Cardiovascular health in men on androgen deprivation therapy for prostate cancer

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STATEMENT OF ORIGINALITY

I hereby declare that all the work contained in this thesis is original and was undertaken by the author unless otherwise stated. Where reference is made to the work of others citations are included with the authors name and location of publication.

ABBREVIATIONS

Abbreviation	*Description*
Δ	Change
95% CI	95% confidence interval
ADT	Androgen deprivation therapy
AHT	Adjuvant hormonal therapy
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
BL	Baseline
BMI	Body mass index
CRP	C-Reactive protein
CV	Coefficient of variation
DEXA	Dual-energy x-ray absorptiometry
DHT	Dihydrotestosterone
DNA	Deoxyribonucleic acid
DRE	Digital rectal examination
EBRT	External beam radiotherapy
EP	End-point
EQ-5D	EuroQol-5D
FACT-F	Functional assessment of cancer therapy-fatigue
FACT-P	Functional assessment of cancer therapy-prostate
FAI	Free androgen index
FFA	Free fatty acid
FMD	Flow-mediated dilatation
FSH	Follicle-stimulating hormone
FU	Follow-up
Godin LSI	Godin leisure-score index
GTN	Glyceryl-trinitrate
HDL-C	High-density lipoprotein cholesterol
HR	Hazard ratio
ICC	Intraclass correlation coefficient

IRS	Insulin receptor substrate
LDL-C	Low-density lipoprotein cholesterol
LH	Luteinizing hormone
LHRH	Luteinizing hormone releasing hormone
Log_n	Natural log
MCID	Minimum clinically important difference
METs	Metabolic equivalents
MMP	Matrix metalloproteases
mRNA	Messenger ribonucleic acid
NCSI	National cancer survivorship initiative
NHT	Neoadjuvant hormonal therapy
NO	Nitric oxide
OR	Odds ratio
PI3K	Phosphatidylinositol 3-kinase
PSA	Prostate specific antigen
PWV	Pulse wave velocity
RM	Repetition maximum
RPE	Rating of perceived exertion
RR	Risk ratio
rTEM	Relative technical error of measurement
SD	Standard deviation
SEM	Standard error of measurement
SHBG	Sex-hormone binding globulin
SPSS	Statistical package for the social sciences
SR	Shear rate
SR AUC	Shear rate area under the curve
TNM	Tumour node metastases
TRUS	Trans-rectal ultrasound
VLDL-C	Very-low-density lipoprotein cholesterol

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PRESENTATIONS AND PUBLICATIONS ARISING FROM THIS THESIS

Presentations

- British Association of Urological Surgeons, June 2012
  Persistence of response to lifestyle modification in men with prostate cancer on AST: updated results from an on-going randomised controlled trial
  Gilbert, S.E., Bourke, L., Tew, G.A., Winter, E.M. and Rosario, D.J.

Publications

- Gilbert, S.E., Tew, G.A., Bourke, L., Winter, E.M. and Rosario, D.J. (2013). Assessment of endothelial dysfunction by flow-mediated dilatation in men on long-term androgen deprivation therapy for prostate cancer. *Experimental Physiology*, DOI: 10.1113/expphysiol.2013.073353

ABSTRACT

Androgen deprivation therapy (ADT) is a cornerstone treatment option for men with metastatic or locally advanced prostate cancer, however, treatment with ADT has been associated with increased incidence of adverse cardiovascular events. Strategies to investigate and monitor cardiovascular risk, as well as to reduce such treatment-related morbidity are urgently required in this population.

Study 1 of this thesis investigated the differences in endothelial function between men with advanced prostate cancer treated with ADT and matched controls using a case-control design. Flow-mediated dilatation (FMD) and glyceryl-trinitrate (GTN)-mediated dilatation of the brachial artery were assessed in 20 men (69 ± 7 years) with prostate cancer treated with ADT for a median of 22 months (range 6-133 months) and compared against 20 controls (69 ± 5 years) matched for age, history of cardiovascular disease and physical activity levels. FMD was reduced in men on ADT compared to controls (P <0.05) but no differences were observed between groups for GTN-mediated dilatation (P >0.05). These findings provide novel data to suggest endothelial function is impaired in men with prostate cancer treated with ADT, which is in agreement with evidence of increased cardiovascular risk in this population.

Study 2 investigated the effects of a 12-week lifestyle intervention including supervised exercise training and dietary advice on markers of cardiovascular health and general well-being in men treated with ADT for prostate cancer. Fifty men treated with ADT for ≥6 months were randomly allocated to receive the intervention or usual care. Assessments of vascular function, blood pressure, body composition, exercise tolerance and psychological well-being were undertaken prior to randomisation (baseline) and after completion of the intervention (end-point), with a follow-up assessment completed a further 12 weeks after end-point assessments. Statistically significant differences between groups were observed for changes in skeletal muscle mass, body fat percentage, exercise tolerance, quality of life and fatigue (P <0.05). In addition, clinically meaningful effect sizes were observed for the difference between groups for the change between baseline and end-point in FMD and diastolic blood pressure (d >0.51), with post-hoc analysis demonstrating a statistically significant change in FMD in men in the intervention group (P = 0.038). These findings support evidence that diet and exercise can improve general well-being of patients treated with ADT, and provide novel data on the effects of such an intervention on cardiovascular health.

1.0 INTRODUCTION

The concept of *cancer survivorship* has been redefined over the years. When cancer was considered incurable, the term "*survivor*" described family members who survived the loss of loved ones to cancer (Leigh, 1996). More recently however the term "*cancer survivor*" has been used to describe any person living with or beyond cancer (Macmillan Cancer Support, 2008). An individual will be considered a cancer survivor from the time of cancer diagnosis through the remaining years of life.

Data for the UK shows the number of people meeting this definition has steadily increased over the past decade (Maddams *et al.*, 2009) and is projected to continue to rise over the next 20 years (Mistry *et al.*, 2011). There are currently 1.8 million cancer survivors in England and 2 million across the whole of the UK, but in consideration of the growing and aging population and the improvements in cancer survival rates, these numbers are expected to rise by 3% per year; it has been estimated that there will be 3 million cancer survivors in England by 2030 (National Cancer Survivorship Initiative, 2013). Accordingly, there is growing incentive to develop strategies to support and care for this population. This has led to the Department of Health, in collaboration with Macmillan Cancer Support, developing a National Cancer Survivorship Initiative (NCSI) in the UK, which was launched in January 2010. The NCSI has sought to engage patients, clinicians, policy makers and members of the research community to review and develop the most effective models of services, care and cancer support to address the physical, psychological, social and economic needs of cancer survivors (Richards *et al.*, 2011).

Increasing attention to accommodate these needs of individuals with cancer is clearly warranted in consideration of the relatively poorer health and well-being reported among cancer survivors. Comparing the health of individuals with a previous cancer diagnosis to individuals who had never been treated

for cancer, the 2008 national population-based survey in the UK found that cancer survivors had worse general health, with greater on-going health problems, resulting in greater use of health services (Elliott *et al.*, 2011). These data are further supported by evidence of increased prevalence of depression (Massie, 2004; Burgess *et al.*, 2005), osteoporosis (Khan *et al.*, 2011; Reuss-Borst *et al.*, 2012), heart failure (Hooning *et al.*, 2007; Chen *et al.*, 2012) and coronary artery disease (Krone, 2010; Zöller *et al.*, 2012) in cancer survivors.

