Cognitive decline in prostate cancer patients undergoing ADT: a potential role for exercise training

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Abstract

Androgen deprivation therapy (ADT) is an effective and widely prescribed treatment for prostate cancer (PCa), but it is associated with multiple treatment-induced adverse effects that impact on various musculoskeletal and cardiometabolic health outcomes. Emerging research has shown that ADT is also associated with cognitive impairment, which has been linked to a loss of independence, increased falls and fracture risk and greater use of medical services. The aim of this review is to outline the evidence related to the effect of ADT use on cognitive function, and propose a role for exercise training as part of usual care to prevent and/or manage cognitive impairments for PCa survivors on ADT. The following results have been obtained from this study. ADT has been shown to adversely affect specific cognitive domains, particularly verbal memory, visuomotor function, attention and executive function. However, current clinical guidelines do not recommend routine assessment of cognitive function in these men. No studies have examined whether exercise training can preserve or improve cognitive function in these men, but in healthy adults', multimodal exercise training incorporating aerobic training, progressive resistance training (PRT) and challenging motor control exercises have the potential to attenuate cognitive decline. In conclusion, as treatment with ADT for men with PCa has been associated with a decline in cognition, it is recommended that cognitive function be routinely monitored in these men and that regular exercise training be prescribed to preserve (or improve) cognitive function. Assessment of cognition and individualised exercise training should be considered in the usual treatment plan of PCa patients receiving ADT.

Key Words
- exercise
- cognitive function
- prostate cancer
- androgen deprivation therapy

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Introduction

Prostate cancer (PCa) is the most prevalent non-dermatological male cancer globally (Australian Institute of Health and Welfare 2014). Despite improved PCa survivorship, men suffer a range of adverse effects from treatment. Androgen deprivation therapy (ADT) is a commonly prescribed treatment that reduces androgens, such as testosterone, to castration levels in an attempt to slow tumour progression and improve overall survival in men with appropriately selected locally advanced and metastatic disease (Grossmann *et al.* 2013). ADT prescription has increased for all stages and grades of PCa (Shahinian *et al.* 2005). Despite improving survival, research has consistently reported a range of adverse effects associated with the use of ADT including deterioration in

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musculoskeletal health, an increase in cardiometabolic risk and a reduction in health-related quality of life (HR-QoL) (Gardner *et al*. 2014). A growing body of evidence indicates that ADT may also adversely affect cognitive function, including information processing (Green *et al*. 2002), spatial abilities (Cherrier *et al*. 2009) and memory (Bussiere *et al*. 2005), visuo-motor speed (McGinty *et al*. 2014) and executive function (Cherrier *et al*. 2009). However, current guidelines for the assessment and management of PCa for men treated with ADT do not recommend an assessment of cognitive function or methods for attenuating cognitive decline associated with treatment (Bussiere *et al*. 2005, Grossmann & Zajac 2011). There is emerging evidence that exercise training can play an important role in minimising the risk of cognitive deterioration with advancing age in healthy older adults (Colcombe & Kramer 2003). Importantly, regular exercise may also assist in managing various other adverse effects of ADT, such as cardiometabolic risk, which have been linked to cognitive impairment and related disorders (Papachristou *et al*. 2015). The aim of this review is to outline the evidence related to the effect of ADT use on cognitive function and propose a role for exercise training as part of usual care to prevent and/or manage cognitive impairments for PCa survivors on ADT.

