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Effects of a multicomponent resistance-based exercise program with protein, vitamin D and calcium supplementation on cognition in men with prostate cancer treated with ADT: secondary analysis of a 12-month randomised controlled trial

Niamh L Mundell ,[1] Patrick J Owen ,[1] Jack Dalla Via,[1,2] Helen Macpherson ,[1] Robin M Daly,[1] Patricia M Livingston ,[3] Timo Rantalainen,[1,4] Stephen J Foulkes,[1,5] Jeremy L Millar ,[6] Declan G Murphy,[7,8] Steve F Fraser[1]

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For numbered affiliations see end of article.

Correspondence to
Niamh L Mundell;
niamh.mundell@deakin.edu.au

ABSTRACT

Objectives The aim of this preplanned secondary analysis of a 12-month randomised controlled trial was to investigate the effects of a multicomponent exercise programme combined with daily whey protein, calcium and vitamin D supplementation on cognition in men with prostate cancer treated with androgen deprivation therapy (ADT).

Design 12-month, two-arm, randomised controlled trial.

Setting University clinical exercise centre.

Participants 70 ADT-treated men were randomised to exercise-training plus supplementation (Ex+ Suppl, n=34) or usual care (control, n=36).

Intervention Men allocated to Ex + Suppl undertook thrice weekly resistance training with weight-bearing exercise training plus daily whey protein (25 g), calcium (1200 mg) and vitamin D (2000 IU) supplementation.

Primary and secondary outcome measures Cognition was assessed at baseline, 6 and 12 months via a computerised battery (CogState), Trail-making test, Rey auditory-verbal learning test and Digit span. Data were analysed with linear mixed models and an intention-to-treat and prespecified per-protocol approach (exercise-training: ≥66%, nutritional supplement: ≥80%).

Results Sixty (86%) men completed the trial (Ex + Suppl, n=31; control, n=29). Five (7.1%) men were classified as having mild cognitive impairment at baseline. Median (IQR) adherence to the exercise and supplement was 56% (37%–82%) and 91% (66%–97%), respectively. Ex + Suppl had no effect on cognition at any time.

Conclusions A 12-month multicomponent exercise training and supplementation intervention had no significant effect on cognition in men treated with ADT for prostate cancer compared with usual care. Exercise training adherence below recommended guidelines does not support cognitive health in men treated with ADT for prostate cancer.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Strengths of this study included the use of objective cognitive function tests validated in patients with cancer and assessing domains recommended by the International Cancer and Cognition Task Force.
⇒ A further strength is the randomised controlled design of the study, whereby androgen deprivation therapy-treated men with prostate cancer were allocated to an exercise training and nutritional supplementation intervention or usual care control.
⇒ A limitation of this study is that only five (7.1%) men were classified as having mild cognitive impairment at baseline.
⇒ This was a secondary analysis of a randomised controlled trial designed to primarily detect change in bone-based outcomes.
⇒ A further limitation is the suboptimal adherence to the exercise intervention.

Trial registration number Australian and New Zealand Clinical Trial Registry (ACTRN12614000317695, registered 25/03/2014) and acknowledged under the Therapeutic Goods Administration Clinical Trial Notification Scheme (CT-2015-CTN-03372-1 v1).

INTRODUCTION

Prostate cancer (PCa) is the second most frequently diagnosed cancer in male worldwide, with a projected incidence of 1.6 million in 2021.[1] Androgen deprivation therapy (ADT) for local and advanced PCa is effective at reducing androgens, such as testosterone, to castration levels (<1.7 nmol/L) and thus

inhibiting tumour progression.[2] However, testosterone reduces the production of a highly neurotoxic protein (amyloid beta peptide 40), which is linked with the development of dementia and Alzheimer's disease.[3] In older men with PCa, ADT has been associated with an increased risk of developing dementia (HR (95% CI): 1.21 (1.11 to 1.33)) and Alzheimer's disease (1.16 (1.09 to 1.24)) compared with non-ADT PCa controls over duration of ≥12 months.[4] Indeed, ADT exposure has been associated with a deterioration in visuomotor, memory and executive function domains of cognitive function,[2 5] which may in part be explained by ADT-induced cardiovascular and metabolic comorbidities known to underpin cognitive decline.[4] Notably, these declines appear greater than in men experiencing normal cognitive ageing associated with age-related reductions in testosterone levels.[6] Updated guidelines by the International Society of Geriatric Oncology recommend that clinicians include cognitive screening and discuss potential adverse effects of ADT, particularly in older men (>75 years) with PCa.[7] Given that therapeutic benefits of existing treatments for cognitive impairment or dementia are uncertain,[8] there is a need to explore viable options for managing the potential adverse cognitive changes related to ADT exposure.[2]

Meta-analyses suggest that regular exercise training provides benefits to executive function and memory in healthy middle-aged and older adults (>50 years),[9] as well as in general population with cancer.[10] In older adults with cognitive impairment, short duration (≤30 min), high frequency (≥4 per week) exercise training, was shown to improve global cognition (Cohen's d: 0.37) and executive function (Cohen's d: 0.27).[11] Few studies have examined an effect of exercise training on cognition in men with PCa. An randomised controlled trial (RCT) of 54 men (mean age: 66 years) receiving various treatments for PCa found that a 12-week aerobic and resistance training programme comprising two supervised and one home-based session per week had a small non-statistically significant effect in self-reported cognition compared with usual care (Cohen's d (95% CI): 0.34 (−0.02 to 0.70)), yet this study did not differentiate an independent effect of ADT.[12] Another RCT including 57 men (mean age: 70 years) with PCa on ADT reported improvements to subjective cognitive function (QLQ-C30) following 12 weeks of supervised aerobic and progressive resistance group-based exercise-training (2–3 times per week) compared with usual care (Cohen's d (95% CI): 0.88 (0.33 to 1.42)).[13] Self-reported improvements to cognitive function were also reported following 6 months of progressive resistance training in 72 ADT-men compared with usual care, however these were no longer evident at 12 months.[14] Despite these findings, subjective assessment of cognition does not represent a valid assessment of cognitive performance.[2 15] Thus, there is a need for further intervention studies investigating the effects of exercise-training on cognition in ADT-treated men with validated objective cognitive tests.[5]

