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Does androgen deprivation impact associations between cognition and strength, fitness and function in community-dwelling men with prostate cancer? A cross-sectional study

Niamh L Mundell ,[1] Patrick J Owen ,[1] Jack Dalla Via ,[1,2] Helen Macpherson ,[1] Robin M Daly ,[1] Steve F Fraser [1]

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[1]Institute for Physical Activity and Nutrition (IPAN), School of Exercise and Nutrition Sciences, Deakin University, Burwood, Victoria, Australia
[2]Institute for Nutrition Research, School of Medical and Health Sciences, Edith Cowan University, Perth, Western Australia, Australia

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

ABSTRACT

Objectives We investigated whether there were differences in associations between cognition with muscle strength, fitness and function in men with prostate cancer (PCa) treated with, and without androgen deprivation therapy (ADT) and non-PCa controls. A secondary aim was to compare differences in the prevalence of cognitive impairment.

Design This cross-sectional study compared 70 ADT-treated men with PCa aged 50–85 years to non-ADT-treated men (n=52) and non-PCa controls (n=70).

Setting University clinical exercise laboratory.

Interventions Nil.

Primary and secondary outcome measures Standardised assessments were conducted for cognition (learning, memory, attention, processing speed and executive function), muscle strength (grip strength and leg press), fitness (400 m walk), gait speed (4 m walk) and dual-tasking mobility (timed-up-and-go with a cognitive task).

Results ADT-treated men showed stronger associations between fitness and executive function and task switching relative to controls (both: p≤0.03). For both PCa groups (independent of ADT use), poorer dual-task mobility was more strongly associated with decreased psychomotor attention (both: p≤0.027) and global cognitive function (both: p≤0.031) compared with non-PCa controls. The overall prevalence of cognitive impairment was low (4%–13%) and did not differ between the groups.

Conclusions The presence of PCa, with or without ADT treatment, did not increase the risk of cognitive impairment relative to non-PCa controls, yet did alter the associations between physical fitness and some measures of functional performance with certain cognitive domains. This highlights the importance of men with PCa maintaining fitness and functional capacity to optimise cognitive health.

Trial registration number This study was registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12614000317695).

Strengths and limitations of this study

- This study was strengthened by the use of a comprehensive battery of cognitive tests and a range of physical outcomes that related to strength, fitness and function.
- A further strength was that we followed recent guidelines from the International Cancer Cognition Task Force with regards to defining cognitive impairment
- A limitation is that this study was a nested cross-sectional substudy within a larger randomised controlled trial, including exercise training and nutritional supplements for androgen deprivation therapy (ADT)-treated men; hence, men treated with ADT with a penchant for exercise may have been more likely to participate.
- Another limitation is that men on ADT recruited to the study had all been treated for a minimum of 3 months; thus, we are unable to draw any conclusions in men who have recently commenced ADT (ie, <3 months).
- Finally, given the cross-sectional design, causality cannot be established between fitness, physical function and certain cognitive domains with ADT.

INTRODUCTION

Prostate cancer (PCa) has the second highest worldwide incidence of all male cancers (14% in 2018), yet a high relative survival rate (8% of cancer-related deaths).[1] Androgen deprivation therapy (ADT) is a mainstay in the treatment of appropriately selected men with metastatic and non-metastatic PCa.[2] ADT is associated with numerous adverse effects, including cardiovascular and metabolic complications, loss of lean (muscle) mass,[3] increase in fat mass and impaired physical performance, beyond that of natural ageing.[4] Many ADT side effects may accelerate cognitive ageing, but evidence is inconclusive regarding effects to risk of developing cognitive impairment.[5] However, heterogeneity in how cognitive impairment is defined and

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quantified has affected the degree to which cognitive impairment has been detected and reported.[6]

ADT has been negatively associated with cognitive performance in a range of domains, including reaction time, spatial and verbal memory, visuomotor speed and executive function, with the largest effects noted for visuomotor function.[7] Nevertheless, it has been difficult to extricate the effects of PCa itself from those of ADT. Androgens, such as testosterone, are proposed to support male memory and visuospatial ability[8] and may play a role in maintaining hippocampal plasticity,[9] yet the differential contributions of cognitive and motor abilities to motor cognitive task performance are less clear.[7] Declines in visuomotor performance associated with ADT use may be secondary to overall declines in motor function caused by ADT, rather than a direct effect of androgen depletion on cognitive processes. To our knowledge, no studies have evaluated the relationship between different cognitive domains reportedly affected by ADT and measures of muscle strength, cardiorespiratory fitness and physical function (mobility) in men with PCa. Importantly, the adverse effects of ADT on physical performance and cognition may be amenable to intervention, thereby reducing treatment-induced comorbidities from ADT.

The interdependence of physical and cognitive declines during normal ageing is speculated to be bidirectional.[10] Age-related and disease-related increases in inflammation, changes in hormonal production and signalling (eg, insulin-like growth factor 1 (IGF-1) resistance, insulin-receptor substrate 1 and growth hormone dysregulation) and cardiometabolic dysfunction, can all directly contribute to both cognitive decline and muscle loss.[11] There is also evidence that reduced muscle strength is prognostic for cognitive status in older adults,[12] and declining muscle strength with age has been linked to an increased risk of Alzheimer's disease.[13] Mobility impairments, particularly slow gait speed, have been associated with poorer cognitive function in older adults.[12] The physiological mechanism(s) underlying this link between muscle strength, physical function and cognition are not completely clear. Skeletal muscle contractions upregulate various anti-inflammatory myokines, neurotrophic and growth factors that are important for neuroplasticity.[14] Cardiorespiratory fitness may also protect against precursors to cognitive impairment such as cerebrovascular, endothelial and neurological degeneration.[15] Associations between muscle strength and function with cognition have been identified in cancer survivors generally.[16] However, whether reduced muscle strength, cardiorespiratory fitness and/or function are directly related to poorer cognitive function in men with PCa-receiving ADT is unknown.