The effects of androgen deprivation on cognitive function

Cognitive decline is part of the normal ageing process, particularly in the domains of information processing speed, memory, reasoning, reaction time and spatial abilities (Salthouse 2009). However, in men with PCa treated with ADT, the rate of decline in these processes appears to be accelerated (McGinty *et al*. 2014). Furthermore, the use of ADT has been associated with an almost two-fold increased risk for developing Alzheimer's disease (AD), with the risk increasing with treatment duration (Nead *et al*. 2016). Thirteen prospective studies have objectively assessed cognitive function in patients receiving ADT (Table 1) (Green *et al*. 2002, 2004, Cherrier *et al*. 2003, 2009, 2010, Salminen *et al*. 2003, Almeida *et al*. 2004, Alibhai *et al*. 2010, Matousek & Sherwin 2010, Mohile *et al*. 2010, Chao *et al*. 2012, Tan *et al*. 2013, Gonzalez *et al*. 2015). Five of these studies reported no effect (Almeida *et al*. 2004, Matousek & Sherwin 2010, Mohile *et al*. 2010, Chao *et al*. 2012, Tan *et al*. 2013), which is likely related in part to methodological differences in participant characteristics, study design and analyses. For instance, four of the 11 studies did not include non-ADT control participants (Almeida *et al*. 2004, Matousek & Sherwin 2010, Mohile *et al*. 2010, Tan *et al*. 2013).

Longitudinal studies of men with various cancers have identified that 16–48% had lower-than-normal cognitive performance prior to cancer treatment (Janelsins *et al*. 2014, Wefel *et al*. 2015). As cognitive function is rarely measured prior to ADT administration, many studies are observational, and few studies have provided a measure of estimated cognitive reserve. This is important because cognitive reserve provides a retrospective estimated baseline for cognitive function (Roldán-Tapia *et al*. 2012), and the degree of cognitive decline can be a function of ADT treatment duration (Nead *et al*. 2016). The National Adult Reading Test (NART), which provides a measure of reading intelligence that is more stable over time than other facets of intelligence, is one example of a relatively simple and easy-to-administer neurocognitive instrument that estimates cognitive reserve (Bright *et al*. 2016). To determine the cognitive performance in PCa survivors on ADT, standardised, objective measures of cognitive domains shown to be affected by ADT should be included (Wefel *et al*. 2011).

As indicated earlier, there is a growing body of evidence that ADT can accelerate cognitive decline; however, there has been only one longitudinal randomised controlled trial (RCT) examining cognitive function in men with PCa prior to and during ADT administration that also included a non-ADT control group (Green *et al*. 2002). Green and coworkers (Green *et al*. 2002) objectively assessed cognitive function in 77 men (mean age; 73 years) with PCa prior to commencing ADT, and six months after random allocation to ADT, or a watchful waiting control (Green *et al*. 2002). In 24 of the 50 men randomised to ADT, significant declines were evident in one or more cognitive tests at 6 months when compared to non-ADT controls, who showed no cognitive decline (Green *et al*. 2002). Importantly, the ADT group did not show a practice effect in comparison to the non-ADT controls, which may indicate a lack of learning ability (Green *et al*. 2002). A limitation of this study was the absence of a healthy control group, thus, potential cognitive effects linked to the cancer itself were not differentiated from the potential adverse effects of ADT (Wefel *et al*. 2011). Nevertheless, these findings highlight the negative influence of ADT on certain cognitive domains, including visuomotor control, verbal fluency, verbal memory, visual memory and attention (Green *et al*. 2002).

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Table 1 Characteristics of longitudinal studies objectively assessing cognitive function in prostate cancer survivors on androgen deprivation therapy (ADT).