Combining progressive resistance training with an adequate intake of dietary protein is recommended to mitigate muscle loss associated with ageing.[16] This is important given that muscle loss is associated with reduced muscle strength and impaired muscle function (eg, gait speed), all of which have been implicated with compromised cognitive function.[16] Preserving or improving muscle mass, strength and physical function may provide health benefits that offset cerebrovascular and neurological functional declines occurring with cognitive ageing. Secondary analyses of data from two parallel 24-week RCTs including 127 frail/prefrail older adults (≥65 years) observed that combined progressive resistance training and protein supplementation (15 g whey protein concentrate 80%) improved information processing speed, but had inverse associations with verbal fluency when compared with progressive resistance training and placebo supplementation.[17] However, a 24-week follow-up may have been insufficient to observe cognitive ageing in the control group.[17] Whether a synergistic effect of protein supplementation and exercise training occurs for cognition in men treated with ADT is unknown, yet warrants investigation given burgeoning evidence for exercise and dietary approaches to address adverse treatment-related effects. Therefore, the aim of this study, which represents a secondary analysis of a 12-month RCT, was to investigate the effects of a multicomponent resistance-based exercise programme with daily protein, vitamin D and calcium supplementation on cognitive function compared with usual care in PCa survivors treated with ADT.

METHODS

Study design

As reported previously,[18] this study was a 12-month, single-blinded, two-arm RCT involving men aged 50–85 years currently undergoing continuous ADT (>3 months) treatment for PCa. The study was conducted from April 2014 to November 2017. The primary aim of this study was to examine the effects of the intervention on bone mineral density,[19] which have been reported elsewhere.[18] This study represents analysis of secondary outcomes regarding cognitive function. The study methods and protocol have been described in detail previously.[19] Briefly, all assessments aside from pathology were conducted at Deakin University, Melbourne. Participants were randomised (1:1 ratio) after baseline assessment by an independent researcher using automated random number sequencing. Allocation was block stratified by age (<65 or ≥65 years) and body mass index (BMI; <30 and ≥30 kg/m^2) to either: (1) multicomponent exercise intervention including progressive resistance training, bodyweight impact and balance exercises, as well as a daily nutritional supplement containing whey protein, calcium and vitamin D (Ex + Suppl), or (2) usual care control receiving 1000 IU vitamin D only. Follow-up assessments were conducted at 6 and 12 months. Participants were

required to provide written informed consent and physician approval to participate.

Patient and public involvement

Participants were invited to participate after discussion with and approval from their treating physicians. Following analysis at completion of the study, participants were provided with an individualised report in plain language detailing the results of each assessment in comparison to population norms and/or prior test results. Selected outcome measures were previously validated in a population with cancer.[19] Community presentations were provided to facilitate both recruitment and dissemination of the results from the study.

Participants

Men aged 50–85 years with PCa pharmacologically treated with ADT for 12 weeks or greater were recruited via referral from The Alfred Hospital (Melbourne, Australia), Peter MacCallum Cancer Centre (Victoria, Australia), private urology practices (Victoria, Australia), PCa support groups (Victoria, Australia) and newspaper advertisements. Exclusion criteria were: (1) inability to communicate in English; (2) current smoker; (3) body-weight exceeding 159 kg; (4) pre-existing disorder or pharmacotherapy affecting bone, calcium or vitamin D metabolism; (5) dietary supplementation with protein; (6) participation in progressive resistance training (>1 session/week) or weight-bearing/impact exercise-training (>150 min/week) within the last 3 months; and (7) any absolute contraindications to exercise testing.[20]

Intervention

Multicomponent exercise program

The 12-month exercise-training protocol was designed to achieve improvements in the primary musculoskeletal outcomes. Specific details of the multicomponent exercise programme and progressions have been previously reported.[19] In brief, participants allocated to the intervention were asked to complete three sessions per week. In weeks 1–26, two gym-based sessions were completed in small groups (~6 men) supervised by an accredited exercise physiologist (Deakin University Clinical Exercise Centre, Melbourne), with participants asked to also undertake one home-based session. In weeks 27–52, participants were supervised for one gym-based session, completed one independent gym-based session at a community gym and one home-based session. All home-based exercise sessions were structured similarly to the gym-based sessions, but utilising body-weight and resistance bands (provided). Participants were familiarised with the home-based programme under supervision before being provided with instructions and a home exercise card to complete. Gym-based sessions (approximately 60 min duration) commenced with a 5–10 min aerobic warm-up (eg, treadmill, rower, stationary cycle), 5–6 progressive resistance exercises incorporating large compound movements using free weights or weight-training machines (two sets, 8–12 repetitions, moderate to hard intensity (rating of perceived exertion (RPE): 5–8/10)). The resistance training was progressed over time by increasing the load to repetition ratio. Weight-bearing impact exercises (three sets, 10–20 repetitions), and two (30–60 s or a given number of repetitions) challenging functional/mobility/balance exercises and two core/postural exercises were incorporated. Weight-bearing impact exercises were progressed by increasing jump height, weight, rate or adding directional change. Progressions were only implemented when a given exercise was no longer sufficiently challenging (RPE ≤6/10). All programmes were individually tailored and modified based on individual considerations (eg, metastases, comorbidities and relative contraindications).[20]

Nutritional supplement

Participants in the intervention group were asked to consume a daily nutritional supplement in addition to their usual diet, consisting of 25 g of whey protein concentrate 80% (ie, approximately 20 g of the supplement was protein) containing approximately 2.4 g of leucine, 1200 mg calcium carbonate (equivalent to 480 mg elemental calcium) and 1000 IU vitamin D (Omniblend, Campbellfield, Australia). This was prepared with 150 mL of water and consumed within 1–2 hours of each exercise sessions or prior to breakfast on non-training days. Participants in the intervention group were also asked to take a daily vitamin D tablet containing 1000 IU (Ostelin, Macquarie Park, Australia), increasing daily intakes to 2000 IU.