The incidence of cardiovascular disease among cancer survivors is one area of growing concern with increasing evidence describing greater cardiovascular risk among patients with different site-specific cancers (Hooning *et al.*, 2007; Yusuf *et al.*, 2008; Keating *et al.*, 2010; Fu *et al.*, 2011; Daher *et al.*, 2012; Weaver *et al.*, 2013). Studies have shown increased prevalence of cardiovascular risk factors (Daher *et al.*, 2012; Weaver *et al.*, 2013) and increased incidence of cardiovascular events among cancer survivors (Hooning *et al.*, 2007; Keating *et al.*, 2010; Fu *et al.*, 2011). Moreover, cardiovascular disease is now considered a leading cause of death for patients with cancers of the breast, prostate, colon-rectum and endometrium (Baade *et al.*, 2006; Patnaik *et al.*, 2011; Shikanov *et al.*, 2012; Ward *et al.*, 2012)

Although the evidence describing an increase in cardiovascular risk in cancer survivors has continued to grow this has been primarily focussed around traditional cardiovascular risk factors (e.g. blood pressure, body composition, lipid profile), with limited data currently available on changes in more novel markers of cardiovascular risk (e.g. markers of vascular inflammation, endothelial progenitor cells, endothelial function) in this population. Such a paucity of data in this area could mean that there is limited understanding of the increase in cardiovascular risk in cancer survivors, while possible means of monitoring cardiovascular health in this patient group are also not being utilised. Furthermore, strategies to reduce cardiovascular risk in cancer survivors are currently also sparse. Although drug therapies have been described for the treatment of cardiovascular complications such as heart

failure, hypertension, thromboembolism and arrhythmias occurring after treatment with radioactive or chemotherapeutic agents (Yeh and Bickford, 2009), such additional treatment regimens must be used with care due to the possible further side-effects that are inherent in individual drug therapies (Lamy, 1988; Tomlinson and Mangione, 2005; Born and Patrono, 2006) or that can result from interactions between drugs. Accordingly, the use of non-pharmacological therapies to reduce the risk of cardiovascular disease could provide a preferable treatment pathway as an adjunct to individual cancer therapeutic strategies.

In disease-free individuals and other patient groups, lifestyle interventions including diet and exercise have been shown to lead to reductions in cardiovascular risk (Myers, 2003; Green *et al.*, 2008) and reduced incidence of cardiovascular events and mortality (Lee *et al.*, 1999; Hamer *et al.*, 2012), yet evidence for the benefits of such strategies in cancer survivors is sparse. The possible use of lifestyle interventions to reduce cardiovascular risk has been specifically described for patients with prostate or breast cancer (Galvão *et al.*, 2009; Knobf and Coviello, 2012), and has been noted in reviews of possible benefits of lifestyle changes in cancer survivors (Schmitz *et al.*, 2010; Rock *et al.*, 2012; Sabiston and Brunet, 2012), however, evidence to support such claims remains very limited. Where evidence exists, it is strongest in breast cancer survivors.

Further research is clearly warranted into the mechanisms of development, monitoring and management of cardiovascular risk in cancer survivors. With the projected increase in the number of cancer survivors, such research could help to reduce the burden of comorbidity upon patients and the burden of treatment costs on health-care providers. As such, such research is in line with the latest guidance on improving outcomes for cancer survivors recently published by the NCSI (Department of Health, 2013).

In this regard, investigations in men with prostate cancer treated with long-term androgen deprivation therapy (ADT) are of particular interest. The widespread use of this form of treatment, which has itself been associated with numerous side-effects including the deterioration of cardiovascular

health, means that a large number of men are potentially at risk, with attendant morbidity and treatment costs.

The studies described in this thesis aim to fill some of the gaps in knowledge which exist in this area. In the first part, concluding with the cross-sectional study of the effects of treatment of prostate cancer with ADT on endothelial function, prostate cancer and its treatment are considered with particular regards to the potential effects of ADT on cardiovascular risk. In the second part, concluding with the intervention study of the effects of supervised exercise training and dietary advice on markers of cardiovascular risk in men treated with ADT for prostate cancer, the effects of a 12 week lifestyle intervention including supervised exercise training and dietary advice on markers of cardiovascular health and general quality of life are examined. The final discussion at the end of this thesis aims to bring together the findings of these two studies and consider the implications for further research into the management of cardiovascular health in prostate cancer survivors in the future.

2.0 REVIEW OF LITERATURE: Study 1

2.1 Cancer

Cancer can be defined as a molecular disease characterised by progressive accumulation of a mass of cells, as a result of excessive reproduction of cells not compensated by cell loss; these cells progressively invade and damage the tissues and organs of the host (Lowitz and Casciato, 2012). Cancer cells develop as a result of alterations in cellular signalling caused by mutations of the primary nucleotide sequence of cellular deoxyribonucleic acid (DNA). Mutations that develop in genes responsible for cellular growth (oncogenes or tumour suppressor genes) or preserving DNA repair (so-called 'caretaker' gene) might not influence cell function, but can lead to increased cellular proliferation and subsequent tumour development (neoplasm). These mutations can be the result of various mechanisms, which can include imprecise DNA repair, random replication errors, messenger ribonucleic acid (mRNA) processing errors, exposure to carcinogens, or incorporation of exogenous DNA into the genome (O'Dwyer and Frattini, 2010).

Tumours can be classified as benign or malignant. Benign (non-cancerous) tumours will remain localised and encapsulated and are considered safe unless they impede vital tissues or organs. Conversely, malignant tumours possess the ability to spread from the original tumour site to infiltrate other tissues and organs around the body. This spread is termed *metastasis*, and can lead to secondary tumour development, possibly affecting the function of tissue / organs at the new site (Clancy and McVicar, 2009).

There are different types of cancer, with the defining characteristic of each being the types of cell in which the cancer originates. While the term *carcinoma* is used to describe cancers of epithelial origin (e.g. the skin or tissues that line or cover internal organs), *sarcoma* describes cancers that originate from tissues of mesodermal components, namely bone, cartilage, fat, muscle, blood vessels or other connective or supportive tissues. Other

types of cancer include leukaemia (cancers starting in blood forming tissues, e.g. bone marrow), lymphoma and myeloma (cancer beginning in the cells of the immune system) and gliomata, central nervous system cancers (cancers originating in the tissues of the brain or spinal cord; National Cancer Institute, 2012).

Although current knowledge of cancer is based on many recent scientific discoveries, cancer has been known about since the time of Hippocrates (460 BC - 377 BC) when it was termed *karcinos* (Porter, 1997). Later, Galen (130 AD - 200 AD) considered cancer a species of inflammation, while endorsing the Hippocratic counsel view that deep or hidden cancers should not be treated. The hypothesis from these early scholars was that a tumour might form because of too much blood in the veins, or as a transmutation of a scirrhus formed by a flux of black bile mixed with blood.

2.1.1 *Cancer incidence and mortality*

Currently cancer is more prevalent than ever, with an estimated 12.7 million new cancer cases and 7.6 million cancer deaths occurring worldwide in 2008 (International Agency for Research on Cancer, 2009a). This represents a continual increase in both cancer diagnosis and mortality through the past 20 years, with 10.9 million new cases and 6.7 million deaths reported in 2002, 10.1 million new cases and 6.2 million deaths in 2000 and 8.1 million new cases and 5.2 million deaths in 1990 (Parkin *et al.*, 1999; Parkin, 2001; Parkin *et al.*, 2005). It has been predicted that this trend for increasing cancer incidence will continue through the next two decades with an estimated 22.2 million new cases worldwide by 2030 (Bray *et al.*, 2012).