Study	PCa ADT (*N*)	PCa controls (*N*)	Healthy controls (*N*)	Study duration (months)	Mean age (years)	Cognitive domains tested	Outcomes
Alibhai *et al.* (2010)	77	82	82	12	69	Attention, processing speed, verbal fluency, visuospatial ability, executive functions	Possible lack of learning effect, no consistent evidence for adverse effects to cognitive function
Almeida *et al.* (2004)	37	NA	NA	9	72	Verbal memory, verbal fluency, visual memory, visuomotor ability, visuospatial ability, working memory, attention	No effect in any domain tested. Improvements in memory after treatment discontinuation
Chao *et al.* (2012)	18	18	NA	6	69	Working memory, cognitive control	No effect on cognitive test scores. Decreased functional connectivity during resting state fMRI, decreased cortical activation during cognitive control tasks
Mohile *et al.* (2010)	21	NA	NA	6	71	Verbal fluency, verbal memory, visual memory, working memory, visuomotor ability, fine motor	No effect in any domain tested
Salminen *et al.* (2004)	25	NA	52	12	65	Verbal fluency, verbal memory, visual memory, visuospatial ability, visuomotor ability, working memory, spatial memory, attention	Visuomotor slowing, slowed reaction times in working memory, impaired hit rate in a vigilance test, impaired delayed recall and recognition speed of letters, improvement in object recall
Tan *et al.* (2013)	24	NA	NA	12	71	Verbal memory, learning	No effect in any domain tested
Cherrier *et al.* (2003)	19	NA	15	12	65	Verbal fluency, verbal memory, spatial memory, visuospatial ability, attention	Significant declines in visuospatial ability and spatial memory, improved story recall
Cherrier *et al.* (2009)	19	NA	19	12	64	Verbal fluency, verbal memory, visual memory, visuospatial ability, spatial memory, attention	Significant declines in visuospatial ability, spatial memory and attention
Cherrier *et al.* (2010)	5	NA	7	9	65	Visuospatial ability and spatial memory	Reduced task-related BOLD-fMRI activation during mental manipulation and spatial recall
Green *et al.* (2002)	77	15	NA	6	73	Verbal fluency, verbal memory, visual memory, attention	Significant declines in verbal memory, attention and executive function
Green *et al.* (2004)	37	14	15	12	72	Verbal memory, visual memory, working memory , attention	Significant declines in verbal memory, coding and inhibitory tasks
Gonzalez *et al.* (2015)	58	84	88	12	68	Verbal memory, visual memory, attention	No difference in mean cognitive performance between groups. ADT patients were more likely to show impairment in one or two test categories
Matousek & Sherwin (2010)	21	NA	NA	3	71	Verbal fluency, visuomotor ability, working memory, visuospatial ability, attention	No effect in any domain tested

BOLD, blood oxygenation level dependent; fMRI, functional magnetic resonance imaging; NA, not assessed.

An important question that requires further investigation is whether ADT leads to a greater rate of deterioration in specific cognitive domains. Several studies have reported that spatial memory and spatial ability are often adversely affected by ADT (Cherrier *et al.* 2003, 2009, Jenkins *et al.* 2005). Other studies have reported adverse

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effects of ADT on spatial memory, spatial ability, verbal memory and working memory (Table 1) (Green *et al.* 2002, 2004, Salminen *et al.* 2003, Cherrier *et al.* 2010), with reports that at least one of these measures of cognitive function decline by 47–69% in men on ADT over 9–12 months (Cherrier *et al.* 2003, Jenkins *et al.* 2005). Brain imaging studies have also shown that the adverse effects to spatial ability and memory are related to changes in cerebral function and brain volume (Cherrier *et al.* 2009, Chao *et al.* 2012, 2013). However, a meta-analysis of 14 studies that objectively measured cognitive function in PCa survivors on ADT confirmed that the largest effect size in relation to ADT and cognitive function was for the visuomotor control domain (effect size, g=–0.67) (McGinty *et al.* 2014), which may indicate an effect of reduced testosterone on tasks involving both vision and manual manipulation.

