum heart rate -Aerobic duration: 30 minutes	• Cancer specific fatigue: assessed using the Brief Fatigue Inventory questionnaire
Winters-Stone 2014	Exercise n=29, Control n= 22	Baseline, six and 12 months	• Tumour stage(s): unclear • Current cancer treatment: all men on ADT. 45 and 50% of men received radiotherapy (exercise vs control, respectively) and 7 and 14% of men received chemotherapy (exercise vs control, respectively). • Metastatic disease: exercise = 27.6%, control = 13.6%	-Resistance frequency: three times per week -Resistance sets: displacement 1 to 10, lower body 1 to 2, upper body 1 to 2 -Resistance reps: displacement 10, lower body 8 to 12, upper body 14 to 8 -Resistance load: lower body and displacement 0 to 15% of body weight. Upper body, 15 to 10 repetition max	• Adverse events: reported • Cancer specific fatigue: Schwartz Cancer Fatigue Scale • Physical function: Bench press 1RM (kg), Leg press 1RM (kg), Chair stand (s), 4-m fast walk (m/s)

Key. FACT-P = Functional assessment of cancer therapy - prostate. FACT-G = Functional assessment of cancer therapy - general. FACT-F = Functional assessment of cancer therapy- fatigue. QLQ-C30 European Organisation for Research and Treatment of Cancer core quality of life questionnaire. QLQ-PR25 = European Organisation for Research and Treatment of Cancer Prostate-specific module (QLQ-PR25). EPIC = Expanded Prostate Cancer Index Composite. RM = Repetition maximum. HR = Heart rate.