Similarly, in the UK cancer incidence and mortality have continued to increase. In the most recent data presented by the Office for National Statistics (2012), there were 324,579 new cancer cases and 157,275 cancer deaths in 2010 alone. This represents an 18% increase in new cancer cases and a 2% increase in cancer deaths since 2001. Maddams *et al.* (2009) estimated that there would be around 2 million cancer survivors in the UK at

the end of 2008. Moreover, they suggested that approximately one in three people in the UK would be diagnosed with cancer in their lifetime and one in four would die from it.

This pattern of increasing cancer incidence is mirrored by the growing financial burden of the disease. Cancer spending in the UK in 2009-2010 was £5.86 billion, accounting for 5.6% of total health spending for the year (Sullivan *et al.*, 2011). In the USA cancer spending has increased from $27 billion in 1990 to $90 billion in 2008. It is predicted that by 2020 it will reach $173 billion, a rise of >600% in 30 years (Mariotto *et al.*, 2011).

These data highlight the need for more strategies to reduce the burden of cancer. As the number of people living beyond a diagnosis of cancer continues to rise, it is important that their needs for maintaining quality of life can be met in a cost-effective manner.

2.2 The prostate

The prostate gland is described in Dorlands Medical Dictionary (2007) as "*a gland in the male that surrounds the bladder neck and urethra. It consists of a median lobe and two lateral lobes, and is made up partly of glandular matter whose ducts empty into the prostatic part of the urethra, and partly of muscular fibres that encircle the urethra*".

The prostate is doughnut shaped, and about the size of a golf ball, measuring approximately 4 cm across, 3 cm in height and 2 cm deep (Figure 2.1). The anatomy of the prostate is widely known by the zonal subdivisions first described by McNeal (1968) which uses the urethra as the primary anatomic reference point. The central zone constitutes about 25% of the prostate gland and is located at the base of the prostate surrounding the ejaculatory ducts. The peripheral zone makes up around 70% of the glandular prostate and is described as the sub-capsular portion of the posterior aspect of the prostate gland that surround the distal urethra. The transitional zones accounts for around 5% of the prostate and are located along the proximal urethra.

Prostate size increases in three main phases throughout life; from birth to puberty it expands slowly, from puberty to approximately 30 years of age it expands rapidly and after 45 years of age further growth can also take place (Tortora and Derrickson, 2006). In normal function the prostate secretes an alkaline fluid that neutralizes acidic vaginal secretions, thus increasing sperm motility by creating a slightly alkaline environment. Additionally, the prostate secretes clotting enzymes, including prostate-specific antigen (PSA), and fibrinolysin into semen prior to ejaculation. Clotting enzymes interact with fibrinogen from the seminal vesicles to produce fibrin which clots semen, and hence helps to ensure ejaculate remains in the female reproductive tract after withdrawal of the penis. Subsequently, the fibrin-degrading capacity of fibrinolysin breaks the clot down to release mobile sperm within the reproductive tract (Sherwood, 2007).

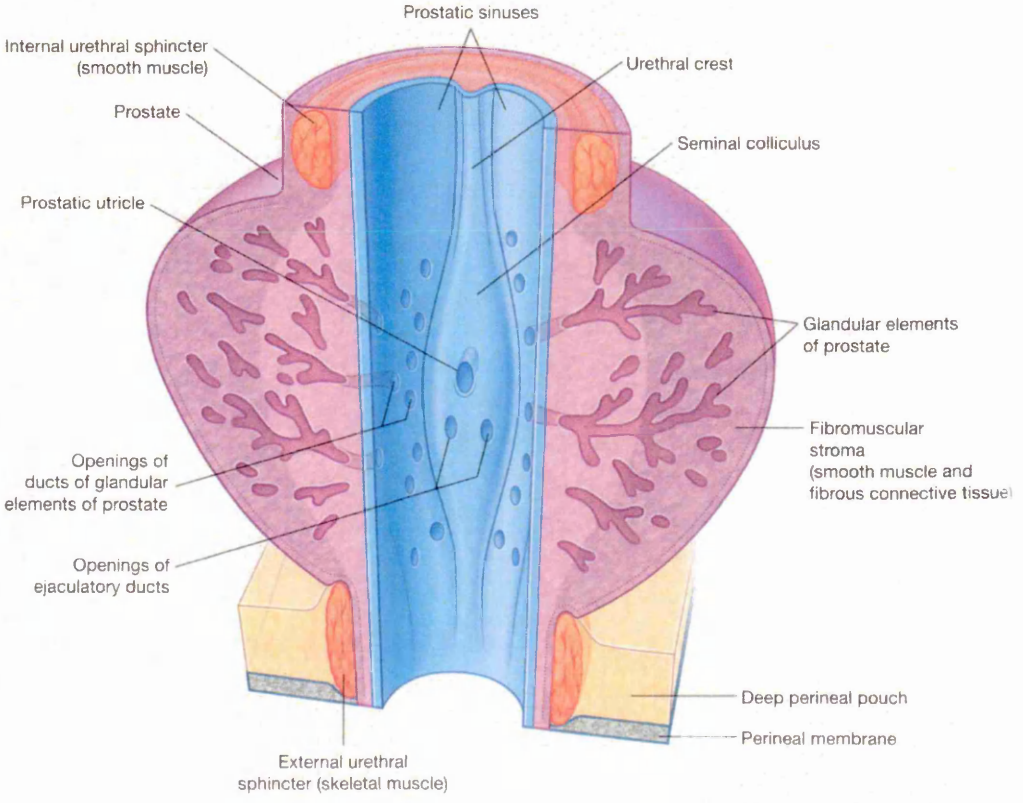


Figure 2.1. The prostate. Image taken from Drake *et al.* (2010)

2.3 Prostate cancer

The majority of malignancies of the prostate are a form of carcinoma termed adenocarcinomas (cancers developing in glandular cells lining certain internal organs and that have gland-like properties). Other forms of prostate cancer can include small-cell carcinoma or prostate sarcoma, however both of these forms of prostate cancer are rare accounting for about 1% and 0.1% of prostate malignancies, respectively (Nuttings *et al.*, 1997; Pace *et al.*, 2010).

Approximately 70% of prostatic adenocarcinomas form in the peripheral zone of the gland, around 20% arise in the transitional zone and fewer than 10% arise in the central zone (Byar and Mostofi, 1972). Local tumour growth results in invasion of the prostate gland and surrounding tissues, with the seminal vesicles, bladder and rectum the most common sites for infiltration. Metastases of the spine are most common although all parts of the skeleton could be affected bringing about potential pathological fractures, spinal cord compression, or neurological symptoms dependent upon metastases location (Neal and Hoskin, 2003; Mehta *et al.*, 2007).

Although prostatic tumours can remain latent and are discovered only at autopsy (Damber and Aus, 2008), the implications of symptomatic disease can be physiologically and psychologically damaging for the patient. Presenting symptoms can include: prostatic obstruction of urine affecting frequency, hesitancy, poor stream, nocturia and terminal dribble; haematospermia; bone pain or infrequently spinal cord compression as an effect of bone metastases; hypercalcemia and general symptoms of malignancy including malaise, anorexia and weight loss (Neal and Hoskin, 2003), although currently, the commonest presentation is with an elevated serum PSA concentration identified during opportunistic screening.