Recent guidelines for measuring cognitive impairment in cancer research advocated the use of objective, validated, domain-specific measures and standardised criteria.[6 17] A variety of cognitive test batteries may be incorporated; however, prior studies have varied in their application and approach to analyses.[18] Therefore, the primary aim of this study was to determine the strength and direction of any associations between muscle strength, cardiorespiratory fitness and physical function with cognitive function in men with PCa treated with and without ADT and non-PCa controls. A secondary aim was to compare the prevalence of cognitive impairment between men with PCa treated with and without ADT and non-PCa controls using standardised test batteries.

MATERIALS AND METHODS

This study was a nested cross-sectional study embedded alongside the baseline of a randomised controlled trial designed to evaluate the combined effects of exercise–training and nutritional supplementation on health outcomes in men with PCa treated with ADT.[19] Recruitment of ADT-treated men was achieved via clinician referral from participating hospitals and support groups and newspaper advertisements from April 2014 to November 2017. PCON and CON were recruited via PCa support groups and newspaper advertisements from October 2014 to February 2016.

Patient and public involvement

Participants were not involved in the development of the research question, or design of the study. All participants were offered an individualised report outlining the results of their assessment in comparison to population-based norms. Additionally, ADT-treated men were eligible to participate in a 12 month exercise and nutritional intervention.[19]

Participants

A total of 70 men aged with PCa pharmacologically treated with ADT for 12 weeks or greater (ADT), 52 men diagnosed with PCa not treated with ADT (prostate cancer control [PCON]) and 70 men not diagnosed with PCa (control [CON]) were included in the study. All men were aged 50–85 years. Exclusion criteria were: (1) non-English speaking; (2) any disorder known to affect bone, calcium or vitamin D metabolism (other than hypogonadism in the ADT group); (3) any current pharmacological intervention known to affect bone metabolism (other than ADT); (4) supplementation with protein, calcium (>600 mg/day) or vitamin D (>1000 IU/day) in the past 3 months; (5) current progressive resistance training (more than one session/week) or weight-bearing impact exercises (>150 min/week) in the past 3 months; (6) current smokers; (7) weight greater than 159 kg; (8) plans to travel for longer than 6 weeks continuously within the following 52 weeks and (9) any absolute contraindications to exercise training (eg, musculoskeletal, cardiovascular or neurological disorders) according to the American College of Sports Medicine.

Measures

Standardised neurocognitive tests were used to assess cognitive function, including domains shown to be

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sensitive to disease and treatment-related changes in patients with cancer (eg, learning and memory, processing speed and executive function).[6] This included the Trail Making Test to assess visuomotor speed (TMTA), task switching (TMTB) and executive function (TMTB minus TMTA).[20] Immediate recall, verbal learning and delayed memory were assessed using the Rey Auditory Verbal Learning Task (RAVLT, Rey auditory verbal learning test: trial 1, trial 1–5 total, trial 7 respectively).[21] The RAVLT is a word list measure for immediate and delayed recall, and verbal learning.[21] Temporary verbal memory and verbal working memory were assessed with the Digit-Span test, which has also been validated in patients with cancer.[22] The National Adult Reading Test was included to provide an estimate of cognitive reserve 6, rather than as a measure proposed to be influenced by ADT.

The CogState Computerised Battery (CCB) (CogState, Melbourne, Australia) was also included to assess cognition, and has been customised and validated for patients with cancer.[22 23] Briefly, participants completed five tests that included game-like stimuli such as playing cards and tasks that measure a range of different cognitive domains: (1) Groton Maze Learning Test (GMT)—executive function, (2) detection task (DET)—processing speed and simple reaction time, (3) identification task (IDN)—choice reaction time and visual attention, (4) one card learning task (OCL)—attention and visual learning and (5) one back task (ONB)—working memory and visuomotor speed.[23] Written and verbal instructions were given and a practice trial undertaken prior to each test. Outcomes were obtained for measures of reaction time of correct responses (in milliseconds) (IDN, DET, ONB), proportion of correct responses (OCL) and total number of errors on five consecutive trials at a single session (GMT). The IDN, DET and ONB reaction time scores were log10 transformed, while the square root of the proportion of correct responses on the OCL task was arcsine transformed.[24] These subtests were used to calculate raw scores, from which z-scores were derived using the mean and SD of the total sample.[25] Three composite scores were calculated by averaging z-scores from specific tests: (1) global cognition (DET, IDN and OCL); (2) psychomotor-attention composite (DET and IDN), and (3) working-memory and learning composite (OCL and ONB).[25] Higher composite scores represent better overall cognitive function.

We used two approaches to determine cognitive impairment (CI). Both approaches align with the International Cancer Cognition Task Force (ICCTF) proposed guidelines for assessing cognitive function in patients with cancer.[26] The first method (standard battery (SB)) was based on scores 2-SD below the sample mean on at least two of eight tests from the TMT (TMTA, TMTB, TMTB-TMTA), digit span and RAVLT tests (trials 1, 1–5, 7, DS forward, DS backwards).[6 17] The second method used five cognitive domains from the CCB: psychomotor function/processing speed (detection), attention (identification), working memory (one-back), visual memory (one-card-learning) and executive function errors (the GMT). For this method, CI was indicated by a z score −1.0 SD or below the sample mean on three of the five tests.[17] Both of these approaches are conservative selections within the range of appropriate test batteries possible under the ICCTF criteria, with the probability of exceeding cut-off criteria by chance p≤0.015 to ≤0.032, respectively.[27]

As previously reported,[19] lower limb muscle strength (kg) was measured using a three repetition maximum (3-RM) protocol (leg press, Synergy Omni Leg Press S-31OPD, Yatala, QLD, Australia) while upper limb strength was assessed using grip strength (Jamar Plus Digital, Lafayette Instrument Company, IN, USA), with the highest score (kg) of three attempts from either the left or right hand recorded. Dual-task mobility was measured using the timed-up-and-go test with an additional cognitive task (DT TUG) using methods described previously.[19] The time to complete the test was recorded with a stopwatch. Number of correct digits was also recorded; however, studies in non-cancer adults have indicated that an increase in cognitive load while dual tasking produces a trade-off effect to gait speed, regardless of the degree of difficulty of the cognitive task.[28] Therefore, the DT TUG speed (sec) was used as an indication of physical performance (mobility) under cognitive load. Gait speed and estimated cardiorespiratory fitness were measured with the 4 m usual walk test and 400 m walk test, respectively.[29] Resting blood pressure was calculated after an initial 10 min, seated rest using the means of the final two of three measurements taken by an automatic sphygmomanometer (TM-2655P, A&D, Tokyo, Japan).[30] Height was measured using a stadiometer to the closest 0.1 cm, (220, Seca, Hamburg, Germany). Body mass was be measured using electronic scales (UC-321, A&D, Tokyo, Japan) to the closest 0.1 kg. Body mass index (BMI) was calculated to the closest 0.1 kg/m^2.