One of the challenges in comparing the results across different studies is the inconsistent definitions used for cognitive impairment or decline. For example, Mohile and coworkers (Mohile *et al.* 2010) defined cognitive impairment as scoring >1.5 standard deviation (s.d.) below the age- and education-adjusted population reference means (Mohile *et al.* 2010). Alibhai and coworkers (Alibhai *et al.* 2010) defined cognitive decline as a reduction of at least one s.d. in at least one cognitive test (Alibhai *et al.* 2010), whereas Gonzalez and coworkers (Gonzalez *et al.* 2015) defined impaired cognitive performance as a score >1.5 s.d. below population norms on two or more tests or >2 s.d. below published norms on one test (Wefel *et al.* 2011, Gonzalez *et al.* 2015). A more consistent interpretation of cognitive impairment would assist in evaluating the effects of ADT on cognitive performance (Gonzalez *et al.* 2015). However, recent longitudinal trials have shown greater rigour in test selection (for example including the NART, Hopkins verbal learning test, digit span and controlled oral word association test) and study design for assessing cognitive function in PCa patients, which assists with the validity of inter-study comparisons (Gonzalez *et al.* 2015).

In summary, the available evidence indicates that ADT adversely affects the cognitive domains of verbal, visual, spatial and working memory (Green *et al.* 2002, 2004, Beer *et al.* 2006, Cherrier *et al.* 2009), spatial reasoning and spatial ability (Cherrier *et al.* 2003, 2009), psychomotor and visuomotor function (Green *et al.* 2004, Salminen *et al.* 2004), auditory learning (Bussiere *et al.* 2005), executive function and processing speed (Green *et al.* 2002, 2004, Cherrier *et al.* 2009), with the most significant effects on visuomotor ability (McGinty *et al.* 2014). Given that a randomised study design of ADT use is not ethical for men with advanced PCa, future observational studies that aim to measure cognitive function in PCa patients should closely adhere to current guidelines for assessing the cognitive function in cancer patients, such as those recommended by the International Cognition and Cancer Task Force (ICCTF) (Wefel *et al.* 2011). A brief overview of these guidelines will be discussed below.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Guidelines for assessing cognitive function in prostate cancer patients

Neuropsychological assessment is indicated where treatment for a disease influences cognitive function and should be performed by (or under the guidance of) a psychologist (Harvey 2012). It is important to supplement cognitive function testing with the assessment of other factors that may contribute to cognitive dysfunction, such as mood and motivational state (Harvey 2012). In men treated with ADT, consideration should also be given to the effects of confounding variables such as age, education levels, depressive symptoms, fatigue and hot flash interference (Nelson *et al.* 2008, Gonzalez *et al.* 2015). The ICCTF guidelines for the assessment of cognitive function in chemotherapy patients (Wefel *et al.* 2011) have also been applied in patients with PCa (Gonzalez *et al.* 2015) and recommend that validated, objective measures of cognitive function be used in cancer patients, which assess those domains shown to be affected (Wefel *et al.* 2011). Where possible, clinical significance should be determined according to the respective norms or cut points for each specific neurological test (Wefel *et al.* 2011). Impaired cognitive performance should be uniformly determined by a performance of 1.5 s.d. below population norms on two or more tests or 2 s.d. below published norms on one test (Wefel *et al.* 2011). Cognitive test selection should include objective tests that have been previously shown to differentiate the effects of ADT in PCa survivors (Wefel *et al.* 2011) and which include specific cognitive domains such as visuomotor and visuospatial ability, attention, working memory, spatial memory, spatial ability, verbal memory and executive functions (Green *et al.* 2002, 2004, Cherrier *et al.* 2003, 2009, Salminen *et al.* 2004, Bussiere *et al.* 2005, Beer *et al.* 2006). Commonly used neuropsychological tests of

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Table 2 Domains of cognitive function and common neuropsychological tests used to assess each domain.