2.3.1 *Prostate cancer risk factors*

Prostate cancer incidence is known to increase with age with the majority of men presenting between 60-80 years, and only rarely will men less than 50 years be diagnosed with the disease (Mehta *et al.*, 2007). Furthermore, family genetics have been linked to prostate cancer risk. In a study of cancer incidence in 44,788 pairs of twins from Sweden, Denmark and Finland, 42% of prostate cancer cases were attributed to inheritable risk, more than shown with any other form of cancer (Lichtenstein *et al.*, 2000). These results are in agreement with others also showing high genetic risk in prostate cancer development (Steinberg *et al.*, 1990; Page *et al.*, 1997; Ahn *et al.*, 2008). Indeed, Steinberg *et al.* (1990) reported that males with one, two or three first-degree relatives affected by prostate cancer would themselves have their risk for the disease increased by a factor of 2, 5 or 11, respectively.

Prostate cancer incidence has also been associated with several additional risk factors, although this is an area in which further research is clearly warranted as there is much contradictory evidence. Serum androgen concentrations have been linked to prostate cancer risk, however there is little consensus on the details of such an association. In the largest meta-analysis performed on the relationship between sex hormones and prostate cancer risk, the Endogenous Hormone and Prostate Cancer Collaborative Group reported no link between the risk of prostate cancer and serum concentrations of total testosterone, free testosterone or 5α-dihydrotestosterone (DHT). Pooling data from 18 studies, including more than 10,000 men (3,886 with prostate cancer and 6,438 controls), a moderate inverse relationship was found however between sex-hormone binding globulin (SHBG) and prostate cancer risk (Roddam *et al.*, 2008). Men in the highest fifth of SHBG concentrations had a risk ratio (RR) for the development of prostate cancer of 0.86 (95% CI, 0.75-0.98) compared to men in the lowest fifth of SHBG, although this relationship did not achieve statistical significance. Notably, more recent studies in this area have reported alternative findings that do not fully support these results. Later in 2008, Weiss *et al.* (2008) found no relationship between any serum sex

hormones and prostate cancer risk, but did report an increase in disease risk with increased testosterone:SHBG ratio. Moreover, Daniels *et al.* (2010) found a strong relationship between increasing estrone concentrations and prostate cancer risk, but did not find disease incidence to be linked to any other sex hormones. Unfortunately, comparisons between these studies are complicated because of differences in the sex hormones investigated. Although both Weiss *et al.* and Daniels *et al.* contradicted the finding of an association between SHBG and disease risk, the evidence of relationships between testosterone:SHBG ratio and estrone concentrations with prostate cancer also cannot be confirmed as neither of these markers were reported in the other studies. These conflicting findings could be the result of differences between studies in sample size, or potentially influenced by different factors being used for adjustment of results for each study.

Lifestyle is also considered highly important in development of prostate cancer. High incidence rates (>31.0 cases per 100,000) in westernised countries such as Australia, Northern America and Western Europe, and lower incidence (<9.8 per 100,000) in parts of Africa and much of Asia suggest an environmental effect (Hsing *et al.*, 2000; Quinn and Babb, 2002; Parkin *et al.*, 2005; Garcia *et al.*, 2007). This is further evidenced by the increased prostate cancer incidence among migrants moving from areas of low disease prevalence to areas of high disease prevalence (Shimizu *et al.*, 1991; Nasseri *et al.*, 2007).

Dietary factors have been widely cited in this change in disease risk (Nelson *et al.*, 2003). Data from the Health Professionals Follow-up study, a prospective cohort study involving 51,529 men, demonstrated that consumption of animal fat, especially from red meat, was linked with advanced cancers after 2 years of follow-up (Giovannucci *et al.*, 1993), while after 10 years of follow-up there was a strong association between intake of red meat or processed meats and incidence of metastatic prostate cancer (Michaud *et al.*, 2001). These findings are supported by others who also report a positive association between consumption of red and processed meats and risk of prostate cancer diagnosis (Rodriguez *et al.*, 2006; Sinha *et*

al., 2009; Ukoli *et al.*, 2009). Although mechanisms behind this association have not been identified, it is hypothesized that cooking methods might be influential (Nelson *et al.*, 2003). Studies in rats have shown eating meat cooked at high temperatures or broiled on charcoal grills can cause prostate cancer through the effects of heterocyclic aromatic amine and polycyclic aromatic hydrocarbon carcinogens formed in the cooking process (Stuart *et al.*, 2000). These carcinogens have been reported to induce genetic damage resulting in cellular apoptosis or mutation, with the latter of these outcomes thought to be key in cancer development (Gooderham *et al.*, 2002).

Additionally, calcium intake has been related to risk of prostate cancer incidence (Chan *et al.*, 2001; Ahn *et al.*, 2007). Chan *et al.* (2001) reported that in a cohort of 20,885 men, those who had a daily calcium intake >600 mg per day, had a 32% higher risk of prostate cancer (95% CI, 1.08-1.63) compared with men consuming ≤150 mg. Similarly, Ahn *et al.* (2007) described a 34% increased risk (95% CI, 0.93-1.94) of prostate cancer in men consuming >2,000 mg per day compared to those consuming <1,000 mg per day. However, the mechanisms underlying such an association are unclear and these findings have been contradicted by others who have reported no effect or a benefit of calcium intake on prostate cancer risk (Koh *et al.*, 2006; Williams *et al.*, 2012). Assessing the association between dietary calcium and prostate cancer in a sample of 500 men, Williams *et al.* (2012) reported lower disease risk in men in the highest tertile of calcium intake from food (median intake = 1,093 mg per day) compared to those in the lowest tertile of calcium from food (median intake 367.3 mg per; Odds ratio (OR) = 0.37; 95% CI, 0.15-0.90). Although the smaller sample size of the study by Williams *et al.* (2012) suggests this finding might be the result of a sampling issue, the fact that the statistically significant findings focus on calcium from food instead of total calcium is of interest, and thus these contradictory findings suggest further research in this area is clearly warranted.

Obesity is also recognised as a risk factor for prostate cancer with excess body fat reported to influence disease incidence, progression and mortality (Cooper-Buschemeyer and Freedland, 2007). Increasing body mass index

(BMI) has been positively associated with increased risk of prostate cancer in several large cohort studies including more than a million men (Andersson *et al.*, 1997; Engeland *et al.*, 2003). Moreover, investigations into whether or not BMI influences disease stage or grade at diagnosis demonstrated that men with a higher BMI were less likely to be diagnosed with localised disease, but were more likely to have high-grade or metastatic/fatal disease (Rodriguez *et al.*, 2007; De Nunzio *et al.*, 2011). This propensity towards higher-grade disease could be the result of several factors. Greater difficulty in diagnosis of prostate cancer in the obese could lead to a detection bias in which tumours are diagnosed only at more advanced stages in men with higher BMI (Cooper-Buschemeyer and Freedland, 2007). Additionally, there is evidence of physiological effects of increased adiposity predisposing overweight individuals to develop higher-grade cancers. Although, as previously described, there is some contradictory evidence of an association between serum androgens and total prostate cancer risk, lower pre-diagnosis serum androgens concentrations, as can be found with obesity, have been linked to increased risk for future high-grade disease (Platz *et al.*, 2005; Severi *et al.*, 2006). Furthermore, analyses of serum concentrations of oestradiol at diagnosis have demonstrated possible evidence of a positive association with more aggressive disease. Oestradiol concentrations have been shown to be increased in obese men due to high aromatase activity in adipose tissue (Vermeulen *et al.*, 2002), and higher oestradiol has been linked to greater risk of more aggressive prostate cancer. Salonia *et al.* (2011) demonstrated that oestradiol concentrations ≥50 $pg \cdot ml^{-1}$ were associated with a 3.24 fold increased risk of high-grade prostate cancer.