A questionnaire incorporating demographics, lifestyle and clinical information was used to obtain specific age, education, comorbidities, alcohol intake, PCa status and treatment details. Any discrepancies or queries with prior treatment details were resolved by checking medical records supplied by participants, or by their referring clinician. The Community Healthy Activities Model Programme for Seniors physical activity questionnaire was used to determine participation in a broad list of low, moderate and vigorous physical activities, with moderate-vigorous physical activity (kJ per week) reported.[31] The Depression Anxiety and Stress Scale was used to provide a measure of depression, anxiety, stress and general psychological distress, all of which have been shown to be altered by PCa diagnosis.[32]

Data analysis

All analyses were performed using Stata statistical software V.15 (StataCorp, College Station, Texas). Normality of the distribution of residuals was assessed visually via quantile–quantile plots and histograms. Between-group

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comparisons of participant characteristics were assessed by χ^2 tests for categorical variables and analyses of variance for continuous variables. The strength and direction of associations between cognitive outcomes and measures of muscle strength, cardiorespiratory fitness and function were first assessed using Pearson's correlation coefficient in each group of men separately and all men combined. Analyses of covariance was then used to compare regression line slopes between groups for significant correlations between measures of muscle strength, cardiorespiratory fitness and function with cognitive function. To reduce the risk of type II error due to multiple comparisons, post hoc analyses applied the Tukey test. If no differences in slopes were identified, intercepts were compared between groups assuming identical slopes.[33] An alpha level of <0.05 was adopted for all statistical tests.

RESULTS

Participant characteristics of each group are presented in table 1. The mean (SD age of the total sample was 70 (7) years. Median (range) ADT duration was 12 (3–166) months. The treatment methods for ADT were as follows: goserelin (n=40, 57.1%), leuprorelin (n=14, 20%), goserelin and bicalutamide (n=5, 7.1%), leuprorelin and bicalutamide (n=3, 4.3%), triptorelin (n=3, 4.3%), degarelix (n=2, 2.9%), abiraterone (n=1, 1.4%), degarelix and bicalutamide (n=1, 1.4%) and enzalutamide (n=1, 1.4%). Stage of PCa differed between ADT and PCON, with approximately two-thirds (64%) of the former having had localised PCa (with or without previous prostatectomy) and most (85%) of the latter unsure of PCa stage. On average, ADT had a higher BMI than PCON (mean difference, 2.2 kg/m^2, p=0.010), but not CON. Men treated with ADT had 9.5% (p=0.003) and 13% (p<0.001) lower grip strength compared with PCON and CON, respectively. The 400 m walk test took 4.0% (p=0.002) and 8.0% (p<0.001) longer for the ADT compared with PCON and CON, respectively. PCON participants had fewer anxiety symptoms than CON (p=0.007), but not ADT (p=0.060). There was no significance between-group differences for alcohol consumption, total/cardiometabolic comorbidities, IQ, highest level of schooling or depressive/anxiety/stress symptomatology.

Comparisons of cognitive function across the three groups are shown in table 2. On average, ADT had 17% and 13% slower visuomotor speed (TMTA) than PCON (p=0.011) and CON (p=0.042), respectively. Both ADT and PCON had 0.5 SD (p=0.003) to 0.7 SD (p<0.001) slower simple reaction time (DET) and 0.4 SD (p=0.035) to 0.6 SD (p=0.001) slower choice reaction time when compared with CON. Choice reaction time (IDN) was also 0.4 SD to 0.6 SD slower in ADT (p=0.035) and PCON (p=0.001) compared with CON. Psychomotor-attention composite scores (Cogstate) were lower in both ADT (−0.4 SD, p=0.006) and PCON (−0.6 SD, p<0.001) compared with CON. Finally, global cognition was lower in PCON (−0.3 SD, p=0.019) with a trend for ADT (−0.3 SD, p=0.073), compared with CON. Notably, in further analyses that adjusted for obesity and anxiety, the only difference to the initial analyses was that working memory speed in ADT was slower compared with PCON (p=0.006), with no change to any other results.

Associations between muscle strength, cardiorespiratory fitness and physical function with cognition for each of the three groups separately are shown in table 3. For leg press and grip strength, there were little or no associations with the RAVLT or digit span cognitive measures in any of the groups. In contrast, there were a number of significant correlations in each group between these two measures of muscle strength with the TMT and Cogstate composite cognitive outcomes (table 3), indicating that greater muscle strength was associated with better cognitive performance. However, when these associations were compared between groups, there were no group differences in the strength (slope) of the muscle strength to cognition relationships (online supplemental figure 1). Pooled data showed that when all men were combined, there were a number of significant associations between measures of lower and upper limb strength with several cognitive domains (online supplemental table 1)

The associations between physical function and cardiorespiratory fitness with cognition by group are shown in table 3. For gait speed, there were little or no associations with any of the cognitive measures in any of the groups. In contrast, there were a number of significant relationships within each of the groups between cardiorespiratory fitness and DT TUG with various cognitive measures. Specifically, the findings indicate that a greater level of fitness and dual task mobility were associated with better cognitive function across a number of domains for all. When these associations were compared between the three groups of men, the following significant differences in the slope were identified: (a) poorer cardiorespiratory fitness (slower 400 m walk time) was more strongly associated with a worse task switching performance (TMTB) in ADT compared with both PCON (p=0.018) and CON (p=0.032) (figure 1A), (b) poorer cardiorespiratory fitness was more strongly associated with a worse executive function (TMTB-A) in ADT when compared with PCON (p=0.009) and CON (p=0.037) (figure 1B), (c) slower dual task mobility (DT TUG) was more strongly associated with a worse psychomotor-attention composite scores in both ADT (p=0.027) and PCON (p=0.012) relative to CON (figure 2A), (d) slower dual task mobility was more strongly related to a worse working-memory and learning composite scores in ADT compared with CON (p=0.006), and to a lesser degree PCON (p=0.051) (figure 2B), (e) slower dual task mobility was more strongly associated with a worse global cognition in both ADT (p=0.001) and PCON (p=0.031) relative to CON (figure 2C); (f) slower dual task mobility was similarly associated with poorer performance in tests of task switching (figure 3A) and executive function (figure 3B) for all groups. However, comparison of the intercepts revealed that for a given dual task mobility time, ADT performed

