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Effects of a lifestyle intervention on endothelial function in men on long-term androgen deprivation therapy for prostate cancer

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Background: Treatment of prostate cancer with androgen deprivation therapy (ADT) is associated with metabolic changes that have been linked to an increase in cardiovascular risk.

Methods: This randomised controlled trial investigated the effects of a 12-week lifestyle intervention that included supervised exercise training and dietary advice on markers of cardiovascular risk in 50 men on long-term ADT recruited to an on-going study investigating the effects of such a lifestyle intervention on quality of life. Participants were randomly allocated to receive the intervention or usual care. Cardiovascular outcomes included endothelial function (flow-mediated dilatation (FMD) of the brachial artery), blood pressure, body composition and serum lipids. Additional outcomes included treadmill walk time and exercise and dietary behaviours. Outcomes were assessed before randomisation (baseline), and 6, 12 and 24 weeks after randomisation.

Results: At 12 weeks, the difference in mean relative FMD was 2.2% (95% confidence interval (CI) 0.1–4.3, $P = 0.04$) with an effect size of 0.60 (95% CI <0.01–1.18) favouring the intervention group. Improvements in skeletal muscle mass, treadmill walk time and exercise behaviour also occurred in the intervention group over that duration ($P < 0.05$). At 24 weeks, only the difference in treadmill walk time was maintained.

Conclusions: This study demonstrates that lifestyle changes can improve endothelial function in men on long-term ADT for prostate cancer. The implications for cardiovascular health need further investigation in larger studies over longer duration.

Treatment with androgen deprivation therapy (ADT) has established benefits for men with locally advanced or metastatic prostate cancer (Schubert *et al*, 2012), but has been associated with the development of adverse events that can impact physical and mental well being (Nguyen *et al*, 2015). Evidence of metabolic complications of ADT that lead to increased cardiovascular risk is accumulating (Zhao *et al*, 2014). Increased incidences of abdominal adiposity, insulin resistance, hyperglycaemia and hyperlipidaemia have been reported in men on such treatment (Nguyen *et al*, 2015).

An increase in cardiovascular risk factors through the development of metabolic complications to long-term ADT has been

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supported by evidence of a reduction in flow-mediated dilatation (FMD) of the brachial artery in men treated with long-term ADT (Gilbert *et al*, 2013). Reduced FMD indicates endothelial dysfunction (Deanfield *et al*, 2007), which is regarded as an important early stage in the development of atherosclerosis (Celermajer, 1997). Endothelial function, as measured by brachial artery FMD, is also an established predictor of future cardiovascular events (Ras *et al*, 2013).

The traditional approach for presenting the results of FMD has been in the form of absolute change in arterial diameter after release of cuff occlusion or a simple ratio of the change of arterial diameter over the resting arterial diameter, so-called relative FMD (Gokce *et al*, 2002; Edwards *et al*, 2004; Green *et al*, 2011). Concerns have been expressed as to the appropriateness of simple ratio standards for such physiological variables, with allometric scaling being deemed to be both biologically and mathematically superior (Tanner, 1949; Packard and Boardman, 1999; Curran-Everett, 2013). More recently, the validity of this approach has been demonstrated for FMD data (Atkinson and Batterham, 2013; Atkinson *et al*, 2013).

Given the established benefits of exercise and dietary changes to cardiovascular health in other patient groups (Rippe and Angelopoulos, 2014), we hypothesised that a supervised exercise training and dietary advice intervention would result in a reduction in cardiovascular risk factors in sedentary men on ADT. We tested this hypothesis in a randomised controlled trial and report the results herein.

MATERIALS AND METHODS

During the course of a randomised controlled trial investigating the effects of a lifestyle intervention on quality of life in men with prostate cancer on ADT (trial registration number ISRCTN88605738), a protocol amendment was approved by the Yorkshire and Humber NHS Research Ethics Committee to commence the collection of additional measures of cardiovascular risk.

The patient population and intervention for the full trial have been described in detail previously (Bourke *et al*, 2014). Here we present results for the subset of men recruited after the amendment was implemented.

Sample size. A sample size of 50 men was deemed sufficient to detect an absolute difference in relative brachial artery FMD of 2.6%; a difference reported in exercise studies in elderly patients at increased cardiovascular risk (Gokce *et al*, 2002; Edwards *et al*, 2004). This sample size assumed a s.d. of 3%, an alpha of 0.05, 80% power and 10% attrition (Bourke *et al*, 2011).

Randomisation. Participants were randomised 1 : 1 to receive 12 weeks of supervised exercise training and dietary advice in addition to usual care or to receive usual care alone. A randomly ordered list of group allocation was generated at study commencement using the nQuery Statistical Software (nQuery Advisor 6.01, nQuery Statistical Solution, USA). Neither the researchers nor the participants were informed of treatment allocation until completion of baseline assessments.