Usual care control

Participants allocated to the control group received ongoing care from their physician/specialist and a daily vitamin D supplement (1000 IU).

Outcome measures

Cognitive tests

The cognitive outcome measures were compiled based on established guidelines with a focus on domains shown to be sensitive to disease and treatment-related changes in patients with cancer.[5 15] Standardised validated neuropsychological tests for objective assessment of cognitive function used in this study included: (1) the trail making test (TMT), a reliable (inter-rater: r=0.74–0.85)[21] measure of psychomotor speed (TMTA), working memory (TMTB) and executive function (TMTB-A); (2) the Rey Auditory Verbal Learning Test (RAVLT), a reliable test (ICC: 0.76)[22] for verbal memory and learning; (3) the digit span forwards (DSF) and backwards (DSB) test, a reliable (inter-rater: r=0.83)[23 24] measure of working memory and processing ability, respectively; and (4) the National Adult Reading Test (NART), a reliable (Cronbach alpha: 0.93; test–retest: r=0.98; inter-rater: r=0.96–0.98)[25] measure of verbal intelligence and estimate of cognitive reserve (premorbid cognitive function).

The CogState Brief Battery was also included, which is a sensitive battery of five computerised cognitive tests, validated in patients with cancer.[26 27] These tests are considered reliable (ICC: 0.72–0.93)[28] with minimal learning effects.[29] The battery takes 10–20 min to complete and provides outcomes for: (1) executive function via the Groton Maze Learning Task, (2) psychomotor function via the Detection Task, (3) attention via the Identification Task, (4) visual memory via the One Card Learning Task and (5) working memory accuracy and visuomotor speed via the One Back Task.[26 27] Prior to commencing each test, participants were given written and verbal instructions and allowed a practice of each test. Outcomes were attained for reaction time for accurate responses (in milliseconds; Identification Task, Detection Task, One Back Task), percentage of correct responses (One Card Learning Task) and number of errors on five sequential trials (Groton Maze Learning Task).[26 27] Reaction time outcomes were analysed after $\log_{10}$ transformation and percentage of correct response outcomes were analysed after square root/arcsine transformation. Raw scores for each test were transformed into a Z-score (using the mean (SD) of the total sample). Time-based tasks were multiplied by −1 when converted to z-scores. Three composite scores were calculated by averaging z-scores: (1) global cognition (Detection, Identification, One Card Learning and One Back task); (2) psychomotor-attention composite (Detection and Identification) and (3) working-memory and learning composite (One Card Learning and One Back Task).[26] Higher z-scores indicated better performance for all measure. Mild cognitive impairment was defined as scoring ≤−1 z-score on three of the five individual tasks.[30]

Anthropometry and blood pressure

Height was measured to the nearest 0.1 cm without shoes, using a stadiometer (SECA, Hamburg, Germany). Body mass was measured to the nearest 0.1 kg using electronic scales (A&D, Tokyo, Japan). BMI was calculated to the nearest 0.1 kg/m^2. Resting blood pressure was measured after a 10 min rest (seated) using an automatic sphygmomanometer (TM-2655P, A&D, Tokyo, Japan), with three measurements taken 1 min apart and the mean of the second and third measurements used.

Demographic, health and medical information

A demographic, clinical and lifestyle questionnaire was used to obtain information on age, education and clinical and lifestyle information including past and current medical conditions (including self-reported cardiometabolic conditions: angina/stroke/heart condition, diabetes, hypertension or hypercholesterolaemia), use of prescription and non-prescription medications, PCa diagnosis date, severity (localised, advanced, presence and location of metastases), treatment history, current treatment(s) and ADT use. Information related to PCa was cross-checked against clinical records provided by the referring clinician.

Physical activity and diet

Habitual physical activity levels were assessed using the Community Healthy Activities Model Programme for Seniors physical activity questionnaire.[31] A 24-hour food recall questionnaire was used to obtain information on usual diet, with all dietary data analysed using Australia-specific software (FoodWorks, Xyris Software, Highgate Hills, Australia).

Depression and anxiety

The Depression Anxiety and Stress Scale (DASS) was also administered.[32] DASS is valid and reliable measure of depression, anxiety, stress and general psychological distress,[32] which are commonly affected by PCa diagnosis.[33] For each scale component, mild symptoms are indicated with a score >4 (depression), >3 (anxiety) and >7 (stress).

Adherence

Adherence to the supplements was assessed using a daily calendar completed by the participants and counting any remaining sachets at 6-month and 12-month follow-up. Exercise training cards were used to monitor exercise adherence which were collected at 6-month and 12-month follow-up.

Adverse events

Adverse events were defined by any unfavourable or unintended health-related event or issue that developed or worsened during the study period as a result of the intervention. Adverse events were recorded at exercise sessions for the Ex +Suppl group and at follow-up testing sessions for controls.

Statistical analyses

A priori sample size calculations were based on the primary bone outcomes and are reported in detail elsewhere.[19] An additional a priori sample size calculation was conducted based on the limited research to date in relevant population groups[34] for the RAVLT cognitive test (sum of trials 1–5; verbal learning) using the following observations: (1) mean (SD) scores were reported to decrease 0.98 (5.04) points following 6 months of ADT,[34 35] and (2) mean (SD) scores were shown to increase 4.93 (7.81) points following 6 months of resistance training in older adults (without PCa) with probable mild cognitive impairment.[35] Given the lack of previous data related to long-term age-related and exercise-related changes in cognition in men with PCa treated with ADT, we conservatively used these within group changes to estimate our between-group effect size after 12 months follow-up. Based on these findings, we estimated (two-sample t-test) that 42 men with PCa treated with ADT (21 per group) would provide 80% power ($p<0.05$, two-tailed) to detect a net difference of 5.9 points (assuming a SD of 5.5) in RALVT (sum of trials 1–5; verbal learning) from baseline to 12-month follow-up.