Although the evidence reviewed above suggests a strong relationship between BMI and prostate cancer, other studies have reported no relationship between BMI and disease risk (Lund Nilsen and Vatten, 1999). Part of the lack of agreement in results could be because of differences in body composition between study samples. Fowke *et al.* (2012) demonstrated that increases in disease risk with increasing BMI and waist circumference were mediated by measurement of total body fat free mass. It was suggested

that this association was probably the result of measures of fat free mass reflecting shared genetic, hormonal and nutritional factors for maintenance of lean body mass and prostate carcinogenesis.

2.3.2 *Prostate cancer epidemiology*

International data for the year 2008 showed that prostate cancer was the second most frequently diagnosed cancer in men (after lung cancer) with 13.8% of new male cancers diagnosed being of the prostate, a total of 913,000 new cases (International Agency for Research on Cancer, 2009b). Through the past five decades, disease incidence has continued to steadily rise in many nations through both the developed and developing world (Hsing *et al.*, 2000; Quinn and Babb, 2002; Quaglia *et al.*, 2003; Kvåle *et al.*, 2007; International Agency for Research on Cancer, 2009b), with worldwide mean age-adjusted disease incidence increasing 1.1% annually from 1985 to 2002 (Parkin *et al.*, 2005). Recent data for England demonstrate prostate cancer more than doubled between 1992 and 2010, with 15,705 registered new cases in 1992 increasing to 34,892 new cases in 2010 (Office for National Statistics, 2012).

Currently, prostate cancer is the sixth highest cause of male death attributed to cancer worldwide (behind cancers of the lung, liver, stomach, colon-rectum and oesophagus) with 258,000 cases annually (International Agency for Research on Cancer, 2009a). However, despite the worldwide incidence of prostate cancer continuing to rise, mortality rates have stabilised or begun to decline in many westernised nations (Oliver *et al.*, 2001; Baade *et al.*, 2004; Hussain *et al.*, 2008). This pattern has been evident in England and Wales where despite disease mortality rates more than doubling from 4421 in 1979 to 9169 in 2004, the greatest proportion of this increase was between 1979 and 1992, where there was an estimated mean increase of 1.72 deaths per 100,000 population per year (from 46.33 per 100,000 to 67.33 per 100,000). This trend was reversed from 1992 to 2004 with an estimated annual decline in mortality rates of 1.61 per 100,000, to 49.64 deaths per 100,000, or a total

fall of 26% in absolute terms (Hussain *et al.*, 2008). These trends were reflected across the UK as a whole, as is displayed in Figure 2.2 which shows prostate cancer incidence and mortality rates for the UK from 1975-2010.

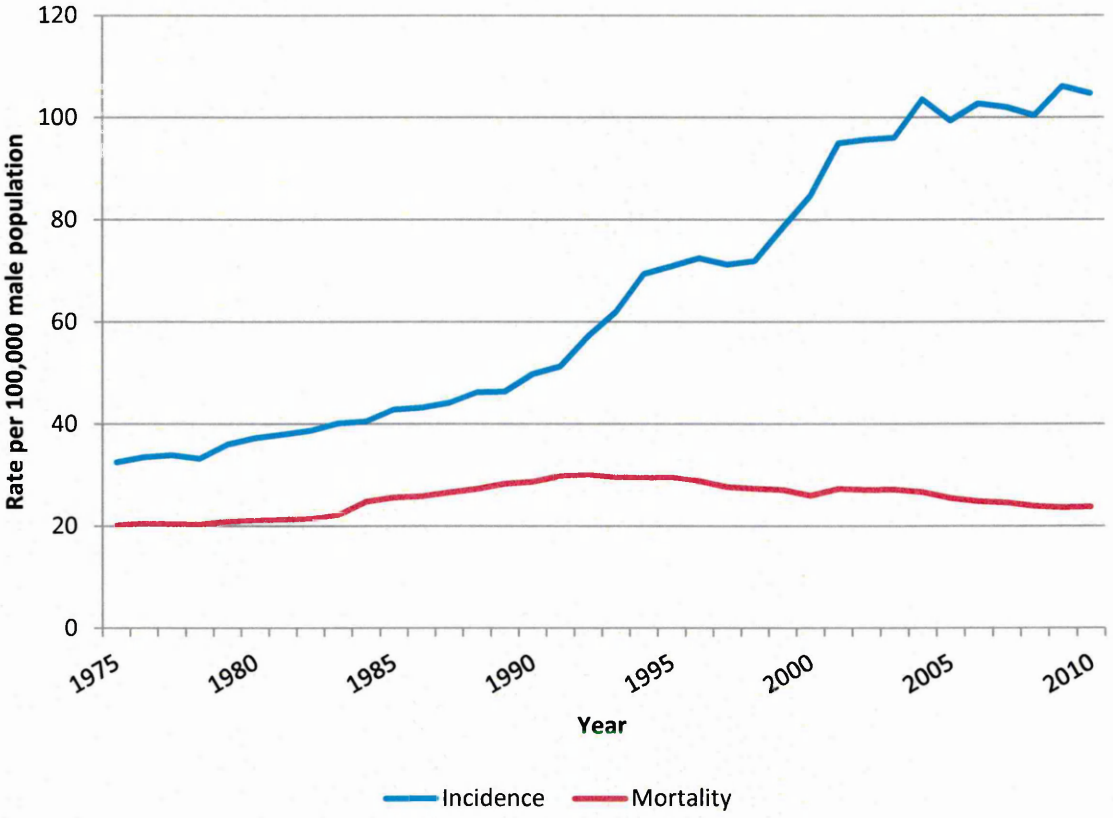


Figure 2.2, Age-standardised incidence and mortality rates per 100,000 male population for prostate cancer in the UK from 1975-2010. Data obtained from Cancer Research UK (2013).

It must therefore be asked, what factors account for these widespread changes in prostate cancer incidence and mortality? Consensus from several authors considering this conundrum appears to be that while increased screening for PSA has led to dramatic increases in incidence, advances in disease treatment could be playing an integral role in changes in mortality rates (Albertson, 2003; Baade *et al.*, 2004; Damber, 2004). Earlier disease detection combined with more aggressive treatment could be responsible for

the decline in cancer related mortality. Indeed, it has been reported that men diagnosed with prostate cancer have a risk of dying from cardiovascular disease of equivalent levels to the risk of dying from prostate cancer (Ketchandji, *et al.*, 2009).

2.4 Cardiovascular disease

The cardiovascular system includes the heart and the networks of blood vessels (Oxford Medical Dictionary, 2007). This system is responsible for the circulation of blood around the body, which supplies nutrients and oxygen to the tissues in addition to removing waste products. Disruption to the homeostasis within this system can lead to the development of cardiovascular disease including conditions such as ischemic heart disease, heart failure, arrhythmias or vascular diseases, which can lead to clinically significant morbidity or mortality (Griffin and Topol, 2009).

Cardiovascular disease is the number one cause of death globally accounting for an estimated 17.3 million deaths in 2008 alone, representing 30% of deaths worldwide (World Health Organization, 2013), yet this global burden is continuing to rise. More recent data for Europe shows that cardiovascular disease was responsible for 47% of all deaths in 2012 (European Heart Network, 2013). Moreover, the World Health Organization predicts that by 2030 cardiovascular disease will be responsible for 23.3 million deaths worldwide (World Health Organization, 2013).