Intervention and usual care. Participants were prescribed three exercise sessions per week, tapering the supervision over the intervention (2 : 1 supervised to home based in weeks 1–6 and 1 : 2 in weeks 7–12). An experienced exercise physiologist led supervised sessions that lasted ∼1 h and consisted of a mixture of aerobic, resistance and balance exercises. Aerobic exercise was 30 min at 55–75% of age-predicted maximum heart rate or 11–13 on the Borg Rating of Perceived Exertion (RPE) scale (Borg, 1982) using stationary cycles, rowing ergometers and treadmills. Resistance exercises were performed for two to four sets of 8–12 repetitions beginning at an intensity of 60% of one repetition maximum and progressed through increasing volume before weight was increased. Advice on suitable exercises to perform at home for a minimum of 30 min was provided (e.g., brisk walking, cycling and gym exercise). Participants were instructed how to monitor intensity using RPE.

Small-group healthy-eating seminars led by the exercise physiologist, lasting ∼20 min, were delivered every 2 weeks throughout the intervention. Advice included: reduction in dietary fat intake to ∼25% of total energy intake, consumption of at least five portions of fruit and vegetables each day, increased fibre consumption, decreased intake of refined carbohydrates and limiting alcohol intake to 1–2 units per day.

The control participants were men randomised to usual care who were followed up in the urology clinic as per usual clinical protocol. No restrictions were placed on them in relation to exercise or dietary behaviours over the period of the study.

Outcome measures. The primary outcome was brachial artery FMD (endothelium-dependent arterial dilatation) expressed as the percentage change in arterial diameter at 12 weeks. Secondary outcomes include glyceryl trinitrate (GTN)-mediated brachial artery dilatation (endothelium-independent arterial dilatation), resting blood pressure, treadmill walk time, body mass and composition, lipid profile, biomarkers of disease status, physical activity and dietary behaviours. Outcome measures were assessed at baseline, at 6 and 12 weeks of the intervention and at 24 weeks (12 weeks after cessation of the intervention).

Vascular assessments. Ultrasound assessments of the right brachial artery were performed while the participant rested supine. All assessments were undertaken by one researcher (coefficient of variation for repeated FMD measures 10.97%) using a 7-mHz linear array transducer attached to a high-frequency ultrasound system (Terason T3000, Teratech Corporation, Burlington, MA, USA). Participants rested quietly for a minimum of 15 min before commencing assessments.

For FMD assessments, a pneumatic rapid inflation/deflation cuff (Hokanson E20 cuff, D.E. Hokanson Inc, Bellevue, WA, USA) was placed distal to the olecranon process, with arterial imaging performed in the distal third of the upper arm. Resting measurement of vessel diameter was performed for 1 min before cuff inflation to a pressure 50 mm Hg above systolic blood pressure. Occlusion was maintained for 5 min. Recordings were restarted 30 s before cuff release and continued for a further 3 min thereafter (Black *et al*, 2008).

After 15 min rest following FMD assessments, GTN-mediated brachial artery dilatation was assessed. Arterial imaging was performed for 1 min before administration of a sublingual dose (0.4 mg) of GTN, and continued for a further 6 min thereafter (Corretti *et al*, 2002) with recording maintained throughout.

The ultrasound on-screen display was recorded at a rate of 15 Hz (Camtasia Studio software, v5.0.0, TechSmith Corporation, Okemos, MI, USA). Subsequently, analysis was undertaken using the Brachial Analyser for Research software package (v5.6.19, Medical Imaging Applications, Iowa, USA). All scans were analysed in full by a researcher external to the research team who was blinded to participant group allocation.

Raw data for arterial diameter were smoothed before determination of the magnitude of arterial dilatation using the same method as previously described (Black *et al*, 2008). Arterial data are displayed as the absolute (millimetres) and relative (percentage) change in arterial diameter from resting arterial diameter (D_{rest}) to peak arterial diameter (D_{peak}). For analysis, data were allometrically scaled (Atkinson *et al*, 2013). Arterial shear rate (SR) for FMD assessments was calculated using the equation $\mathrm{SR} = 4 \times V/D$, where V is Doppler velocity and D is vessel diameter (Parker *et al*, 2009). Shear rate area under the curve was calculated as the sum of arterial shear from cuff release through to D_{peak}.

Anthropometry. Stature (Holtain Stadiometer, Holtain Ltd, Pembrokeshire, UK) and body mass (Weylux Beam Balance Scales, Weylux, UK) were assessed using standard laboratory techniques to 0.1 cm and 0.05 kg, respectively, and body mass index (BMI) was calculated. Body composition was assessed via bioelectrical impedance (Inbody 720, Biospace, Seoul, South Korea).

Resting blood pressure. Resting blood pressure and heart rate were assessed in the left arm with an automated sphygmomanometer (Dinamap, Dash 2500, GE Healthcare, Waukesha, WI, USA) while participants rested supine before FMD assessments.

Exercise tolerance. A sub-maximal walking test was performed on a treadmill (H/P/ Cosmos Pulsar Treadmill, Traunstein, Germany) using the BSU/Bruce protocol (Kaminsky and Whaley, 1998). Participants were given time walking on a treadmill before the test to allow them to become comfortable with treadmill use. A chest-strap heart rate monitor (Polar F4, Polar Electro, Kempele, Finland) was fitted and participants were accustomed to the 6–20 Borg scale (Borg, 1982). Heart rate and RPE were recorded at the end of every minute of exercise. The test ended when participants achieved an RPE of 15 (‘Hard’) or earlier if the participant requested to stop. Treadmill tests were conducted by a researcher external to the research team who was blinded to participant group allocation.