All analyses were conducted using Stata statistical software V.16 (College Station, Texas, USA). The primary analyses

were conducted with an intention-to-treat approach. A per-protocol analysis was also employed including participants with ≥66% exercise-training and ≥80% nutritional supplement adherence. Normality of distribution was assessed using Q–Q plots of residuals from unadjusted models (online supplemental figure S1). Linear mixed models with random effects (participants) were used to evaluate within-group and between-group changes by time and group-by-time interactions (fixed effects) via the following models: (1) unadjusted; (2) adjusted for age, BMI, depressive symptoms (DASS), ADT duration, habitual physical activity, level of education and presence of cardiometabolic comorbidities (yes/no; hypertension (systolic ≥130 or diastolic ≥80), dyslipidaemia (cholesterol ≥5.5 mmol/L, low-density lipoprotein-cholesterol ≥3.5 mmol/L, high-density lipoprotein-cholesterol <1.0 mmol/L, triglycerides ≥2.0 mmol/L or taking lipid-modifying medication)), self-reported diagnosis of type 2 diabetes, cardiovascular disease or if taking cardiometabolic medication); and (3) model 2 plus changes in body mass. Sensitivity analyses were employed for treatment-based, disease-based and dietary-based factors. No data imputations were made as linear mixed models utilised the maximum likelihood estimation. Changes in proportions of dichotomised cardiometabolic comorbidities (hypertension, dyslipidaemia, type 2 diabetes, cardiovascular disease, cardiometabolic medication) variables by time were examined via McNemar test. Differences in proportions of dichotomised cardiometabolic comorbidities by group were examined via χ^2 test. An alpha-level of 0.05 was adopted for all statistical tests.

RESULTS

Participant characteristics

In total, 214 men expressed interest in participating in the study from which 70 were randomised into Ex + Suppl (n=34) or CON (n=36) (figure 1). On average, men were aged 71 years, with 53% and 30% classified as overweight and obese, respectively (table 1). Collectively, 93% of men reported the presence of at least one cardiometabolic comorbidity. Mean serum 25-hydroxyvitamin D levels were 69.8 nmol/L, with 12 (17%) men classified as having insufficient levels (<50 nmol/L). Median time since diagnosis of PCa was 3.3 years and median treatment duration with ADT was 12 months. Overall, 64% of men were classified as having advanced PCa and 29% as having bone metastases. Regarding treatment, 49% had prior prostatectomy, 69% radiotherapy and 16% chemotherapy. Five (7.1%) men had mild cognitive impairment.

Adherence

Ten (14%) of the 70 participants who completed baseline testing did not complete 12-month follow-up testing (Ex + Suppl: n=6, CON: n=4). Of the 34 participants randomised to Ex + Suppl, 1 did not commence the exercise programme due to a perceived lack of time, while 5 discontinued the exercise programme

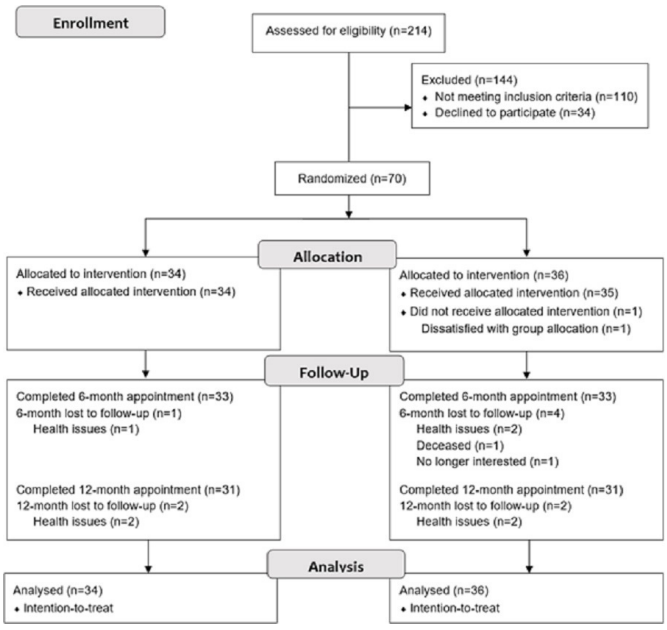

Figure 1 Consolidated Standards of Reporting Trials diagram of participant flow through the study.

(4 within 3 months and 1 after 9 months) due to reasons unrelated to the study (health (n=3); lack of time (n=1); personal reasons (n=1)). Of those who discontinued with the exercise training, four men continued with the supplement alone, and five attended follow-up testing. Mean (SD) and median (IQR) exercise adherence was 56% (30%) and 56% (37%–82%), respectively. Mean (SD) adherence was higher for the supervised versus unsupervised sessions (65% (25%) vs 49% (38%)). Mean (SD) adherence to the nutritional supplement was 77% (30%).

Safety and tolerability

No serious adverse events occurred over the 12-month intervention period. There were 21 musculoskeletal complaints recorded among 14 (41%) patients. Of these n=19 were minor (no treatment required) and resulted in participants either missing or modifying between one and four exercise-training sessions per incident. Two participants required temporary modification of their programmes (<6 weeks) due to exacerbation of pre-existing knee problems. Three participants ceased the nutritional supplement during the first 6 months due to reported digestive discomfort.