Domains of cognitive function	Description	Neurocognitive tests
Processing speed	Speed of cognitive or perceptual performance	- Trail making test A - Simple and choice reaction time - Symbol digit modalities test – written and oral
Executive functions	Planning, judgement, problem solving, impulse control, and abstract reasoning. Important for goal oriented behaviour, including performance monitoring, goal setting, and adjust of behaviour in response to feedback	- Conditional associative learning test - D-KEFS color-word interference test - Digit symbol substitution (WAIS-R; WAIS-III) letter-number sequencing (WAIS-III) - Stroop color word interference task - Symbol digit modalities test - Trail making test B
Memory	Visual memory Episodic memory – personally experienced events; antegrade, retrograde Procedural memory	- Nonverbal selective reminding test - Continuous recognition memory test - Brief visuospatial memory test - Object recall - Rey-Osterrieth complex figure delayed recall visual memory index (WMS-R) - Visual reproduction (WMS-III) - WMS-III visual memory index
Verbal and semantic memory	The ability to acquire and retain verbal information, for example verbal lists or instructions word meaning and general knowledge	- California verbal learning test II - Hopkins verbal learning test - Logical memory task (WMS-R) - Proactive interference - Rey auditory verbal learning test - Toronto word pool (encoding, retention, and recognition) verbal memory index (WMS-R) - Verbal paired associates (WMS-R; WMS-III) - Word list recall - Word lists (WMS-III)
Working memory	Temporary information storage, mental manipulation of information	- Attention and concentration index (WMS-R) - Digit span forward and backward (WAIS-III; WMS-III) spatial span forward and backward (WMS-III) - Subject-ordered pointing test
Working memory	Temporary information storage, mental manipulation of information	- Attention and concentration index (WMS-R) - Digit span forward and backward (WAIS-III; WMS-III) spatial span forward and backward (WMS-III) - Spatial working memory task - Subject-ordered pointing test - Subtraction
Language	Naming, repetition, comprehension, reading, writing	- Animal fluency - Controlled oral word association test - Letter word fluency - Object naming - Picture naming - Similarities (WAIS-III) - Vocabulary (WAIS-R)
Visuo-spatial ability	The ability to perceive and interpret visuo-spatial information and relationships such as maps or figures	- Block design (WAIS-R; WAIS-III) - Paper folding test - Rey-Osterrieth complex figure copy - Judgment of line orientation - Hooper visual organization test
Attention	Ability to maintain a consistent behavioural response throughout a consistent or repetitive behaviour, and avoid irrelevant stimuli	- Attention and Concentration Index (WMS-R) - Digit span forward and backward (WAIS-III; WMS-III) spatial span forward and backward (WMS-III) - Spatial working memory task - Subject-ordered pointing test - Subtraction - Trail making test A - Vigilance

(Continued)

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Table 2 Continued.

Domains of cognitive function	Description	Neurocognitive tests
Visuo-motor ability	Synchronization of visual perception and motor skills	- Card rotations - Environmental memory task encoding and recognition judgment of line orientation - Puget sound route learning test - Vandenberg and Kuse mental rotation test - Visuo-motor integration test – block design

Data from Kulkarni & Moningi (2015) and McGinty *et al.* (2014).
D-KEFS, Delis-Kaplan executive function system; WAIS-R, Wechsler adult intelligence scale-revised; WAIS-III, Wechsler adult intelligence scale-third edition; WMS-R, Wechsler memory scales-re-vised edition; WMS-III, Wechsler memory scales-third edition.

cognitive function which meet these criteria are shown in Table 2.

Effects of exercise training on cognitive function in men on ADT

Although exercise has been shown to be important for the prevention and management of cognitive impairment in cancer patients generally (Zimmer *et al.* 2016), various reviews have also associated exercise interventions with improved cognitive function in men treated with ADT (Trost *et al.* 2013, Ahmadi & Daneshmand 2014, Gardner *et al.* 2014, Nguyen *et al.* 2015). However, as shown in Table 3, many of these exercise trials are limited by the use of a generalised quality of life (QoL) questionnaire containing subjective measures of cognitive function, such as the European Organization for Research and Treatment of Cancer quality of life questionnaire (EORTC-QLQ C30) (Culos-Reed *et al.* 2007, 2010, Livingston *et al.* 2011, Oh *et al* 2012, Cormie *et al.* 2014*a*, Buffart *et al.* 2015). Subjective reports of cognitive function have not been validated as a means to assess cognitive function in cancer patients and are more closely associated with mood than objective measures of cognitive function (Wefel *et al.* 2011).