Such mortality rates are of little surprise in consideration of the widespread incidence of cardiovascular disease. In the recent review of heart disease and stroke statistics for the American Heart Association, Go *et al.* (2013) reported that around 11%, 35%, 70% and 85% for people aged 20-39 years, 40-59 years, 60-79 years and over 80 years, respectively, had been diagnosed with some form of cardiovascular disease (including coronary heart disease, heart failure, stroke and hypertension). Similarly, data for Great Britain also demonstrates high rates of cardiovascular disease incidence (British Heart Foundation, 2012). Data for the year 2010 shows

coronary heart disease or stroke had been diagnosed in 2%, 12%, 28% and 33% of individuals aged 16-44 years, 45-64 years, 65-74 years or over 75 years, respectively.

Consequently, with such high prevalence rates for cardiovascular disease the economic costs are also high. Data from the British Heart Foundation (2012) shows that in 2009 cardiovascular disease cost the UK health care system around £9 billion, representing a cost per capita of £141. Hospital care account for around 50% of these costs with drug treatments making up approximately 23%. Furthermore, it was estimated that the cost of lost production for cardiovascular disease morbidity or mortality was over £6 billion for the year 2009.

2.4.1 *Cardiovascular disease risk factors*

The development of cardiovascular disease can be the result of both modifiable and non-modifiable factors. Modifiable risk factors are considered behavioural and include physical inactivity, unhealthy diet, tobacco use and harmful use of alcohol. These four behaviours can lead to key physiological changes that increase cardiovascular disease risk by promoting the development of raised blood pressure, overweight or obesity, hyperglycaemia and hyperlidemia (World Health Organization, 2013). It has been reported that modifiable risk factors account for approximately 80% of the incidence of coronary heart disease and cerebrovascular disease (World Health Organization, 2011). The link between each of these risk factors and the development of cardiovascular disease is reviewed in greater detail later in this chapter (2.8.7 Cardiovascular risk).

Non-modifiable cardiovascular disease risk factors include attributes that will influence the chance of cardiovascular disease development, but are not within the control of an individual. Being of advanced age is one such risk factor. In the Framingham Heart Study age is considered the most important determinant of the 10 year risk of cardiovascular disease (D'Agostino *et al.*, 2008). The American Heart Association (2013) report that the risk of having a

stroke approximately doubles for each decade of life after 55 years. Such increases in risk can be partly explained by structural and functional adaptations in the cardiovascular system occuring with age (Priebe, 2000). Priebe (2000) reported that aging is associated with changes in cardiac and vascular function, with reduced contractile efficiency in the heart and greater vascular stiffness shown with age.

Being of male gender has been considered to be important in cardiovascular risk, with men having a greater risk than premenopausal women but a similar risk to post-menopausal women (World Heart Federation, 2013). It has been reported that differences in iron concentrations may be important in this discrepancy in risk of cardiovascular events explaining the changing risk in women with menopause (Kiechl *et al.*, 1997). In addition, differences between genders for components of the metabolic syndrome including insulin resistance, adiposity, dyslipidemia, and hypertension have also been reported to potentially influence the development of cardiovascular disease (Regit-Zagrosek *et al.*, 2006). Current evidence on both of these mechanisms remains limited however, and thus further research in this area is required to substantiate these data.

Ethnicity has also been reported to influence cardiovascular risk. The British Heart Foundation (2010) reported that incidence of myocardial infarctions was higher in South Asian individuals than in non-South Asians, while incidence of stroke was highest in people of a black ethnic group compared to those of a white ethnic group. There could be both physiological and socio-economic reasons for these discrepancies between ethnic groups however. Physiologically, individuals from different ethnic groups will store fat in different places influencing the subsequent cardiovascular risk accrued. Although conversely, it is also reported that very few people from ethnic minority groups attend cardiac rehabilitation programmes, thus increasing their risk of subsequent events.

In addition, family history can also influence an individuals risk of developing cardiovascular disease. The World Heart Federation (2013) state that an individual's risk of developing heart disease will be increased if a first-degree

male relative has suffered a myocardial infarction before the age of 55, or a first-degree female relative has suffered one before the age of 65. They report that if both parents have suffered from heart disease before the age of 55, the risk of their children developing heart disease can be increased by 50% from the general population. This familial link could be partly attriuted to a genetic component in the development of hypertension, abnormal lipid concentrations and diabetes (Siervogel, 1983; Klein *et al.*, 1996; Soutar and Naoumova, 2007), although, additional genetic links have also been speculated upon (Tymchuk *et al.*, 2006). In-fact, Hamer *et al.*, (2009) reported that only a small portion (15%) of the increase in cardiovascular risk associated with a family history was accounted for by conventional risk factors (blood pressure, cholesterol, adiposity), suggesting an important role for such additional genetic mechanisms.

The Interheart study undertook a case-control investigation across 52 countries to examine the contribution of risk factors for the development of acute myocardial infarction (Yusuf *et al.*, 2004). It was reported that nine potentially modifiable risk factors (smoking, abnormal lipids, hypertension, abdominal obesity, diabetes, psychosocial factors, consumption of fruits and vegetables, alcohol intake and regular physical activity) accounted for more than 90% of the risk.

Data from the British Heart Foundation (2012) provides the most recent evidence for the prevalence of cardiovascular risk factors across the UK, with the findings showing that many risk factors are widespread. Data for men aged 65 years or older demonstrates both behavioural and physiological risk factors are widely apparent. Behavioural data shows physical inactivity, excessive alcohol intake and cigarette smoking were shown in 45%, 22% and 13% of the population. Consequently, physiological risk factors including high blood pressure, high cholesterol concentrations, obesity and diabetes were also evident in 70%, 45%, 26% and 15% of men of such an age group, respectively.

Although it is concerning that cardiovascular risk factors are so abundant, evidence that such a large proportion of the risk of cardiovascular disease

can be accrued through factors that are modifiable is encouraging for the prevention of such diseases in prostate cancer survivors in whom incidence has been shown to be raised. Attention must therefore turn to investigating whether modifying risk factors in such a population can decrease cardiovascular risk, in addition to maintaining general health and overall quality of life. The NCSI has stated that with increasing numbers of people living beyond a cancer diagnosis dealing with the concerns of these patients and the consequences of their treatment must become a priority (Richards *et al.*, 2011). Greater research into patient physical and mental well-being after diagnosis and the development of strategies to ensure patients can maintain or improve their standard of living are clearly warranted.

2.5 Prostate cancer diagnosis and staging

2.5.1 *Prostate-specific antigen*

Described by Pal *et al.* (2012) as a serine protease that serves as a marker unique to the prostate, PSA is an enzyme produced by the glandular epithelium of the prostate. In normal function PSA is secreted into seminal plasma where, via interactions with semenogelin I, semenogelin II and fibronection, it causes liquefaction of the seminal plasma clot after ejaculation (Diamandis, 1998). However, in light of the potential prognostic value of high PSA concentrations in men with prostate cancer the clinical importance of this enzyme has increased. First described by Hara *et al.* (1966), it wasn't until 1980 that the clinical use of PSA as a blood-borne marker of prostate cancer was first described (Papsidero *et al.*, 1980). These discoveries led to increasing use of PSA testing for tracking the progression of patients with confirmed disease, and then subsequently for screening asymptomatic patients (Loeb and Catalona, 2007).