Prostate cancer treatment

Details regarding treatment types have been previously reported.[19] In summary, median ADT duration was 5 months greater in the control compared with Ex + Suppl group (table 1). At 6-month follow-up, eight patients (Ex + Suppl: n=1, CON: n=7) had ceased ADT. Another eight patients (Ex + Suppl: n=4, control: n=4) stopped ADT between 6-month and 12-month follow-up. The proportion of men stopping ADT

Table 1 Baseline characteristics of participants

	Ex + Suppl (n=34)	Control (n=36)	Total (n=70)
Age (years)	71 (6)	71 (7)	71 (6)
Height (cm)	175.3 (6.6)	175.0 (6.4)	175.1 (6.4)
Weight (kg)	87.6 (16.9)	89.4 (17.6)	88.5 (17.1)
Body mass index (kg/m^2)	28.4 (4.3)	29.2 (5.7)	28.8 (5.1)
Overweight, n (%)	19 (55.9)	18 (50.0)	37 (52.9)
Obese, n (%)	10 (29.4)	11 (30.6)	21 (30.0)
Cardiometabolic comorbidity*	1.2 (1.0)	1.3 (1.1)	1.2 (1.0)
Prescription medication, n (%)	27 (79.4)	28 (77.8)	55 (78.6)
If yes, total number of medications	2.7 (1.7)	4.1 (2.5)	3.5 (2.5)
Education			
Primary or some high school, n (%)	4 (11.8)	1 (2.8)	5 (7.1)
Completed high school, n (%)	5 (14.7)	6 (16.7)	11 (15.7)
Tech/trade certificate, n (%)	5 (14.7)	7 (19.4)	12 (17.1)
Tertiary, n (%)	20 (58.8)	22 (61.1)	42 (60.0)
Physical activity (kJ/day)	3043 (1770)	2248 (1571)	2634 (1706)
Diet			
Energy (kJ/day)	8920 (2941)	8412 (2178)	8666 (2579)
Protein (g/kg/day)	1.12 (0.42)	1.01 (0.28)	1.07 (0.36)
Carbohydrate (g/day)	219 (99)	210 (76)	214 (87)
Fat (g/day)	75 (31)	79 (37)	77 (34)
Calcium (mg/day)	821 (369)	860 (384)	841 (375)
PCa diagnosis (months), median (IQR)	34 (13–78)	53 (17–137)	40 (14–103)
Stage of PCa, n (%)			
Localised/removed	10 (29.4)	10 (27.8)	20 (28.6)
Advanced	22 (64.7)	23 (63.9)	45 (64.3)
Unknown	2 (5.9)	3 (8.3)	5 (7.1)
Prostate-specific antigen (µg/L), median (IQR)	0.38 (0.02–1.04)	0.17 (0.02–1.20)	0.28 (0.02–1.04)
ADT duration (months), median (IQR)	8 (4–22)	13 (8–24)	12 (5–23)
Depression Anxiety Stress Scale, points	11.2 (8.9)	8.6 (8.4)	9.9 (8.7)
Muscle strength			
Leg press three repetition maximum (kg)	148.6 (29.9)	136.4 (54.0)	142.3 (44.1)
Chest press three repetition maximum (kg)	34.5 (7.0)	38.9 (10.6)	37.8 (9.2)
Seated row three repetition maximum (kg)	45.6 (8.8)	48.3 (10.3)	47.0 (9.6)
Physical function			
30 s sit-to-stand (repetitions)	13.5 (5.5)	12.6 (3.8)	13.0 (4.7)
Timed up-and-go with cognitive task (seconds)	10.95 (3.04)	11.83 (4.48)	11.40 (3.85)
Gait speed (seconds)	1.41 (0.16)	1.43 (0.22)	1.42 (0.19)
400-m walk (seconds)	271.6 (37.1)	290.9 (37.7)	281.53 (38.39)
Balance/mobility			
Four square step test (seconds)	9.56 (1.69)	9.62 (2.25)	9.59 (1.98)
Berg balance (points)	55.5 (0.8)	54.3 (2.6)	54.9 (2.0)

Data are mean (SD) unless stated otherwise.
*Angina/stroke/heart condition, diabetes, hypertension or hypercholesterolaemia.
ADT, androgen deprivation therapy; Ex + Suppl, multi-component exercise program combined with protein, calcium and vitamin D supplementation; PCa, prostate cancer.

did not statistically differ between groups (p=0.114). Other treatments that commenced during the study were radiotherapy (Ex + Suppl: n=4), chemotherapy (Ex + Suppl: n=5, control: n=1) and additional anti-androgens (ie, combined androgen blockade; Ex +Suppl: n=4, control: n=3).

Cognitive function

For all measures of cognitive function, whether analysed unadjusted or adjusted for relevant confounders, there were no significant between-group differences for the changes after 6 or 12 months (table 2). Both groups demonstrated improvements in immediate recall (mean change, Ex + Suppl: 11%, control: 21%), verbal learning (Ex + Suppl: 13%, control: 12%), visuomotor speed (Ex + Suppl: 19%, control: 16%) and task switching (Ex + Suppl: 16%, control: 21%) after 12 months, with the Ex + Suppl group also exhibiting improvements in verbal recall (7.3%), verbal working memory (9.4%) and the CogState working memory learning score (0.24 z-scores) after 12 months (table 2). Per-protocol analyses that included only Ex + Suppl men (n=11) adherent to the intervention (exercise-training ≥66% and nutritional supplement ≥80%) and controls did not alter any of the results related to the between-group effects. Sensitivity analyses revealed similar results when models were adjusted for baseline energy, protein, carbohydrate and fat dietary intake (online supplemental table S1). Results were also similar following adjustment for treatment-based and disease-based factors: (1) ADT duration at baseline, (2) stopping ADT during the study, (3) bone metastases at baseline, (4) starting radiotherapy during the study or (5) starting chemotherapy during the study (online supplemental table S2).