Blood markers. A fasting blood sample (20 ml) was drawn from the antecubital vein using standard venepuncture techniques. Samples were analysed in duplicate in the Department of Clinical Chemistry at the Royal Hallamshire Hospital, Sheffield, UK, for blood lipid profile (total cholesterol, HDL-C, LDL-C and triglycerides), prostate-specific antigen and male sex hormones (testosterone, SHBG). In addition, free androgen index was calculated.

Exercise and dietary behaviour. Leisure time physical activity was quantified using the Godin Leisure Score Index (LSI; Godin and Shephard, 1985). A higher score indicated more activity. The Godin LSI has been successfully used with men on ADT (Culos-Reed *et al*, 2010).

Participants completed 3-day diet diaries at baseline, 12 and 24 weeks. Where possible, participants were asked to use the same 3 days of the week for each assessment. Nutritional data were analysed using NetWisp (version 3.0, Tinuviel Software, Anglesey, UK).

Statistical analysis. Analyses were performed in Stata v13 on an intention-to-treat basis including all available participants in the groups to which they were randomised, using two-sided significance at the 5% level. Treatment effects are presented as the difference in adjusted means (intervention minus control) and Hedge’s g effect sizes with 95% confidence intervals (CIs) and *P*-values.

Arterial diameter data (FMD- and GTN-mediated dilatation) were allometrically scaled and analysed as follows. The difference between logarithmically transformed D_{rest} and D_{peak} was calculated for each participant and time point, and then analysed using a covariance pattern mixed model, with treatment group, time and a treatment group-by-time interaction as fixed factors, and log D_{rest} as a time-varying covariate. Means for diameter change on the logged scale for each treatment group and time point were obtained and then back transformed by antilogging to provide an adjusted ratio of D_{peak}/D_{rest}, subtracting a value of 1 and multiplying by 100 to provide a D_{rest} adjusted estimate of relative FMD. An estimate for the s.d. was obtained by multiplying the s.e. of the mean diameter change by the square root of the sample size, antilogging, subtracting 1 and multiplying by 100. Estimates for the difference in mean diameter change between the treatment groups at each time point were extracted from the model with 95% CIs and *P*-values. The *P*-values are presented unchanged in this paper, but the point and interval estimates were transformed as described above.

To allow comparison of the results with previous publications using a simple ratio only, the difference in (simple ratio) relative FMD between the trial arms at 12 weeks was extracted from a single linear covariance pattern mixed model in which relative FMD at each time point was nested within patients (Brown and Prescott, 2006). Relative FMD at baseline, each time point of follow-up, trial arm and a time-by-trial arm interaction were included in the model. The estimates of the treatment effect at 6 and 24 weeks were extracted for secondary investigations. Estimation was based on the method of restricted maximum likelihood (Harville, 1977).

The following outcomes were analysed in the same way as (simple ratio) relative FMD: absolute FMD, relative GTN-mediated dilatation, absolute GTN-mediated dilatation dilation, systolic and diastolic blood pressure, BMI and treadmill walk time.

All other secondary outcomes were compared between the treatment groups at 12 weeks using ANCOVA to adjust for the baseline value. No adjustment for multiple testing was made.

RESULTS

This analysis is of 50 men (mean age 70 years—range 53–84 years) consecutively recruited to the latter part of the primary trial (Bourke *et al*, 2014) with 25 randomised to each trial arm (Figure 1). The median time on ADT at recruitment was 19 and 18 months in the intervention and control groups, respectively. The groups were comparable at baseline with the exception of previous radiotherapy exposure (Table 1).

There were seven withdrawals (three in the intervention and four in the control group) and one death (control group) before the end of the 12-week intervention. There was one additional withdrawal and death (both intervention group) before the 24-week assessment. Both deaths were considered unrelated to the study intervention. For men completing the 12-week intervention, adherence to supervised sessions was 93% (368 out of 396 possible) and to home-based sessions was 76% (301 out of 396 completed), respectively.

At 12 weeks, the difference in allometrically scaled relative FMD was 2.2% (95% CI 0.1–4.3, $P = 0.04$, Hedge’s g 0.60, 95% CI <0.01–1.18) favouring the intervention group (Table 2). The difference in absolute FMD was 0.11 mm (95% CI <0.01–0.23, $P = 0.05$, Hedge’s g 0.59, 95% CI -0.01 to 1.17). This benefit was not maintained at 24 weeks (0.31 s.d., 95% CI -0.27 to 0.88 for allometrically scaled relative FMD and 0.31 s.d., 95% CI -0.27 to 0.89 for absolute FMD). The results for the non-scaled simple ratio FMD are presented alongside the scaled results in Table 2.

There was no meaningful difference in GTN-mediated dilatation (absolute or relative), systolic and diastolic blood pressure values or BMI at any post-randomisation time point (Table 2).