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Table 1 Characteristics of men with prostate cancer treated with androgen deprivation therapy (ADT), prostate cancer controls (PCON) and non-PCA controls (CON)

Variable	ADT	PCON	CON	P-value
N	70	52	70	
Age, year	71±6	69±6	69±7	0.072
Stage of prostate cancer, n (%)				
Localised/removed	45 (64.3)	6 (11.1)	–	<0.001
Advanced	5 (7.1)	2 (3.7)	–	
Unknown	20 (28.6)	44 (84.6)	–	
Previous prostatectomy, n (%)*	34 (48.6)	36 (69.2)	–	0.022
Previous radiotherapy, n (%)*	48 (68.6)	12 (23.1)	–	<0.001
Previous chemotherapy, n (%)*	11 (15.7)	0 (0.0)	–	0.003
Active surveillance, n (%)	–	8 (15.4)	–	–
Weight, kg	85.5±17.1	82.4±13.5	85.1±14.7	0.073
Body mass index, kg/m^2	28.8±5.1	26.6±4.0	27.5±3.1	0.013
Normal, n (%)	12 (17.1)	24 (46.2)	15 (21.4)	0.003
Overweight, n (%)	37 (52.9)	19 (36.5)	41 (58.6)	
Obese, n (%)	21 (30.0)	9 (17.3)	14 (20.0)	
Alcohol consumption, n (%)	32 (53.3)	16 (32.7)	32 (45.7)	0.095
If yes, g/d	25±20	15±10	23±19	0.190
Total comorbidities,† n	2±2	2±2	2±1	0.449
Cardiometabolic comorbidities,‡ n	1±1	1±1	1±1	0.354
Hypertension, n (%)	32 (45.7)	20 (38.5)	24 (34.3)	0.377
Heart disease, n (%)	20 (28.6)	7 (13.5)	20 (28.6)	0.096
Hypercholesterolaemia, n (%)	27 (38.6)	17 (32.7)	26 (37.1)	0.792
Type 2 diabetes, n (%)	7 (10.0)	5 (9.6)	4 (5.7)	0.608
IQ points	117±5	115±5	116±5	0.253
Highest level of schooling				
Some high school, n (%)	5 (7.1)	3 (5.8)	8 (11.4)	0.198
Completed high school, n (%)	11 (15.7)	3 (5.8)	7 (10.0)	
Tech/trade certificate, n (%)	12 (17.2)	17 (32.7)	12 (17.1)	
Tertiary, n (%)	42 (60.0)	29 (55.7)	43 (61.5)	
Depressive symptoms, n (%)	10 (16.1)	9 (17.3)	14 (20.0)	0.838
Normal, n (%)	52 (83.9)	43 (82.7)	56 (80.0)	0.602
Mild, n (%)	6 (9.7)	2 (3.9)	3 (4.3)	
Moderate, n (%)	2 (3.2)	5 (9.6)	6 (8.6)	
Severe, n (%)	0 (0.0)	1 (1.9)	2 (2.8)	
Extremely severe, n (%)	2 (3.2)	1 (1.9)	3 (4.3)	
Anxiety symptoms, n (%)	14 (22.6)	5 (9.6)	21 (30.0)	0.026
Normal, n (%)	48 (77.4)	47 (90.4)	49 (70.0)	0.205
Mild, n (%)	5 (8.1)	3 (5.8)	8 (11.4)	
Moderate, n (%)	5 (8.1)	0 (0.0)	5 (7.2)	
Severe, n (%)	3 (4.8)	2 (3.8)	4 (5.7)	
Extremely severe, n (%)	1 (1.6)	0 (0.0)	4 (5.7)	
Stress symptoms, n (%)	18 (29.0)	13 (25.0)	25 (35.7)	0.426

Continued

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Table 1 Continued

Variable	ADT	PCON	CON	P-value
Normal, n (%)	44 (71.0)	39 (75.0)	45 (64.3)	0.338
Mild, n (%)	3 (4.8)	5 (9.6)	9 (12.9)	
Moderate, n (%)	10 (16.2)	5 (9.6)	6 (8.6)	
Severe, n (%)	3 (4.8)	3 (5.8)	5 (7.1)	
Extremely severe, n (%)	2 (3.2)	0 (0.0)	5 (7.1)	
Muscle strength				
Leg press, kg	139.7±46.9	143.5±42.0	160.3±49.5	0.048
Grip strength, kg	37.9±6.5	41.7±6.7	43.3±8.0	<0.001
Physical function and fitness				
Gait speed, m/sec	1.42±0.21	1.48±0.19	1.50±0.22	0.089
DT TUG, sec	11.33±3.90	11.64±4.58	11.49±4.97	0.933
400 m walk, sec	287.25±38.4	275.92±32.0	265.10±41.70	0.004

Data are mean±SD or number (percentage) within group. DT-TUG, dual task timed-up-and-go.
*ADT versus PCON only.
†Respiratory/pulmonary diseases, musculoskeletal, neurological, or immunological conditions.
‡Hypertension, type 2 diabetes, heart disease, hypercholesterolaemia.

more poorly on the task-switching test (TMTB intercept p=0.031) and executive function test (TMTB-A intercept p=0.037) compared with CON only. There were no other significant differences in slopes or intercepts between the groups (online supplemental figure 2).

Overall, nine (13%) ADT men, two (3.9%) PCON and seven (10%) CON demonstrated cognitive impairment using the standard battery (figure 4A). In contrast, four (5.7%) ADT men, five (9.6%) PCON and four (5.7%) CON had cognitive impairment using the CCB (figure 4B). The prevalence of cognitive impairment did not differ significantly between the three groups for the standard battery (p=0.234) or CCB (p=0.633).