Diet and physical activity

As reported in detail elsewhere,[18] there were no significant within-group changes or between-group differences for daily energy, carbohydrate, protein or fat intake (excluding the supplements; online supplemental table S3). Mean (95% CI) habitual physical activity increased within the control group at 12-month follow-up (453 (70, 835) kJ/day, p=0.040), yet there were no other within-group changes or between-group differences observed at any other time-point (online supplemental table S3).

Cardiometabolic comorbidities

The proportions of men with hypertension, dyslipidaemia, type 2 diabetes and cardiovascular disease did not differ from 0 to 6, 0–12 or 6–12 months among the total sample, Ex + Suppl or CON (online supplemental table S4). Among the total sample, the proportion of men taking cardiometabolic medication increased 16% from 0 to 12 months (p=0.003) and 7% from 6 to 12 months (p=0.025) yet did not change from 0 to 6 months (p=0.059). The proportion of men taking cardiometabolic medication increased for both Ex + Suppl (14%; p=0.025) and CON (17%; p=0.046) from 0 to 12 months, yet not from 0 to 6 (both: p>0.157) or 6–12 months (both: p>0.083). Changes in proportions of men taking cardiometabolic medication did not differ between groups from 0 to 6 months (p=0.435), 0–12 months (p=0.653) or 6–12 months (p=0.596).

DISCUSSION

To our knowledge, this is the first study to investigate the efficacy of a resistance-based multicomponent exercise intervention combined with a multinutrient supplement on objectively measured cognitive function in ADT-treated men with PCa. The main findings from this secondary analysis were that a multicomponent exercise training and nutritional supplementation intervention did not improve cognitive function in men treated with ADT for PCa compared with usual care. Per-protocol analyses (exercise adherence: ≥66%, supplement adherence: ≥80%) yielded similar results, although were limited by the number of participants meeting adherence criteria (n=11).

The finding that there was no effect of our exercise plus nutrition intervention on cognitive function in ADT-treated men is similar to results from two previous RCTs which reported no benefits of 12 months of aerobic and resistance exercise training on a subscale for self-reported cognition (within the Treatment of Cancer Quality of Life Questionnaire C30) compared with an educational material control (ie, patients received printed material regarding physical activity guidelines only) or usual care.[36] The authors noted that individuals with comorbidities were more likely to demonstrate cognitive benefits from the intervention.[36] Our findings also aligned with those of a RCT that demonstrated a 12-month aerobic and resistance exercise programme did not improve on a subscale for self-reported cognition (derived from the European Organization for Research and Treatment of Cancer questionnaire for patients with PCa) compared with usual care in 72 men treated with ADT.[14] However in contrast to our study, prior studies have used self-reported cognitive assessments derived from subscales of quality of life questionnaires (rather than objective tests).[12 14 36] While our study used robust cognitive assessments, including domains previously shown to be affected during ADT, we still did not detect any effect of multidomain exercise and nutrition intervention of any measure of cognitive function.[15] Of note, only 7.1% of men in this study were classified as having mild cognitive impairment at baseline. Collectively, our observations and those of previous studies suggest that multicomponent exercise training alone or with nutritional support may not be a viable therapeutic intervention to improve cognitive function in men treated with ADT for PCa who are largely cognitively intact.

Several reasons may explain the lack of efficacy of our multicomponent exercise training and nutritional supplementation intervention on cognitive function, despite evidence-based recommendations that exercise

Table 2 Mean cognition by domain at baseline, absolute within-group change from baseline and absolute net between-group differences for the change from baseline to 6-month and 12-month follow-up

	Ex + Suppl			Control				
	n	Mean±SD or (95% CI)	P value	n	Mean±SD or (95% CI)	P value	Net difference (95% CI)	P value interaction
Immediate recall, words recalled on trial 1 of Rey Auditory Verbal Learning Test								
Baseline	27	5.3±1.4	–	31	5.7±1.9	–	–	–
Δ 6 months	27	0.9 (0.3 to 1.4)	**0.001**	25	0.0 (–0.7 to 0.7)	0.976	0.4 (–0.4 to 1.3)	0.077
Δ 12 months	26	0.6 (0.1 to 1.2)	**0.024**	24	1.2 (0.5 to 2.0)	**0.001**	–1.0 (–2.1 to 0.0)	0.338
Verbal learning, words recalled on trial 1–5 of Rey Auditory Verbal Learning Test								
Baseline	27	39.0±9.1	–	31	41.1±10.9	–	–	–
Δ 6 months	27	6.2 (3.1 to 9.3)	**<0.001**	25	2.2 (–0.5 to 4.9)	0.104	1.0 (–4.8 to 6.8)	0.062
Δ 12 months	26	5.1 (2.0 to 8.2)	**0.001**	24	4.9 (2.1 to 7.6)	**<0.001**	–2.3 (–8.4 to 3.9)	0.927
Delayed recall, words recalled on trial 7 of Rey Auditory Verbal Learning Test								
Baseline	27	6.9±3.7	–	31	8.1±3.0	–	–	–
Δ 6 months	27	1.2 (0.4 to 2.1)	**0.005**	25	0.5 (–0.2 to 1.3)	0.188	–0.9 (–2.8 to 1.1)	0.224
Δ 12 months	26	0.8 (0.0 to 1.7)	0.055	24	0.2 (–0.6 to 1.0)	0.629	–0.8 (–2.9 to 1.2)	0.273
Verbal recall, sequences recalled on digit span forwards								
Baseline	27	10.9±2.6	–	31	10.5±2.5	–	–	–
Δ 6 months	27	0.2 (–0.5 to 0.9)	0.586	25	0.2 (–0.5 to 1.0)	0.515	0.4 (–0.9 to 1.7)	0.902
Δ 12 months	26	0.8 (0.1 to 1.4)	**0.028**	24	0.5 (–0.2 to 1.3)	0.172	0.6 (–0.7 to 2.0)	0.648
Verbal working memory, sequences recalled on digit span backwards								
Baseline	27	6.4±2.0	–	30	6.4±2.1	–	–	–
Δ 6 months	27	–0.1 (–0.7 to 0.4)	0.619	25	–0.3 (–0.9 to 0.4)	0.422	0.0 (–1.1 to 1.1)	0.778
Δ 12 months	26	0.6 (0.0 to 1.2)	**0.041**	24	–0.1 (–0.8 to 0.6)	0.786	0.5 (–0.7 to 1.7)	0.120
Visuomotor speed, seconds to complete trail making test A								
Baseline	27	35.8±14.0	–	31	35.2±12.3	–	–	–
Δ 6 months	27	–2.0 (–6.1 to 2.1)	0.340	25	–6.2 (–9.5 to 3.0)	**<0.001**	4.4 (–3.4 to 12.2)	0.111
Δ 12 months	26	–6.7 (–10.8 to 2.6)	**0.002**	24	–5.7 (–9.0 to 2.4)	**0.001**	–1.1 (–6.1 to 4.0)	0.716
Task switching, seconds to complete trail making test B								
Baseline	27	75.8±40.0	–	31	85.2±63.3	–	–	–
Δ 6 months	27	–9.1 (–18.9 to 0.7)	0.070	25	–16.8 (v32.7 to 0.9)	**0.039**	–1.1 (–18.9 to 16.6)	0.414
Δ 12 months	26	–12.4 (–22.4 to 2.5)	**0.014**	24	–18.3 (v34.4 to 2.1)	**0.027**	–4.4 (–22.1 to 13.4)	0.544
Executive function, seconds to complete trial making test B minus trail making test A								
Baseline	27	40.1±31.8	–	31	50.0±54.9	–	–	–