Increased testing for PSA has been strongly linked to the rise in prostate cancer diagnoses (Farkas *et al.*, 1998; Barchielli *et al.*, 1999; Hankey *et al.*, 1999; Coldman *et al.*, 2003; Larrañaga *et al.*, 2010). PSA testing has facilitated men being diagnosed younger and with earlier stage disease than

was apparent in the pre-PSA era (Diamandis, 1998; Barchielli *et al.*, 1999; Carsin *et al.*, 2010). In spite of these developments, one major issue of contention remaining with PSA testing is whether or not the improvements in disease detection actually translate into benefits in prostate cancer-specific or all-cause mortality (Concato *et al.*, 2006; Albertsen, 2010). Although there is evidence linking PSA screening to decreased prostate cancer mortality rates (Oberaigner *et al.*, 2006; Schröder *et al.*, 2009) a greater volume of literature describes contradictory findings, suggesting other factors could, at least in part, be responsible for changes in prostate cancer mortality rates (Lu-Yao *et al.*, 2002; Lu-Yao *et al.*, 2008; Marcella *et al.*, 2008; Andriole *et al.*, 2009; Carsin *et al.*, 2010). What has become apparent since PSA testing has become more widely used, is that men are now initiating radical treatments for prostate cancer earlier and staying on treatments longer (Cooperberg *et al.*, 2003; Hussain *et al.*, 2008) increasing the possibility of treatment-associated morbidities such as the increase in cardiovascular risk factors reported in men on long-term ADT (Bourke *et al.*, 2012).

Natural fluctuations in PSA concentrations mean a single high PSA value cannot be used conclusively to diagnose prostate cancer. PSA concentrations will increase with age, with upper limits of normative values of 2.5 $ng \cdot ml^{-1}$, 3.5 $ng \cdot ml^{-1}$, 4.5 $ng \cdot ml^{-1}$ and 5.5 $ng \cdot ml^{-1}$ proposed for men aged <50, 50-59, 60-69 and 70-79 years, respectively (Mehta *et al.*, 2007). Furthermore, PSA values can be increased in patients with benign prostatic hyperplasia, infection and chronic inflammation (Shariat *et al.*, 2008).

A PSA cut-off of 4 $ng \cdot ml^{-1}$ was previously considered suggestive of increased risk of prostate cancer and warranted further investigation. This PSA concentration has sensitivity for prostate cancer detection of 72.1% and a specificity of 93.2% (Mistry and Cable, 2003). However, this cut-off level was highly questioned after studies reported histologically confirmed prostate cancer in patients with PSA <4 $ng \cdot ml^{-1}$ (Catalona *et al.*, 1997; Törnblom *et al.*, 1999; Thompson *et al.*, 2004). Catalona *et al.* (1997) reported prostate cancer was detected in 22% of men with PSA between 2.6 and 4 $ng \cdot ml^{-1}$, while data from Thompson *et al.* (2004) suggests that among men aged 62 -

91 years there is no lower PSA threshold below which prostate cancer can be ruled out with high confidence. These findings have led to the most recent European Association of Urology guidelines on prostate cancer stating that a PSA threshold indicating the highest risk of prostate cancer still needs to be defined, and that use of further investigation is warranted in patients with raised PSA, or in whom prostate cancer is suspected despite low PSA concentration (Heidenreich *et al.*, 2011).

2.5.2 *Digital rectal examination*

First described in 1905 by Young (1905, as cited in Brawley *et al.*, 2009), digital rectal examination (DRE) was for a long time considered the only method for prostate cancer screening. Examinations involve a trained professional palpating the surface of the gland to assess symmetry and texture (Waldman, 2006). Within this process stands a weakness however, as it has been shown that up to 40% of prostatic carcinomas form anterior to the midline of the prostate making them undetectable by DRE (Littrup *et al.*, 1992). In addition, DRE is limited by the difficulty in detecting small-size tumours (Waldman, 2006) and the subjective nature of the test leading to potential inter-observer variability (Gosselaar *et al.*, 2008).

When used alone, DRE provides an insensitive method of prostate cancer detection, as is evident in the work by Thompson *et al.* (1984) who reported that up to two-thirds of patients in whom prostate cancer was detected by DRE had disease that had spread beyond the prostate at time of diagnosis. However, in modern practice DRE is often performed in addition to PSA screening as an additional means of confirming or refuting the presence of carcinoma and as a means of detecting non-PSA secreting tumours (Borley and Feneley, 2009).

2.5.3 *Transrectal ultrasound and prostate biopsies*

Using a 7.5 mHz ultrasound probe inserted into the anus the prostate gland and seminal vesicles can be imaged to determine the outline and volume of the prostate (Borley and Feneley, 2009). Although not suitable for the detection of early stage disease, transrectal ultrasound (TRUS) can identify calcifications, abscesses and cysts, with defects in the periprostatic fat layer symptomatic of extracapsular disease (Mehta *et al.*, 2007).

In addition to the merits of solely imaging the prostate, TRUS is used to guide needle biopsies to specific sites. Under local anaesthetic 10-12 biopsy specimens, dependent upon glandular volume, can be taken from regions around the prostate (Damber and Aus, 2008). These samples subsequently undergo microscopic analysis of cellular disease spread allowing determination of a Gleason score (discussed in 2.5.4 Classification). Samples are predominantly obtained from the periphery of the prostate, with limited benefit shown for biopsies of the transitional zone because of infrequent cancer development in this region (Pelzer *et al.*, 2005). This process is not without risk however, with complications including haematospermia, urinary retention, haematuria, rectal bleeding, and sepsis reported in men post-prostatectomy (de Jesus *et al.*, 2006; Chiang *et al.*, 2007).

Improvements in cancer detection rate of 31% have been reported using the 10-12 samples technique compared with the more traditional sextant technique (6 samples) which was widely used until the late 1990's and early 2000's (Eichler *et al.*, 2006). In patients with no signs of cancer in initial biopsies, but in whom cancer is still suspected, saturation biopsies can be performed. Saturation biopsies will require 20 or more samples from across the gland or from specific targeted regions identified by ultrasound imaging in which a cancer is suspected (Borley and Feneley, 2009).

2.5.4 *Classification*

After cancer detection, clinical staging is performed using the tumour, node, metastasis (TNM) classification system and Gleason score. This information informs clinicians on the development and spread of the disease and will be considered when deciding on the most appropriate treatment.

The TNM system has been used for staging prostate cancer since the 1940's, with updates and improvements subsequently applied to the original design leading to the publishing of the sixth edition in 2002 (Chang and Amin, 2008). The tumour (T) element of the staging refers to the presence and spread of the primary tumour. Node (N) details the extent of regional lymph node involvement. Metastasis (M) describes the existence of any distant metastasis. Table 2.1 displays the TNM staging classification as described by Chang and Amin (2008), with definitions of each stage provided.

Table 2.1. Definition of the tumour, node, metastasis system of prostate cancer staging. Table reproduced from Chang and Amin (2008)

Primary Tumour (T)	
Clinical	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Clinically inapparent tumour neither palpable nor visible by imaging
T1a	Tumour incidental histologic finding in 5% or less of tissue resected
T1b	Tumour incidental histologic finding in more than 5% of tissue resected
T1c	Tumour identified by needle biopsy (e.g. because of elevated PSA)
T2	Tumour confined within prostate*
T2a	Tumour involves one-half of one lobe or less
T2b	Tumour involves more than one-half of one lobe but not both lobes
T2c	Tumour involves both lobes
T3	Tumour extends through the prostate capsule**
T3a	Extracapsular extension (unilateral or bilateral)
T3b	Tumour invades seminal vesicle(s)
T4	Tumour is fixed or invades adjacent structures other than seminal vesicles: external sphincter, bladder, rectum, levator muscles, and/or pelvic wall
* *Note:* Tumour found in one or both lobes by needle biopsy, but not palpable or reliably visible by imaging is classified as T1c. ** *Note:* Invasion into the prostate apex or into (but not beyond) the prostatic capsule is classified not as T3 but as T2.	
Regional Lymph Nodes (N)	
Clinical	
NX	Regional lymph nodes were not assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)
Distant Metastasis (M)*	
MX	Distant metastasis cannot be assessed (not evaluated by any modality)
M0	No distant metastasis
M1	Distant metastasis
M1a	Non-regional lymph node(s)
M1b	Bone(s)
M1c	Other site(s) with or without bone disease
* *Note: When more than one site of metastasis is present, the most advanced category is used.*	

The Gleason system was originally described by Dr Donald Gleason in 1966 and uses a grading system based on microscopic interpretation of stained prostatic tissue obtained from biopsy samples (Humphrey, 2004). Five grading patterns of carcinoma can be generated scoring from 1 to 5. Scores are given for the most prevalent, and second most prevalent levels of carcinoma in the sample that are subsequently summed to give a score from 2 to 10, with higher scores indicative of the most aggressive cancers. For a cancer grading pattern to be counted it must occupy more than 5% of the sample, while if only one grading pattern is present in a sample this score is doubled to give the final Gleason score (Heidenreich *et al.*, 2008).