There is currently little evidence available to support the benefits of exercise training for improving cognitive function in PCa survivors receiving ADT, but the results from studies of older adults and non-PCa cancer survivors are promising. Meta-analyses indicate that exercise can reduce the risk for developing dementia and AD by 28% and 45%, respectively, with the volume of exercise training inversely related to dementia risk (Hamer & Chida 2009). Indeed, greater cardiovascular fitness has shown to be positively associated with cognitive performance in older adults (mean 0.5 s.d. benefit), independent of cognitive task type, exercise training method or participants' characteristics (Colcombe & Kramer 2003). The mechanisms underlying these improvements in cognitive function may relate to changes in brain structure. For example, an RCT of 120 healthy older adults (mean age 67 years) found that aerobic exercise training was associated with improved spatial memory and hippocampal volume in comparison to a non-exercising control (Erickson *et al.* 2011). In another RCT including 120 older adults (mean age 67 years) who completed 12 months of aerobic exercise training (10–40 min of walking at 50–75% maximum heart rate reserve) that increased cardiovascular fitness, there was a corresponding increase in hippocampal volume; an area of the brain which is vulnerable to age-related degradation (Erickson *et al.* 2011). Collectively, these findings provide some evidence that aerobic training that is associated with an improvement in fitness may lead to an improvement in cognitive function in older people.

More recent research has found that progressive resistance training (PRT) and multimodal exercise programmes incorporating aerobic and resistance training can also aid cognitive function in older adults (Liu-Ambrose *et al.* 2010, Nagamatsu *et al.* 2012, Fragala *et al.* 2014). For instance, moderate-to-high-intensity PRT (70–85% of one-repetition maximum (1-RM)) has been shown to improve memory and attention in older men (Cassilhas *et al.* 2007) and spatial awareness in older adults (Fragala *et al.* 2014). Combined or multimodal exercise interventions that include a motor component (movement speed, balance, motor coordination and flexibility) have also been shown to improve cognitive function in older adults (Voelcker-Rehage *et al.* 2010). Although questions still remain as to the optimal type and dose of exercise that is most effective to improve cognitive function in older adults, a meta-analysis of single or bimodal exercise trials indicated a small-to-moderate effect on cognitive performance with combined aerobic and PRT compared to aerobic training alone in older adults (Colcombe & Kramer 2003).

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Table 3 Interventions examining the effects of exercise training on cognitive function in men with PCa treated with androgen deprivation therapy (ADT).

Author (year)	Study design	Population	Intervention: PCa control: healthy control (*n*)	Subjective cognitive measures	Exercise intervention	Results
Buffart *et al.* (2015)	RCT 12 months	PCa ADT + radiotherapy *N* = 100	50:50:NA	EORTC QLQ-C30	RT and aerobic exercise 12 months vs educational material	A statistically significant improvement in subjective cognitive scores at 6 months
Cormie *et al.* (2014*a*, *b*)	RCT 12 weeks	PCa, BCa + mets *N* = 20	10:10:NA	MFSI SF	Group RT, aerobic exercise and stretching, 60 min duration twice per week	No significant improvement in fatigue related mental scores
Culos-Reed *et al.* (2010)	RCT 16 weeks	PCa + ADT *N* = 100	53:47:NA	EORTC QLQ-C30	Home based aerobic and RT 3–5 times/week	Subjective cognitive scores not reported
Culos-Reed *et al.* (2007)	RCT 12 weeks, 4 month follow up	PCa + ADT *N* = 31	18:13:NA	EORTC QLQ-C30	Home based aerobic and RT 3–5 times/week plus a biweekly booster of 60 min exercise and 30 min of education	Subjective cognitive scores not reported
Galvão *et al.* (2010)	RCT 12 weeks	PCa + ADT *N* = 57	29:28:NA	EORTC QLQ-C30	Group aerobic and RT, twice/ week	Significant improvement in subjective cognitive scores
Livingston *et al.* (2015)	RCT 12 weeks + 3, 6 and 12 month follow up	PCa *N* = 147	54:93:NA	EORTC QLQ-PR25, EORTC QLQ-C30	Moderate to strenuous physical activity, 3 times/week (150 min)	Significant improvement in subjective cognitive scores
Miki *et al.* (2014)	RCT 4 weeks	PCa, BCa *N* = 78	38:40:NA	FAB	Speed-feedback training, two five-minute, low intensity sessions per week with cognitive task	Improved prefrontal functions
Oh *et al.* (2012)	RCT 10 weeks	PCa, BCa, LCa, colorectal, stomach cancer *N* = 81	37:44:NA	EORTC QLQ-C30, FACT-Cog	Medical Qigong 2 times/week for 90 min	Intervention group improved on all subjective cognitive measures