Continued

Table 2 Continued

	Ex + Suppl			Control				
	n	Mean±SD or (95% CI)	P value	n	Mean±SD or (95% CI)	P value	Net difference (95% CI)	P value interaction
Δ 6 months	27	−7.1 (−18.1 to 4.0)	0.211	25	−10.7 (−26.0 to 4.5)	0.167	−5.5 (−20.6 to 9.5)	0.698
Δ 12 months	26	−5.9 (−17.1 to 5.3)	0.305	24	−12.7 (−28.1 to 2.8)	0.107	−3.3 (−18.0 to 11.4)	0.478
Psychomotor attention, z-score from CogState composite of detection and identification tasks								
Baseline	31	0.29±0.64	–	34	−0.04±0.86	–	–	–
Δ 6 months	30	−0.31 (−0.59 to to 0.04)	**0.025**	27	−0.09 (−0.38 to 0.21)	0.566	0.08 (−0.38 to 0.54)	0.267
Δ 12 months	30	−0.21 (−0.48 to 0.06)	0.131	24	−0.27 (−0.40 to 0.29)	0.080	0.37 (−0.10 to 0.83)	0.765
Working memory learning, z-score from CogState composite of one back and one card learning tasks								
Baseline	31	0.04±0.71	–	34	−0.14±0.87	–	–	–
Δ 6 months	30	0.02 (−0.20 to 0.24)	0.859	27	0.01 (−0.21 to 0.22)	0.942	0.15 (−0.22 to 0.53)	0.944
Δ 12 months	30	0.24 (0.02 to 0.47)	**0.030**	24	0.13 (−0.09 to 0.36)	0.244	0.33 (−0.02 to 0.68)	0.487
Global cognition, z-score from CogState composite								
Baseline	31	0.11±0.56	–	34	−0.10±0.81	–	–	–
Δ 6 months	30	−0.10 (−0.26 to 0.07)	0.240	27	0.01 (−0.15 to 0.18)	0.865	0.07 (−0.25 to 0.39)	0.348
Δ 12 months	30	0.08 (−0.09 to 0.24)	0.368	24	0.01 (−0.17 to 0.18)	0.938	0.29 (−0.03 to 0.61)	0.575

Baseline values are absolute mean (SD), change values are absolute mean (95% CI) and p value interaction is from the unadjusted model. Ex + Suppl: multicomponent exercise program combined with protein, calcium and vitamin D supplementation.
Bold value signifies P≤0.05.

training, and in particular progressive resistance training, can mitigate cognitive impairment in general population with cancer groups.[10] In older adults, exercise training variables such as adherence, intensity, duration and mode are important determinants with regard to exercise-related changes to cognition.[9] Meta-analyses have shown moderate to large effects to cognition can occur following aerobic, resistance or combined exercise in adults aged ≥50 years,[9 11] with a duration of 45–60 min and at a moderate-to-vigorous intensity and with higher frequencies (eg, most days of the week).[9 11] In older adults with mild cognitive impairment, muscle strength gains following resistance training were also shown to mediate improvements in cognition.[37] Although we observed some improvements in muscle strength and function following the intervention, the magnitude of the changes were modest (14.5% for muscle strength and 9.3%–10.7% for function).[18] This is likely related to poor adherence to exercise sessions (mean 56%) within our study. The reason for the lower adherence to the exercise sessions in our study may in part stem from our inclusion of unsupervised sessions, completed alone rather than in groups (mean adherence to the unsupervised sessions was 49% compared with 65% for supervised sessions). Prior data from a 12-month intervention in men with PCa, observed unsupervised adherence (43%) was approximately half that of supervised sessions (84%).[38] We cannot dismiss that adherence (insufficient frequency, intensity or volume of exercise) was the primary factor underpinning our null results.