Treadmill walk time improved in the intervention group. The difference at 12 and 24 weeks was 88 s (95% CI 52–123, $P < 0.001$, Hedges g 1.41, 95% CI 0.76–2.05) and 69 s (95% CI 33–105, $P < 0.001$), respectively (Table 2).

Exercise behaviour scores from the Godin LSI were improved in the intervention group at all follow-up time points during the intervention with statistically significant differences at 6 and 12

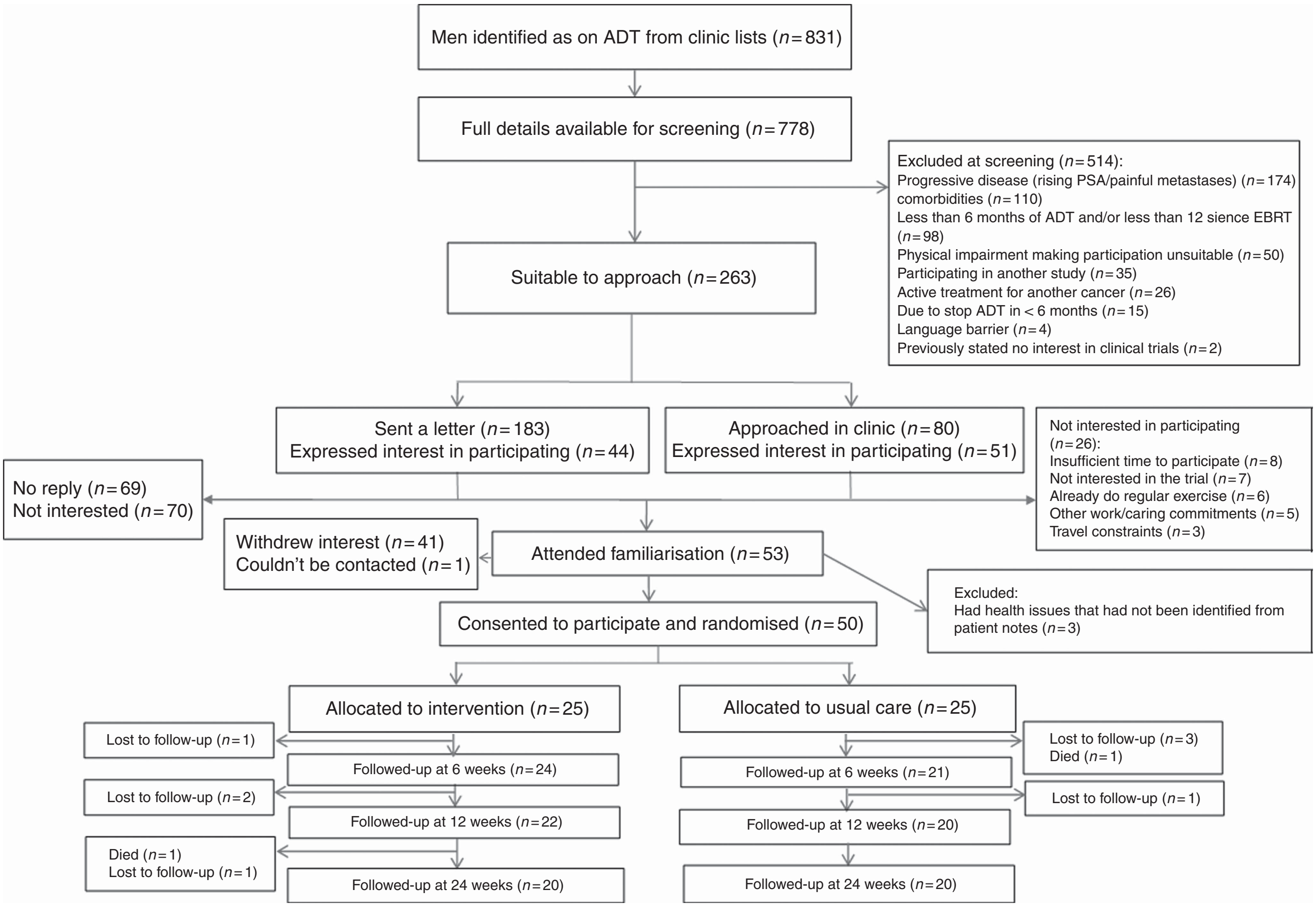

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram for final 50 participants recruited into the main trial.

weeks (6 weeks $P=0.02$; 12 weeks $P=0.05$). At 12 weeks, there was a moderate beneficial effect of the intervention of 0.57 s.d. (95% CI -0.02 to 1.15). There was no difference detected in exercise behaviour at 24 weeks ($P=0.58$).

There were improvements in D_{peak} for the FMD test, skeletal muscle mass (Table 3) and SHBG (Table 4) at 12 weeks. No meaningful change occurred in any other physiological measure or in any dietary outcomes (Supplementary Table 1).

DISCUSSION

At the end of the exercise intervention (12 weeks), a beneficial effect of the intervention on endothelial function occurred with an increased relative FMD of 2.2% (effect size of >0.5 s.d.). These differences between groups were not maintained 12 weeks after withdrawal of the intervention (Figure 2).