BCa, breast cancer; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer, quality of life questionnaire; FAB, frontal assessment battery; FACT-Cog, functional assessment of cancer therapy-cognitive function; FSS, fatigue severity scale; LCa, lung cancer; MFSI SF, moderate fatigue severity index short-form; NA, not applicable; PCa, prostate cancer; RCT, randomised controlled trial; RT, resistance training.

Others have reported that more intense exercise leads to a greater effect on subsequent cognitive performance than light or moderate exercise (Chang *et al.* 2012).

Longer duration interventions (6–12 months) have also been associated with improved neural connectivity and activation in the brain in older adults (Voss *et al.* 2010). For example, one-year long study compared aerobic exercise training for 10–40 min three times per week at 50–75% maximum heart rate reserve (*n* = 30) to moderate intensity stretching and balance

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exercises (n=35) on neural connectivity and cognitive functions in older adults (median age 67.5 years, median VO2 peak 21 mL/kg/min) and reported significant within-group improvements in measures of neural connectivity in brain networks vulnerable to dysfunction with ageing in the aerobic training group (Voss *et al.* 2010). Furthermore, these changes were positively correlated with changes in executive function in the aerobic training group, but the stretching/balance group also showed alterations in functional connectivity, possibly representing experience-dependent plasticity (Voss *et al.* 2010). These findings may be relevant to men with PCa treated with ADT as there is some evidence from a study of 30 PCa survivors (median age 68 years), which found that 6 months of ADT was associated with decreased grey matter volume, reduced brain functional connectivity and reduced neural activations during cognitive control tasks (Chao *et al.* 2012, 2013).

Collectively, the current evidence indicate that regular exercise training can offer protective benefits to cognitive function in healthy older adults, but in men with PCa receiving ADT, the direct link between exercise and cognitive function has not been established. Given the strength of evidence for cognitive decline associated with ADT use for men with PCa and the confirmed benefits of exercise training for cognitive function in older adults, it is reasonable to infer that these benefits will translate to PCa survivors on ADT. It has previously been shown that PRT can provide substantial benefits to musculoskeletal health in men treated with ADT for PCa (Cormie *et al.* 2013) and that aerobic training can improve cardiometabolic risk factors that have been implicated in cognitive decline, but the effects of these modes of exercise training on cognitive function have not been assessed in these men. Exercise training can also reduce the risk of developing diabetes, obesity and cardiovascular disease (Roque *et al.* 2013), which are prevalent in men treated with ADT (Galvão *et al.* 2009, Keogh & MacLeod 2012) and are also risk factors for cognitive decline and neurodegeneration (Cotman *et al.* 2007). Given the need to also redress functional deficits, losses in bone mineral density and muscle mass and increases in cardiometabolic risk factors in PCa survivors on ADT, multimodal exercise programmes which include a combination of aerobic, PRT and motor control components are likely to provide the greatest overall benefits (Voelcker-Rehage *et al.* 2010, Keogh & MacLeod 2012).