DISCUSSION

The main finding from this study was that PCa, with and without ADT treatment, appears to alter the association between physical function and fitness (but not muscle strength), with various measures of cognitive function. For ADT-treated men specifically, stronger associations were evident between cardiorespiratory fitness and task switching ability and between cardiorespiratory fitness and executive function compared with both controls, indicating a stronger link between poorer fitness and reduced cognition in the ADT-treated men. Additionally, in both ADT and non-ADT men with PCa compared with CON, there were stronger inverse associations between dual-task mobility and psychomotor attention as well as dual-task mobility and global cognition. However, the overall prevalence of cognitive impairment based on established criteria was relatively low and similar for men with PCa treated with and without ADT (4%–13%), and no different from controls (6%–10%), although ADT-treated men had 17% and 13% lower visuomotor speed compared with PCON (p=0.011) and CON (p=0.042), respectively.

Previous research has shown that ADT use is associated with a deterioration in muscle strength, cardiorespiratory fitness and functional performance.[3 4] In non-PCa lower muscle strength, fitness and function are linked to reduced cognitive function.[34] Our study is the first to show that the relationship between some of these physical measures and cognitive function differs between ADT-treated men relative to PCa and/or CON. A causal association cannot be established between cardiorespiratory fitness and both task-switching ability and executive function. However, these outcomes offer insight into the previously reported mixed findings reported in prior research regarding the effects of ADT versus non-ADT on cognition in men with PCa.[6 35] These adverse effects are supported by data showing that lower testosterone concentrations are associated with lower fitness and function[36] as well as deficits in memory[37] and greater risk for Alzheimer's disease.[38] It is possible that ADT-induced hypogonadism may accelerate age-related declines in brain processes, contributing in part to deteriorations in certain cognitive domains (eg, memory and visuospatial function).[8] ADT-induced losses in cardiovascular fitness and function[6 39] may also have secondary effects to cognition, creating a bidirectional and compound association.

An interesting finding from this study was that muscle strength was significantly lower in ADT-treated men compared with controls, but any associations between leg press muscle strength or grip strength with the various cognitive measures were either not significant or mixed across the three groups. This suggests that the ADT group had lower muscle strength, and while ageing may affect the association,[10] PCa, with or without ADT, does

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Table 2 Mean scores for the individual cognitive tests and CogState composite Z-scores for men with prostate cancer treated with androgen deprivation therapy (ADT; n=70), prostate cancer controls (PCON; n=52) and non-PCA controls (CON; n=70) and the mean unadjusted differences between the groups

	Unadjusted mean (SD)				Unadjusted mean difference (95% CI)		
Variable	**ADT**	**PCON**	**CON**	**P-value**	**ADT versus PCON**	**ADT versus CON**	**PCON versus CON**
Rey Auditory Verbal Learning Test, n							
Immediate recall	6 (2)	6 (1)	5 (1)	0.564	0 (–1, 0)	1 (0, 1)	1 (0, 1)
Verbal learning	40 (10)	40 (9)	42 (10)	0.608	0 (–4, 4)	–2 (–5, 2)	–2 (–6, 2)
Delayed recall	8 (3)	8 (3)	8 (3)	0.885	0 (–1, 1)	0 (–1, 1)	0 (–2, 1)
Digit span, n							
Verbal temporary memory	11 (3)	11 (2)	11 (3)	0.930	0 (–1, 1)	0 (–1, 1)	0 (–1, 1)
Verbal working memory	7 (2)	6 (2)	7 (3)	0.536	1 (–1, 1)	0 (–1, 1)	–1 (–1, 0)
Trail making test, sec							
Visuomotor speed	35.5 (13.0)	29.9 (8.5)	31.1 (10.9)	0.021	5.6 (1.4, 9.8)*	4.4 (0.5, 8.2)*	–1.2 (–5.3, 2.8)
Task switching	80.8 (53.5)	65.7 (22.5)	70.3 (32.0)	0.107	15.2 (0.5, 29.8)	10.5 (–3.0, 24.0)	–4.7 (–18.8, 9.4)
Executive function	45.4 (45.5)	35.8 (18.8)	39.2 (25.7)	0.289	9.6 (–2.7, 21.9)	6.2 (–5.2, 17.5)	–3.5 (–15.2, 8.6)
CogState composite scores							
Psychomotor-attention	–0.1 (0.9)	–0.3 (0.9)	0.3 (0.8)	0.001	0.2 (–0.1, 0.5)	–0.4 (–0.7,–0.1)**	–0.6 (–0.9,–0.3)***
Working memory learning	0.0 (0.8)	0.0 (0.7)	0.0 (0.8)	0.952	0.0 (–0.3, 0.3)	0.0 (–0.3, 0.2)	0.0 (–0.3, 0.2)
Global cognition	–0.1 (0.7)	–0.1 (0.6)	0.2 (0.7)	0.049	0.0 (–0.2, 0.3)	–0.3 (–0.4, 0.0)	–0.3 (–0.5, 0.0)*

Data are unadjusted mean (SD) and unadjusted mean difference (95% CI). *p<0.05, **p<0.01, ***p<0.001. Visuomotor speed (Trail making Test part A), Task Switching (Trail making Test part B), Executive Function (Trail making Test part B-A); Immediate recall (Rey Auditory Verbal Learning Test (RAVLT) trial 1); Verbal learning (RAVLT trial 1–5 inclusive); Delayed recall (RAVLT trial 7); Verbal temporary memory (Digit Span forwards); Verbal working memory (Digit Span backward). CogState measures: Simple reaction time (DET speed); Choice reaction time (IND speed); Working memory speed (ONB speed), Working memory accuracy (ONB accuracy), Visuospatial executive function (GML errors); Psychomotor-attention (DET and IDN); Working-memory and learning (OCL and ONB), Global cognition (DET, IDN, and OCL).