A lack of improvement in muscle mass and strength may be instrumental to the absence of improvement in cognitive function in our study given the neuroprotective benefits of preserving muscle mass, strength and physical function.[39] Low muscle mass is associated with greater risk for cognitive decline, particularly when combined with low strength.[40] Contrary to our hypotheses and reported in detail elsewhere,[18] the multicomponent exercise training and nutritional supplementation intervention in our study had limited effects to strength and function and did not elicit any significant between-group improvements in lean mass or muscle cross-sectional area compared with usual care.[18] Reasons may include that the intervention group patients within our study tended to have sufficient dietary protein intake (~1.1 g/kg/day; online supplemental table S3), which is close to the recommended intake of at least 1.20 g/kg/day for older adults when undertaking resistance training.[41] Similarly, the 88% (n=71) of men had sufficient baseline serum 25(OH)D (mean: 69.8 nmol/L). Although lower vitamin D levels (<50 nmol/L) have been associated with lower scores for global cognition, and higher risk of Alzheimer's disease,[42] both groups of men received a vitamin D supplement, and as previously reported there were no significant between-group differences in serum 25(OH)D status from the intervention.[18]

The lack of efficacy of our intervention on measures of cognition in our current study may also be explained in part by the sample of men recruited. For example, cardiometabolic comorbidities in our study were highly prevalent (93%), which is important as they are associated with accelerated cognitive ageing (eg, cognitive decline and dementia) due to an overlap in pathogenic processes.[43] Therefore, the cardiometabolic health of patients in our study may have blunted any potential improvements in cognitive function associated with our intervention. Post-hoc exploratory analysis of cardiometabolic outcomes showed no within group improvement or between-group differences in hypertension, dyslipidaemia, type 2 diabetes or cardiovascular disease (online supplemental table S4). Furthermore, the proportion of men treated with cardiometabolic medication increased similarly by 14% (p=0.025) for Ex + Suppl and 17% (p=0.046) for controls over 12-month follow-up. Drug-related adverse changes to cardiovascular and metabolic physiology may partially explain the variations within cognitive status previously reported in ADT-treated men.[43]

Adaptations to the intervention may have been diminished by the effects of low testosterone levels in our men which are reported to influence brain plasticity.[44] Although we adjusted for baseline duration of ADT, PCa treatment over the span of 12 months differed between groups, with 31% (n=11) of controls discontinuing ADT compared with 15% (n=5) in the intervention group. Evidence has shown that cognitive decline following 9 months of ADT resolves 3 months following cessation.[45] This may in part explain some of the within-group improvements observed in the control group, as well as the increase in habitual physical activity when compared with the intervention group. Our speculation regarding physical activity is further supported by evidence that fatigue also resolves 3 months following ADT cessation.[45] Additionally, a greater number of intervention group patients commenced radiotherapy (intervention: n=4 (12%), control: n=0 (0%)) and chemotherapy (intervention: n=5 (15%), control: n=1 (3%)). Both radiotherapy and chemotherapy are independent risk factors for cognitive decline in patients with cancer[46] ; hence, the adverse effects associated with these therapies may have impacted cognitive function within our study. Despite the randomised design of our study, and adjustment for baseline treatment history, PCa treatment associated with cognitive decline appeared to differ between groups across the duration of the intervention. Although results were not altered when treatment changes were considered in analyses, the study was not powered to detect effects of a change in treatment status to cognition and this should be considered when interpreting our results.

This preplanned secondary analysis was registered with the larger RCT.[19] Strengths of this study included the use of cognitive function tests validated in patients with cancer and recommended by the International Cancer and Cognition Task Force.[15] The limitations of the current study should also be considered when interpreting results. First, exercise training adherence was suboptimal. While this may have impacted cognitive function, it does

represent the pragmatic nature of PCa management and therefore increases the generalisability of our findings to the general ADT-treated population group. Second, PCa treatment tended to differ between groups during the intervention period, although in post-hoc adjusted analyses these results remained unchanged, but a lack of statistical power reduces generalisability. Furthermore, the within-group improvements seen for both groups across several measures suggest a potential practise effect. Finally, we cannot discount volunteer bias whereby our study may have attracted individuals with a greater proclivity for exercise training than the general population of ADT-treated men.

Future interventions seeking to improve cognitive function in ADT-treated men should ensure the intervention is also capable of improving muscle mass, strength and physical function given their neuroprotective benefits. It is clear that strategies to improve exercise training adherence, and in particular unsupervised sessions, warrant future attention. Given social support can facilitate exercise training adherence in older adults,[47] strategies should consider this factor. Furthermore, future studies should also explore the effects of other interventions that may improve cognitive function in this susceptible population group, such as dietary modification and cognitive-based training.

In conclusion, our study showed that a 12-month multicomponent exercise training and nutritional supplementation intervention did not improve cognitive function in men treated with ADT for PCa compared with usual care. While speculative, this may be related to the poor adherence to the exercise intervention and subsequent modest changes in measures of muscle strength and physical function and lack of any marked benefits to other cardiometabolic risk factors related to cognitive function. However, we cannot dismiss that cognitive decline associated with ADT may mechanistically differ to that of general age-related cognitive declines, thus examining other intervention modalities is warranted.

Author affiliations
[1]Institute for Physical Activity and Nutrition (IPAN), School of Exercise and Nutrition Sciences, Deakin University, Geelong, Victoria, Australia
[2]Institute for Nutrition Research, School of Medical and Health Sciences, Edith Cowan University, Joondalup, Western Australia, Australia
[3]Faculty of Health, Deakin University, Geelong, Victoria, Australia
[4]Faculty of Sport and Health Sciences, Department of Health Sciences, Jyvaskylan Yliopisto, Jyvaskyla, Finland
[5]Baker Heart and Diabetes Institute, Melbourne, Victoria, Australia
[6]Radiation Oncology, Alfred Hospital, Melbourne, Victoria, Australia
[7]Division of Cancer Surgery, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia
[8]Sir Peter MacCallum Department of Oncology, University of Melbourne, Parkville, Victoria, Australia

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ORCID iDs
Niamh L Mundell http://orcid.org/0000-0001-5406-3216
Patrick J Owen http://orcid.org/0000-0003-3924-9375
Helen Macpherson http://orcid.org/0000-0002-3603-9359
Patricia M Livingston http://orcid.org/0000-0001-6616-3839
Jeremy L Millar http://orcid.org/0000-0001-8202-8602

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