Although there are currently no data on the effects of exercise training on cognitive function specific to ADT and non-ADT men with PCa, a review of trials in women with breast cancer and mixed cancer types show a positive effect of exercise training on cognitive function (Zimmer *et al.* 2016). Thus, despite the lack of direct evidence, there is indirect evidence to support a role for exercise training in attenuating the negative effects of ADT on cognitive function. However, given the unique physiological profile of this patient group, there remains a need for more adequately powered RCTs to investigate the effects of exercise on cognitive function in these men. These studies should include the use of objective, standardised measures of cognitive function.

Exercise guidelines for management of ADT adverse effects

In the management of ADT-related complications, an allied health professional (such as an Accredited Exercise Physiologist in the Australian health care system) should be engaged to assess the patient and individualise exercise prescription (Cheema *et al.* 2014). The current exercise guidelines for cancer survivors advocate normal daily activities and exercise according to age-appropriate physical activity guidelines during and after nonsurgical treatments, with modifications required in the instance of metastatic bone or cardiac disease (Schmitz *et al.* 2010). These guidelines do not include specific prescription parameters for addressing the cognitive decline associated with ADT (Schmitz *et al.* 2010). There is currently insufficient evidence in the literature to guide precise exercise prescription guidelines in terms of the frequency, intensity and duration required for men with PCa treated with ADT to attenuate cognitive decline. With respect to the optimal dose for improving or protecting cognitive function in older adults without PCa, emerging evidence indicates that moderate- and high-intensity (60–80% of maximal strength) PRT performed at least twice per week, including at least two sets of 7–10 exercises performed for 2–12 months may positively affect cognitive function (Yu-Kai *et al.* 2012). However, most of the available data from older adults indicate that the largest effect sizes in terms of exercise training occur with programmes of longer duration (>6 months), sessions of 31–45 min at moderate intensities and consisting of combined aerobic and resistance training performed a minimum of three days per week (Colcombe & Kramer 2003, Bherer *et al.* 2013).

Many cancer survivors are motivated to seek advice on optimal lifestyle advice to aid recovery, optimise management of treatment side effects and improve QoL (Rock *et al.* 2012). Advice given by a health care provider or physician has consistently been shown to

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facilitate health behaviour changes in cancer patients (Rock *et al*. 2012). A 12-week RCT including 100 PCa survivors on ADT (mean age; 71 years) indicated that an intervention involving exercise and dietary advice was feasible and induced sustainable behaviour changes after intervention (Bourke *et al*. 2012). However, advice may be conflicting and unsupported by data (Rock *et al*. 2012), indicating a need for consistent, evidence-based recommendations.

Conclusion

There is convincing evidence for the adverse effects of ADT on cognitive function in men treated with ADT for PCa, and appropriately timed cognitive assessment is warranted. When a measure of pre-treatment or pre-diagnosis cognitive function is not feasible, a reliable measure of estimated cognitive reserve should be implemented at baseline with a battery of neurocognitive tests which comply with ICCTF guidelines (Wefel *et al*. 2011). Emerging evidence indicates that a structured and targeted exercise intervention focussing on improvements in aerobic fitness, musculoskeletal health and function may have multiple benefits for men treated with ADT in terms of addressing such adverse effects as reduced bone mineral density, an adverse metabolic and cardiac health profile, sexual dysfunction, reduced QoL and changes in body composition (Cormie *et al*. 2015). Evidence from older, healthy populations supports the role of exercise as being protective against cognitive decline, and exercise guidelines for those with cardiovascular and metabolic disease should be used to inform exercise prescription in PCa survivors treated with ADT who present with such comorbidities. Although these exercise training recommendations are not intended to replace standard care, due consideration to risk for cognitive impairment is recommended for PCa survivors on ADT. Individualised multimodal exercise training is recommended to compliment usual care and may maximise cognitive function for this vulnerable population.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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