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Table 3 The associations between muscle strength and function and different measures of cognition in men with prostate cancer treated with androgen deprivation therapy (ADT; n=70), prostate cancer controls (PCON; n=52) and non-PCA controls (CON; n=70)

Variable		Leg press 3RM	Grip strength	Gait speed	400 m walk	TUGC
Rey Auditory Verbal Learning Test						
Immediate recall	ADT	0.24	0.083	0.144	**−0.268***	−0.212
	PCON	0.073	−0.029	0.299	**−0.354***	**−0.428****
	CON	0.23	0.239	0.087	**−0.346****	−0.232
Verbal learning	ADT	0.071	0.077	0.122	**−0.284***	**−0.310***
	PCON	0.169	−0.032	0.261	−0.287	**−0.374***
	CON	0.259	**0.257***	**0.191*****	**−0.458****	−0.247
Delayed recall	ADT	−0.013	0.054	0.076	−0.245	−0.247
	PCON	−0.099	−0.097	0.173	−0.266	**−0.322***
	CON	0.183	0.231	0.179	**−0.359****	−0.08
Digit span						
Temporary verbal memory	ADT	0.169	0.199	0.157	**−0.341***	−0.241
	PCON	0.087	0.111	0.021	−0.029	−0.253
	CON	0.158	0.071	0.204	**−0.334****	**−0.288***
Verbal working memory	ADT	−0.051	0.038	0.097	−0.028	**−0.275***
	PCON	**0.368***	0.148	**0.309***	−0.195	**−0.349***
	CON	0.108	0.132	0.209	−0.208	−0.155
Trail making test						
Visuomotor speed	ADT	−0.179	−0.172	**−0.267***	**0.372****	**0.329***
	PCON	**−0.206***	−0.016	−0.269	**0.400****	**0.399****
	CON	**−0.446*****	**−0.313****	**−0.275***	**0.282***	0.217
Task switching	ADT	−0.225	**−0.259***	−0.196	**0.403****	**0.347****
	PCON	**−0.357***	−0.001	−0.133	0.172	**0.358***
	CON	**−0.483*****	**−0.262***	−0.146	**0.330****	0.212
Executive function	ADT	−0.215	−0.255	−0.154	**0.370****	**0.313***
	PCON	−0.321	0.006	−0.038	0.026	0.249
	CON	**−0.416****	−0.194	−0.065	**0.292***	0.172
CogState composite scores						
Psychomotor-attention	ADT	0.261	**0.307***	0.193	−0.176	**−0.389****
	PCON	0.069	0.213	**0.287***	−0.205	**−0.473*****
	CON	**0.358****	**0.317****	0.1	−0.235	−0.073
Working memory learning	ADT	0.264	0.126	0.146	−0.144	**−0.467*****
	PCON	0.179	−0.006	0.066	−0.136	−0.228
	CON	**0.303***	**0.382****	0.132	−0.237	−0.098
Global cognition	ADT	**0.313***	**0.254***	0.209	**−0.289***	**−0.522*****
	PCON	0.174	0.162	0.248	−0.23	**−0.491*****
	CON	**0.402****	**0.444*****	0.155	**−0.294***	−0.099

Data are Pearson's correlation coefficient adjusted for multiple comparisons using Tukey's test. *p<0.05, **p<0.01, ***p<0.001 (**bold**). Visuomotor speed (Trail making Test part A), task switching (Trail making Test part B), executive function (Trail making Test part B-A); immediate recall (Rey Auditory Verbal Learning Test (RAVLT) trial 1); verbal learning (RAVLT trial 1–5 inclusive); delayed recall (RAVLT trial 7); verbal temporary memory (Digit Span forwards); verbal working memory (Digit Span backward). CogState measures: Simple reaction time (DET speed); choice reaction time (IND speed); working memory speed (ONB speed), working memory accuracy (ONB accuracy), visuospatial executive function (GML errors); psychomotor attention (DET and IDN); working memory and learning (OCL and ONB), global cognition (DET, IDN, and OCL).

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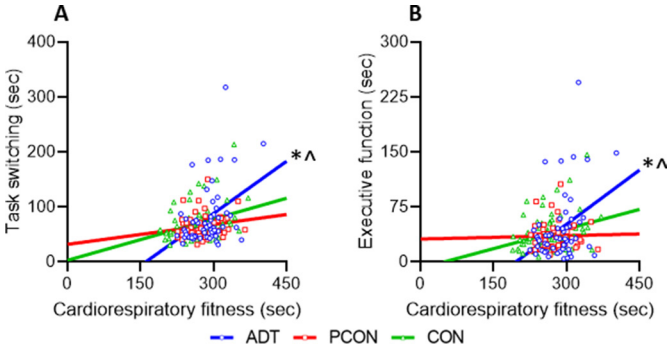

Figure 1 Scatterplots of the relationship between cardiorespiratory fitness (400 m walk test performance) with task switching (trail making test B; A) and executive function (trail making test B-A; B) in men treated with androgen deprivation therapy (ADT), prostate cancer controls (PCON) and non-PCA controls (CON). Slope differences: *p<0.05 compared with PCON, ^ p<0.05 compared with CON.

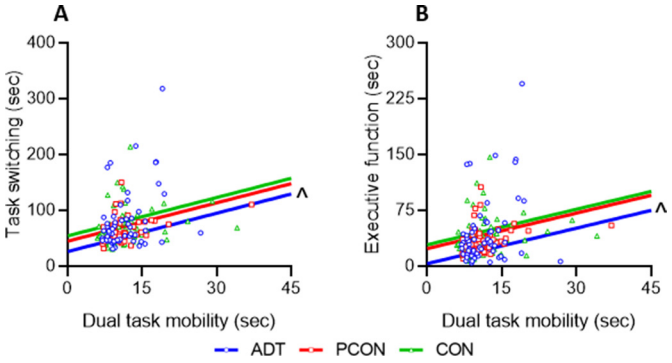

Figure 3 Scatterplot of the relationship between dual-task mobility (timed-up-and-go with cognitive task) with task switching (trail making test B; A) and executive function (trail making test B-A; B) in men treated with androgen deprivation therapy (ADT), prostate cancer controls (PCON) and non-PCA controls (CON). Since there were no differences in the slope, the regression lines assume identical slopes but there were between group differences in the intercepts: ^p<0.05 intercept difference compared with CON.