There is academic debate around how best to report relative FMD, with much of the earlier work using a simple ratio. Problems with these ratios have been identified (Tanner, 1949) and allometric scaling of ratio data for physiological measurements has been shown to be a more appropriate form of data analysis and presentation (Packard and Boardman, 1999; Curran-Everett, 2013). Such scaling more accurately accounts for variability in body and other anatomical sizes. Recently, Atkinson (2014) confirmed the appropriateness of allometric scaling for changes in arterial diameter in FMD analysis. In the current study, without such scaling, the difference in relative FMD expressed as a simple ratio is almost identical in magnitude (2.3%) to the allometric-scaled value with a similar effect size (Table 2).

FMD has been widely associated with changes in cardiovascular health. An inverse relationship between relative FMD and the risk of future cardiovascular events (e.g., myocardial infarction and stroke) exists, with a meta-analysis suggesting reduced cardiovascular risk of 13% (95% CI 8–17%) per 1% higher relative FMD in individuals with any pre-existing cardiovascular risk factor (Ras *et al*, 2013). Although these findings have been developed from non-scaled data, reanalysis of the Multi Ethnic Study of Atherosclerosis indicated that allometric-scaled FMD is robust in the association with cardiovascular health outcomes (Atkinson and Batterham, 2013). Within the current study, 68% of the men had pre-existing evidence of cardiovascular disease (Table 1), but a diagnosis of prostate cancer in itself appears to be associated with increased cardiovascular risk: a comprehensive registry-based study from Sweden found that men diagnosed with prostate cancer appear to constitute a particularly high-risk group for cardiovascular events over matched controls without cancer, with treatment by ADT conferring additional risk (Van Hemelrijck *et al*, 2010). An estimated annual cardiovascular event rate of ~14.2% in the Swedish PCBaSe study referred to above was reported in a recent meta-analysis (Bosco *et al*, 2015). Extrapolating from these data, one can tentatively estimate that, were the changes in FMD seen in this study translated to clinically significant risk reduction, 29% fewer cardiovascular events would be encountered, providing an absolute risk reduction of 4.1%. Otherwise stated, one would have to deliver the intervention to 24 men to prevent a single cardiovascular event per annum. As such, the results of the current study are suggestive of cardiovascular benefit of a 12-week exercise intervention in men on ADT, although further studies are required to correlate changes with cardiovascular outcomes.

Table 1. Baseline characteristics of the participants by treatment group

Characteristic	Intervention (*n* = 25)	Control (*n* = 25)	Total (*n* = 50)
Age (years)	***N* = 25**	***N* = 25**	***N* = 50**
Mean (s.d.)	70.1 (5.3)	70.4 (9.2)	70.2 (7.4)
(Min, max)	(57, 80)	(53, 84)	(53, 84)
Ethnicity, *n* (%)	***N* = 25**	***N* = 25**	***N* = 50**
White	25 (100)	22 (88)	47 (94)
Asian	0 (0)	2 (8)	2 (4)
Black	0 (0)	1 (4)	1 (2)
In employment, *n* (%)	***N* = 25**	***N* = 25**	***N* = 50**
	4 (16)	5 (20)	9 (18)
Smoking status, *n* (%)	***N* = 25**	***N* = 25**	***N* = 50**
Current smoker	1 (4)	0 (0)	1 (2)
Previous smoker	12 (48)	11 (44)	23 (46)
Treatment details, *n* (%)	***N* = 25**	***N* = 25**	***N* = 50**
LHRH agonist alone	25 (100)	23 (92)	48 (96)
MAB	0 (0)	2 (8)	2 (4)
Time on ADT, months	***N* = 25**	***N* = 25**	***N* = 50**
Median (IQR)	19 (12, 36)	18 (9, 25)	19 (9, 36)
(Min, max)	(6, 138)	(6, 92)	(6, 138)
Previous EBRT, *n* (%)	***N* = 25**	***N* = 25**	***N* = 50**
	13 (52)	7 (28)	20 (40)
Time since EBRT (months)	***N* = 12**	***N* = 7**	***N* = 19**
Median (IQR)	17 (12, 28)	20 (14, 58)	18 (12, 33)
(Min, max)	(12, 95)	(12, 130)	(12, 130)
Previous radical prostatectomy, *n* (%)	***N* = 25**	***N* = 25**	***N* = 50**
	1 (4)	3 (12)	4 (8)
Medical history and comorbidities, *n* (%)	***N* = 25**	***N* = 25**	***N* = 50**
Previous MI	2 (8)	2 (8)	4 (8)
Previous stroke	0 (0)	2 (8)	3 (6)
Angina	3 (12)	2 (8)	5 (10)
Diabetes	3 (12)	4 (16)	7 (14)
Hypertension	16 (64)	11 (44)	27 (54)
Hypertension diagnosed since ADT commencement	3 (12)	2 (8)	5 (10)
Medication, *n* (%)	***N* = 25**	***N* = 25**	***N* = 50**
Statin therapy	14 (56)	13 (52)	27 (54)
Beta blockers	8 (32)	6 (24)	14 (28)
Calcium channel blockers	12 (48)	4 (16)	16 (32)
ACE inhibitors	9 (36)	8 (32)	17 (34)
Diuretics	4 (16)	6 (24)	10 (20)
Angiotensin-II inhibitors	3 (12)	3 (12)	6 (12)
Prostaglandin analogues	7 (28)	6 (24)	13 (26)
Anti-coagulant therapy	2 (8)	1 (4)	3 (6)
Anti-diabetic medication	3 (12)	3 (12)	6 (12)

Abbreviations: ADT = androgen deprivation therapy; EBRT = external beam radiotherapy; LHRH = luteinising hormone-releasing hormone; MAB = maximum androgen blockade; MI = myocardial infarction.