not alter the degree to which strength impacts cognition. Mechanistically, muscle contractions can stimulate an increase in circulating brain-derived neurotrophic factor (BDNF), which is used for peripheral muscle metabolic processes.[14] With regards to central cognitive processes, BDNF is thought to partially compensate for testosterone-mediated plasticity in testosterone depletion.[40] However, permeability of muscle-derived BDNF across the blood-brain barrier is uncertain;[14] therefore, peripheral muscle contractions are less likely to be relevant to cognition with or without ADT. By contrast, cardiorespiratory exercise is associated with increased circulating vascular and endothelial growth factors (eg, IGF-1), which may directly upregulate hippocampal BDNF,[14] theoretically facilitating hippocampal synaptic plasticity in the absence of testosterone. Thus, those with greater strength may not necessarily benefit cognitively in the context of androgen depletion, but greater cardiorespiratory fitness may stimulate hippocampal BDNF and, thereby, partially compensate for a cognitive disadvantage with androgen deficiency. As methods of measuring hippocampal BDNF in humans evolve, related future studies may consider, including such a measure.

Testosterone depletion has been linked with dementia risk and AD, and prior research has suggested a role of ADT in progression to AD and dementia.[26] It is worth noting that compromised cardiometabolic health increases the risk of neurocognitive impairment, and imaging studies have demonstrated that patients on ADT show reduced functional connectivity in brain structures (which may be vulnerable to vascular risk) associated with reaction time, attention, memory, information processing and spatial awareness.[41 42] ADT promotes artherogenesis and is associated with compromised cardiovascular health.[3 39] In the current study, matching samples based solely on age may have contributed to between-group differences in demographic characteristics; however; analysis of participant characteristics did not identify any between-group difference in habitual physical activity

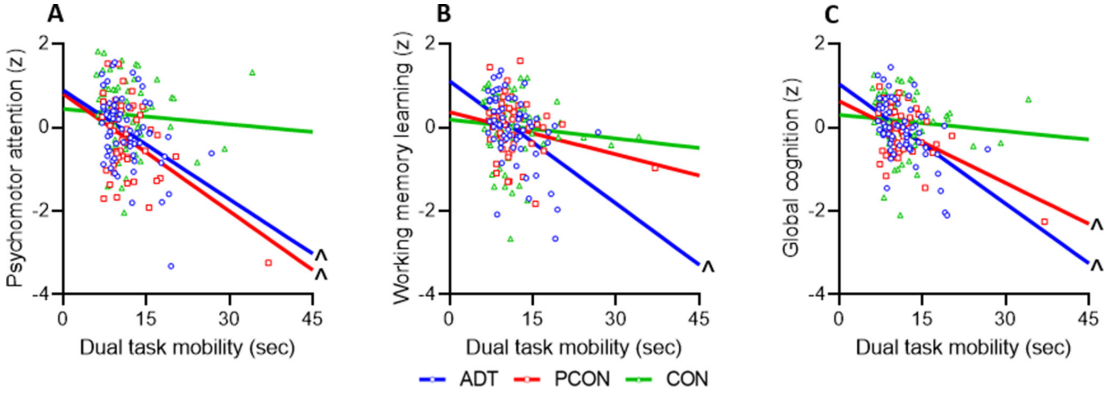

Figure 2 Scatterplots of the relationship between dual-task mobility (timed-up-and-go with cognitive task) with Cogstate psychomotor-attention composite score (A), Cogstate working memory-learning composite score (B) and Cogstate global cognitive function score (panel C) in men treated with androgen deprivation therapy (ADT), prostate cancer controls (PCON) and non-PCA controls (CON). Slope differences: ^p<0.05 compared with CON.

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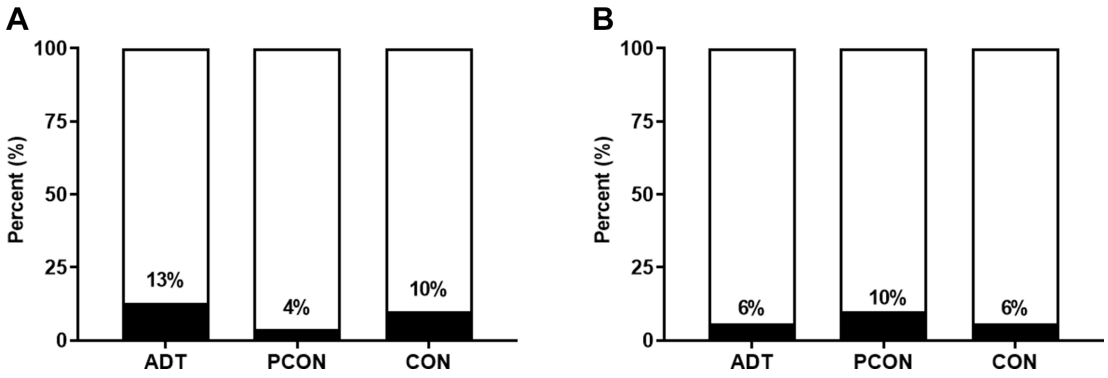

Figure 4 The prevalence of cognitive impairment in men treated with androgen deprivation therapy (ADT), prostate cancer controls (PCON) and non-PCA controls (CON) using the standard battery (A) consisting of the trail making test, Rey auditory verbal learning test and digit span, and the Cogstate computerised battery (B) consisting of the Groton maze learning test, detection task, identification task, one card learning task and one back task. □-No cognitive impairment; ■-cognitive impairment.

levels or the number of comorbid conditions (including hypertension, type 2 diabetes, heart disease, hypercholesterolemia, respiratory/pulmonary diseases, musculoskeletal, neurological or immunological conditions). In addition, in an exploratory analysis when further adjustments were made to account for between-group differences in BMI and anxiety, results were unchanged. However, subclinical levels of cardiometabolic dysfunction have been identified in adults prior to clinical manifestation of disease.[41] Changes to cardiometabolic health that have not reached clinically detectable levels (eg, subclinical atherosclerosis, arterial stiffness, endothelial dysfunction)[41] are less likely with increased cardiorespiratory fitness.[39] These changes may be present in ADT men to a greater degree than for controls. Alternatively, the between-group differences in association between cardiorespiratory fitness and cognitive function may be due to the combined effects of testosterone suppression on neuroplasticity and cardiometabolic health, rather than a direct effect of ADT per se.

Another key finding from this study was the motor–cognitive associations observed in both groups of men with PCa, indicating that this relationship cannot be attributable solely to testosterone suppression. Furthermore, reaction time and psychomotor attention deficits were apparent in all men with PCa regardless of whether they received ADT. The dual-task mobility test comprised multiple motor components (lower limb power, initiation of stepping, acceleration, deceleration, turning ability) and has been linked with executive function and early detection of functional decline in older adults.[43] This study did not measure serum hormones; however, elevated serum IGF-1 has been identified as a marker PCa risk, and serum IGF-1 suppression is a common target of cancer treatments.[44] IGF-1 also plays an anabolic role in tissue regeneration and cerebral neuromodulation (facilitated by exercise), and age-related declines in serum IGF-1 may contribute to declines in cognitive and motor function for men with PCa.[44] Thus, any cancer treatment that impacts IGF-1 may impact motor and cognitive function, which may explain an effect on cognition in PCa patients,[45] thereby affecting both ADT and PCON to varying degrees. Future studies in men with PCa may consider the potential for endocrine and hormonal contributions to motor–cognitive associations for men with PCa. In addition, the merits of cardiorespiratory and multimodal exercise training in men with PCa are worth investigation, as these have shown benefits to function, cardiometabolic and cognitive health in older adults.[46]

This study did not identify any between-group differences in the prevalence of cognitive impairment using recommended criteria. Comparisons to prior studies are difficult as these studies have often yielded inconsistent findings,[6] but an estimated 47%–69% of men with PCa treated with ADT have cognitive deficits in at least one domain over 6–12 months.[46] These mixed findings are likely due to heterogeneous methodology, varying definitions of cognitive impairment and inconsistent use of objective, sensitive, validated tests (eg, an Auditory Verbal Learning Test, Digit Span and TMT).[6 7] There are few studies using recommended criteria,[18] and to our knowledge, none in ADT-treated men, which adjust for multiple comparisons in cognitive test batteries (as the number of cognitive tests used increases, the number of SD from the norm required for an abnormal classification should decrease proportionally).[17] A prospective study observing ICCTF criteria (and adjusting for multiple comparisons) assessed objective cognitive performance in men with PCa (n=58) with ADT and having had prostatectomy only.[47] This study found that men receiving ADT for a period of 6 or 12 months were 70% and 50%, respectively, more likely to demonstrate an impaired performance in executive function than controls, but based on the ICCTF criteria, cognitive impairment did not differ across groups.[47] Our study also showed that the clinical utility of the two batteries used to determine cognitive impairment are comparable in this patient population. According to these criteria, there were no significant differences in cognitive impairment between ADT-treated men, PCa controls and CON in our study. It is possible that this

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finding is due to a recruitment bias inherent in the larger study. Men recruited for this study were offered a free 'health assessment', which may have led to an inclination for more health-focussed individuals to volunteer, biased participation towards individuals with healthy lifestyles and less chronic disease.[48] In addition, batteries selected were highly specific (SB: p≤0.015, CCB: p≤0.032).[17 27] We also adjusted for multiple comparisons, therefore may have underestimated the prevalence of an abnormal result in any one test. Although our study did not identify a difference in the overall prevalence of cognitive impairment, across the specific cognitive domains, we identified deficits in visuomotor function (TMTA) in men treated with ADT compared with both controls. Consistent with our findings of a moderate effect of ADT on visuomotor function compared with non-ADT PCa (g=−0.50) and CON (g=−0.36), a previous meta-analysis also reported a moderate effect size[49] of ADT on visuomotor function (g=−0.67, p=0.008).[7] The visuomotor TMTA measure relies on integration of executive and fine-motor control of the upper limb and hand for visuomotor coordination.[50] The absence of significant comparative deficits in other cognitive measures such as executive function (eg, TMTB-TMTA) in the ADT-treated men suggests that the impairment may be attributed to reduced motor capabilities rather than loss of executive control.

To our knowledge, this is the first study to assess the association between muscle strength, fitness and physical function with cognition in ADT-treated men compared with other patients with PCa not on ADT and healthy controls. A strength of this research is that it included a comprehensive battery of cognitive tests and a range of physical outcomes that related to strength, fitness and function. It also followed recent guidelines from the ICCTF with regards to defining cognitive impairment.[6] Our study does contain limitations, which should be considered when interpreting results. First, this study was a nested cross-sectional substudy within a larger randomised controlled trial, including exercise training and nutritional supplements for ADT-treated men.[19] Men on ADT recruited to the study had all been treated for a minimum of 3 months; however, adjusting for duration of treatment did not alter results. Second, there were differences in PCa stage between ADT and PCON, and a marked proportion (85%) of PCON did not know the stage of their PCa. Finally, although causal direction cannot be established between fitness, physical function and certain cognitive domains with ADT, these findings support the maintenance of fitness and functional capacity for cognitive health in men with PCa.

In summary, reduced cardiorespiratory fitness, but not muscle strength, was associated with compromised cognitive function in men with PCa treated with ADT compared with controls. Additionally, dual-task mobility was associated with the psychomotor-attention composite and global cognition in men with PCa overall compared with controls. ADT-treated men showed significantly slower visuomotor speed compared with both controls; however, ADT did not alter prevalence of cognitive impairment overall. This is the first study to our knowledge that links compromised cardiorespiratory fitness with cognitive function in ADT-treated men, and poor dual-task mobility with cognitive function in men with PCa collectively. These findings reinforce the importance of maintaining physical fitness and functional capacity for cognitive health in men with PCa.

Correction notice This article has been corrected since it first published. Author names 'Robin N Daly' and 'Steve F Fraser' have been updated.

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Patient consent for publication Consent obtained directly from patient(s)

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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
Jack Dalla Via http://orcid.org/0000-0002-1815-0838
Helen Macpherson http://orcid.org/0000-0002-3603-9359
Robin M Daly http://orcid.org/0000-0002-9897-1598
Steve F Fraser http://orcid.org/0000-0003-0202-9619

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