Several mechanisms could be responsible for the changes observed in FMD. Previous studies have demonstrated improvements in endothelial function with increased physical activity are only partly mediated by changes in traditional cardiovascular risk factors (Green *et al*, 2003). A direct effect of periods of increased shear stress on arterial walls during exercise can lead to increased nitric-oxide-dependent vascular dilatation (Tinken *et al*, 2010). Such an explanation could account for the observed changes in FMD, despite only small effects on other cardiovascular risk factors. Changes in SHBG at 12 weeks could be indicative of changes in insulin resistance between groups (Wallace *et al*, 2013), which could influence FMD (Suzuki *et al*, 2004). Although SHBG has been shown to increase after lifestyle interventions including exercise and diet in healthy adult males (Tymchuk *et al*, 1998) consistent with changes in insulin concentrations, the results of the current study could be interpreted as a deterioration in insulin sensitivity in the control group leading to a reduction in SHBG given the association between long-term ADT and increasing risk of developing type II diabetes (Alibhai *et al*, 2009). However, given the small sample size of the study, such an interpretation should be made with caution.

Previous evidence of improvements in cardiovascular health with exercise training in men established on ADT is limited. Recent studies have shown improvements in anthropometric and metabolic markers of cardiovascular risk with exercise training (Nobes *et al*, 2012; Cormie *et al*, 2015); however, in both studies participants started the intervention at the same time as commencing ADT and so whether such results could be achieved in men on long-term ADT remained unclear. Reductions in systolic and diastolic blood pressure were reported by Culos-Reed *et al* (2010) in men on long-term ADT who underwent a 16-week programme of home-based exercise; however, changes of a similar magnitude were also found in a non-exercising control group, resulting in no difference between groups over time. More positively, Galvao *et al* (2010) reported decreased concentrations of C-reactive protein after a 12-week supervised exercise intervention, but this finding was not supported by evidence of benefits in any other markers of cardiovascular health. As such, our finding of an improvement in endothelial function provides the most encouraging evidence of cardiovascular benefits following a lifestyle intervention in men on long-term ADT.

Table 2. Summary of outcome measures by treatment group

Outcome	Intervention ($n=25$) Raw mean (s.d.)	Control ($n=25$) Raw mean (s.d.)	Adjusted mean difference at 12 weeks (95% CI) *P*-value Effect size in s.d. (95% CI)
Allometrically scaled relative FMD (%)[a]			
Baseline	4.5 (3.4)	4.6 (3.4)	2.2 (0.1, 4.3)
Week 6	6.9 (3.4)	4.4 (3.4)	$P=0.04$
Week 12	7.6 (3.4)	5.3 (3.4)	0.60 (0.005, 1.18)
Week 24	7.5 (3.4)	6.3 (3.4)	
Non-scaled relative FMD (%)[a]			
Baseline	4.6 (4.2)	4.7 (4.2)	2.3 (0.1, 4.5)
Week 6	7.0 (3.9)	4.5 (3.8)	$P=0.04$
Week 12	7.7 (4.1)	5.3 (4.0)	0.60 (0.01, 1.19)
Week 24	7.5 (4.0)	6.3 (4.0)	
Absolute FMD (mm)			
Baseline	0.23 (0.18)	0.22 (0.11)	0.11 (0.00, 0.23)
Week 6	0.35 (0.22)	0.23 (0.20)	$P=0.05$
Week 12	0.37 (0.20)	0.25 (0.15)	0.59 (−0.01, 1.17)
Week 24	0.37 (0.18)	0.30 (0.16)	
Allometrically scaled GTN-mediated dilatation (%)[a]			
Baseline	12.3 (4.2)	11.9 (4.2)	0.6 (−2.4, 3.6)
Week 6	11.2 (4.2)	14.6 (4.2)	$P=0.71$
Week 12	11.5 (4.2)	10.9 (4.2)	0.11 (−0.47, 0.68)
Week 24	13.4 (4.2)	11.3 (4.2)	
Non-scaled relative GTN-mediated dilatation (%)			
Baseline	12.5 (5.0)	12.0 (4.3)	1.2 (−2.2, 4.7)
Week 6	12.0 (3.5)	14.6 (6.3)	$P=0.48$
Week 12	12.2 (5.5)	10.4 (4.5)	0.21 (−0.37, 0.78)
Week 24	13.9 (4.5)	11.0 (4.9)	
Absolute GTN-mediated dilatation (mm)			
Baseline	0.62 (0.25)	0.59 (0.20)	0.04 (−0.13, 0.20)
Week 6	0.57 (0.15)	0.74 (0.31)	$P=0.66$
Week 12	0.58 (0.27)	0.52 (0.21)	0.13 (−0.45, 0.70)
Week 24	0.67, (0.22)	0.55 (0.24)	
Systolic blood pressure (mm Hg)			
Baseline	144 (18)	145 (20)	−7.0 (−16.1, 2.2)
Week 6	137 (14)	147 (19)	$P=0.14$
Week 12	138 (20)	145 (20)	0.44 (−0.15, 1.02)
Week 24	139 (19)	141 (23)	
Diastolic blood pressure (mm Hg)			
Baseline	80 (8)	76 (8)	−3.3 (−7.0, 0.4)
Week 6	77 (9)	76 (7)	$P=0.08$
Week 12	76 (10)	76 (7)	0.50 (−0.09, 1.08)
Week 24	77 (11)	75 (8)	
BMI (kg/m^2)			
Baseline	30.6 (5.0)	28.8 (5.2)	0.1 (−0.5, 0.6)
Week 6	30.3 (5.0)	28.4 (3.2)	$P=0.74$
Week 12	29.8 (4.8)	29.0 (4.8)	−0.10 (−0.67, 0.48)
Week 24	28.9 (2.8)	29.0 (4.8)	
Treadmill walk time (s)			
Baseline	344 (144)	346 (162)	87.6 (52.0, 123.3)
Week 6	420 (143)	411 (134)	$P<0.001$
Week 12	435 (133)	389 (115)	1.41 (0.76, 2.05)
Week 24	447 (131)	400 (121)	
Godin LSI			
Baseline	20.5 (13.2)	20.7 (17.3)	12.5 (−0.1, 25.0)
Week 6	31.0 (17.8)	22.4 (22.0)	$P=0.05$
Week 12	38.4 (27.2)	26.2 (21.1)	0.57 (−0.02, 1.15)
Week 24	36.5 (27.5)	31.4 (30.4)	

Abbreviations: CI, confidence interval; FMD = Flow-mediated dilatation; GTN = Glyceryl trinitrate; BMI = Body mass index; LSI = Leisure Score Index.

[a] Adjusted 'corrected' mean relative dilatation.

Table 3. Summary of secondary outcome measures by treatment group

Outcome	Intervention ($n=25$) Raw mean (s.d.)	Control ($n=25$) Raw mean (s.d.)	Adjusted mean difference at 12 weeks (95% CI) *P*-value
FMD D_{rest} (mm)			
Baseline	4.9 (0.6)	4.8 (0.5)	0.1 (−0.1, 0.3)
Week 6	5.0 (0.8)	5.0 (0.6)	$P=0.27$
Week 12	5.0 (0.5)	4.8 (0.5)	
Week 24	4.9 (0.6)	4.8 (0.6)	
FMD D_{peak} (mm)			
Baseline	5.1 (0.7)	5.0 (0.6)	0.2 (0.0, 0.5)
Week 6	5.3 (0.9)	5.2 (0.7)	$P=0.04$
Week 12	5.3 (0.5)	5.1 (0.5)	
Week 24	5.3 (0.6)	5.1 (0.6)	
GTN D_{rest} (mm)			
Baseline	5.0 (0.5)	5.0 (0.6)	−0.2 (−0.6, 0.1)
Week 6	4.8 (0.6)	5.2 (0.6)	$P=0.12$
Week 12	4.9 (0.5)	5.2 (0.6)	
Week 24	4.9 (0.4)	5.1 (0.6)	
GTN D_{peak} (mm)			
Baseline	5.6 (0.6)	5.6 (0.7)	−0.2 (−0.6, 0.1)
Week 6	5.4 (0.6)	5.9 (0.6)	$P=0.18$
Week 12	5.5 (0.6)	5.7 (0.6)	
Week 24	5.6 (0.5)	5.6 (0.6)	
Body fat mass (kg)			
Baseline	34.5 (11.6)	30.4 (11.5)	−0.7 (−2.2, 0.7)
Week 6	32.9 (11.2)	27.9 (7.4)	$P=0.32$
Week 12	31.6 (10.9)	29.6 (10.9)	
Week 24	29.9 (7.1)	29.0 (11.1)	
Skeletal muscle mass (kg)			
Baseline	31.9 (4.2)	31.2 (5.7)	0.6 (0.1, 1.1)
Week 6	32.3 (4.6)	31.6 (6.0)	$P=0.03$
Week 12	32.9 (4.6)	32.3 (5.5)	
Week 24	32.7 (4.0)	32.6 (5.7)	

Abbreviations: CI, confidence interval; D_{rest} = resting arterial diameter; D_{peak} = peak arterial diameter; GTN = glyceryl trinitrate; FMD = flow-mediated dilatation; SR AUC = shear rate area under the curve.

Statistically significant changes in skeletal muscle were observed over the duration of the intervention. These findings support evidence that lifestyle interventions can reverse the decrease in lean body mass experienced by men treated with ADT (Galvao *et al*, 2010; Galvão *et al*, 2014). The largest effect of the intervention was seen in treadmill walk time however. Although improvements from baseline walking distance was seen in the control group this did not match the magnitude of improvements in the intervention group. This evidence demonstrates exercise training can reduce the decline in physical function observed with ADT (Alibhai *et al*, 2010).

Evidence of an increase in exercise behaviour and exercise tolerance in the control group is one limitation of the current study. Although similar changes in exercise behaviour have previously been reported in cancer patients randomised to a control group of an exercise study (Courneya *et al*, 2004), such findings could have a confounding effect on overall conclusions.

A further limitation of this study is that improvements in a number of outcome measures seen at endpoint assessments in the intervention group were lost following withdrawal of supervision. Conducting follow-up assessments after a lifestyle intervention has previously been undertaken by one study that reported a similar pattern of changes (Bourke *et al*, 2011). Designing effective lifestyle interventions for this population that can maintain benefits after removal of supervision is clearly an area in which further investigations are warranted.

Table 4. Summary of lipid profile and blood marker measures by treatment group

Outcome	Intervention ($n=25$) Raw mean (s.d.)	Control ($n=25$) Raw mean (s.d.)	Adjusted mean difference at 12 weeks (95% CI) *P*-value
Lipid profile			
Total cholesterol (mmol l^{-1})			
Baseline	5.0 (1.2)	4.7 (0.9)	−0.0 (−0.3, 0.3)
Week 12	4.9 (1.1)	4.8 (0.8)	$P=0.83$
HDL-C (mmol l^{-1})			
Baseline	1.4 (0.4)	1.5 (0.5)	0.0 (−0.1, 0.1)
Week 12	1.4 (0.4)	1.5 (0.5)	$P=0.60$
LDL-C (mmol l^{-1})			
Baseline	2.7 (1.1)	2.4 (0.8)	−0.0 (−0.3, 0.2)
Week 12	2.8 (1.0)	2.6 (0.8)	$P=0.79$
Triglycerides (mmol l^{-1})			
Baseline	1.9 (0.7)	1.7 (1.0)	−0.1 (−0.3, 0.2)
Week 12	1.6 (0.7)	1.6 (0.8)	$P=0.51$
Blood markers			
Total testosterone (nmol l^{-1})			
Baseline	0.5 (0.2)	0.5 (0.2)	−0.0 (−0.1, 0.0)
Week 12	0.4 (0.1)	0.4 (0.2)	$P=0.43$
SHBG (nmol l^{-1})			
Baseline	54.0 (33.0)	56.9 (31.6)	5.8 (0.8, 10.9)
Week 12	54.6 (23.8)	51.0 (30.2)	$P=0.03$
Free androgen index			
Baseline	1.2 (0.8)	1.2 (1.0)	−0.2 (−0.5, 0.1)
Week 12	1.0 (0.5)	1.3 (1.1)	$P=0.17$
Prostate-specific antigen (ng ml^{-1})			
Baseline	2.1 (4.8)	1.5 (2.7)	0.1. (−1.0, 1.3)
Week 12	3.7 (8.7)	2.3 (4.5)	$P=0.80$

Abbreviations: CI, confidence interval; HDL-C = high-density lipoprotein-cholesterol; LDL-C = low-density lipoprotein-cholesterol; SHBG = sex-hormone-binding globulin

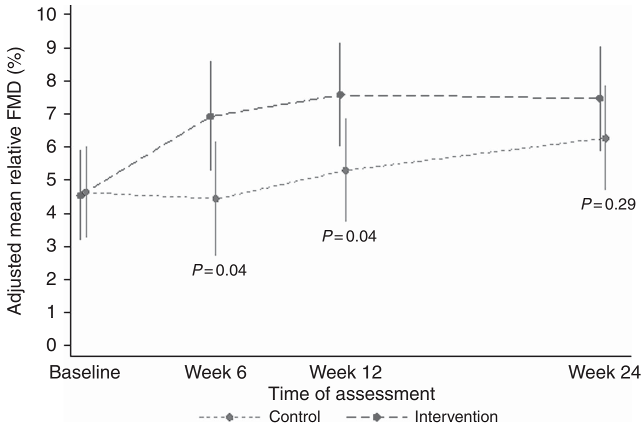

Figure 2. Allometrically-scaled, adjusted mean relative FMD by treatment group at all time points, with 95% confidence intervals and *P*-values.

Finally, the controlled recruitment of men into this study could limit generalisability of the findings. As part of the first study to report an exercise-based intervention in men with metastatic prostate cancer (Bourke *et al*, 2011, 2014), the necessity to maintain rigour and ensure patient safety resulted in the exclusion of 67% of men identified as being treated with ADT. Comparison of this exclusion rate against other studies is difficult due to variations in the detail of recruitment statistics reported; however, the study establishes the principle that such lifestyle interventions are feasible in this population, an important consideration for future studies.

In conclusion, our findings demonstrate evidence of improvements in endothelial function after a lifestyle intervention including supervised exercise training and dietary advice in men on long-term ADT for prostate cancer that were not maintained following withdrawal of the intervention. Larger studies are required to investigate any impact on clinically relevant cardiovascular outcomes, as well as the value of a longer supervised intervention.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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