2.5.5 *Risk Stratification*

Clinical staging, PSA concentrations and Gleason score have also been used to stratify the risk of disease progression in patients with localised and locally advanced disease. The National Institute for Health and Clinical Excellence (NICE, 2008) provide guideline data for categorising low, intermediate and high risk patients (Table 2.2).

Table 2.2. Risk stratification for men with localised prostate cancer

	PSA		**Gleason score**		**Clinical stage**
Low risk	<10 ng·ml^{-1}	**and**	≤6	**and**	T1-T2a
Intermediate risk	10-20 ng·ml^{-1}	**or**	7	**or**	T2b-T2c
High risk	>20 ng·ml^{-1}	**or**	8-10	**or**	T3-T4*

Definition: PSA- Prostate-specific antigen

* Clinical stage T3-T4 represents locally advanced prostate cancer

2.6 Treatments

The treatment of prostate cancer has continued to evolve over many years with new techniques often building upon theory and practice rooted in history (Sriprasad *et al.*, 2009). Improved methods of disease detection can mean that patients are now spending longer undergoing treatment than they would have in the past. Deciding on the most appropriate form of treatment for each patient will depend on balancing the benefits of that form of treatment against the possible negatives of withholding other treatments or treatment side effects

2.6.1 *Expectant management*

Expectant management of prostate cancer is undertaken in-sight of several important facts, 1) a large number of cancers will remain dormant and asymptomatic, 2) if cancers progress, this will take place at different rates, and 3) radical treatment does not come without side effects. 'Watchful waiting' or 'active monitoring' could therefore be preferential options in some patients in which radical treatment is not suitable or not necessary. Although these terms are sometimes used interchangeably they refer to different forms of deferred treatment. Watchful waiting is a suitable option for patients who are asymptomatic but who have locally advanced disease that is considered incurable. These patients are often elderly and are likely to have a cancer that will not affect their life expectancy (Mehta *et al.,* 2007). Watchful waiting is effectively keeping treatment to *control* the cancer in reserve until it is needed (Cancer Research UK, 2009).

Conversely, active monitoring is more appropriate for younger, fitter men diagnosed with early prostate cancer who wish to avoid the negative side effects of radical treatment. Klotz (2005) suggested that men with low risk disease (PSA $<10 ng \cdot ml^{-1}$, biopsy Gleason score ≤6, stage T1c-T2a, life expectancy >10 years) are good candidates for this form of management. Patients under active monitoring will be reviewed regularly with PSA tests every 1-3 months, regular DRE and biopsies taken at least every 2-3 years.

Radical treatment to *cure* the cancer will be planned should progression occur (Cancer Research UK, 2009). Criteria for initiation of secondary therapy will be chosen at the discretion of the clinician and the patient with PSA concentrations and biopsy results used to guide this decision making process (Dall'Era *et al.*, 2008; van den Bergh *et al.*, 2010).

Active monitoring is of considerable use in modern medicine with the increasing number of patients diagnosed with early-stage cancers since the introduction of PSA testing. Use of active monitoring helps lower the number of cases of over-treatment where patients with low stage disease would have previously undergone radical therapy that might have proved to have been unnecessary (Miller *et al.*, 2006). Use of active monitoring allows the patient to be monitored to assess whether or not progression is occurring and thus whether radical therapy is needed.

Investigations of mortality rates in patients undergoing expectant management do not fully support the efficacy of delayed treatment however, with evidence of better disease-specific outcomes and survival in patients treated more aggressively. Although one of the largest studies investigating disease progression and mortality in men with clinically localised prostate cancer reported stable mortality rates 15 years after diagnosis, supporting the notion of treatment with watchful waiting until clinically necessary (Albertsen *et al.*, 2005), these findings are not fully supported by others. Randomised controlled studies of disease progression between men with localised disease randomly allocated to watchful waiting or radical prostatectomy show reduced disease progression, disease-specific mortality and overall mortality over follow-up periods of up to 8 years in men randomised to receive prostatectomy (Holmberg *et al.*, 2002; Bill-Axelson *et al.*, 2005).

2.6.2 *Radical prostatectomy*

Radical prostatectomy is the surgical removal of the prostate gland and seminal vesicles. This treatment option is performed with curative intent in

patients with T1 or T2 disease confined within the prostate (Mehta *et al.*, 2007). The technique for prostatectomy has been developed since it was first performed by Covillard in 1639, who removed prostatic tissue during a lithotomy (Jones, 1936). Although at least nine different approaches to the prostate have been described, it is mainly the retropubic approach that is used in modern practice with laparoscopic and robotic techniques becoming more common place (Sriprasad *et al.*, 2009). Perineal prostatectomies were common practice with surgeons trained prior to 1975, however, with the introduction of pelvic lymphadenectomies for staging purposes, retropubic approaches became preferable. The perineal approach does have advantages of reduced morbidity, operation time, and blood loss, making it suitable for older patients or those with high anaesthetic risk. Furthermore, this approach could be favourable in patients with high amounts of abdominal fat, or with previous lower abdominal pathologies or surgery where the retropubic approach might be inadvisable (Gillitzer and Thüroff, 2002).

Urinary incontinence and impotence can be long-term side effects experienced by patients after both forms of prostatectomy (Gillitzer and Thüroff, 2002). In a study of 203 patients undergoing prostatectomy, Smither *et al.* (2007) reported moderate or severe incontinence in 74% of patients 2 weeks after the operation. Symptoms decreased over time, yet remained in 12% of patients at 18 weeks, and in 4% after 54 weeks. Similarly, Talcott *et al.* (1997) reported that impotence was prolific in men after prostatectomy. At baseline 26% of patients reported erections inadequate for intercourse, however, 3 months after prostatectomy 97% of men were reported to be impotent, and 90% were still impotent 12 months after surgery.

Although radical prostatectomy is performed with curative intent, a large number of patients experience disease recurrence as a result of tumour reappearance in the prostate bed or through disease spread to lymph nodes or distant sites. In a study of disease-specific survival rates, Freedland *et al.* (2005) evaluated data from 5096 men over a mean duration from surgery of 6 years. Results identified biochemical recurrence, defined as a single post-operative PSA ≥ 0.2 $ng \cdot ml^{-1}$, in 979 men (19%). In a subset of 379 men with

recurrence entering the study, the authors report recurrence occurring at a mean of 3.5 years following surgery. Similar results were reported by Roberts *et al.* (2001) who described biochemical recurrence, defined as PSA ≥ 0.4 ng·ml^{-1}, in 879 men (31% of a total of 2079) occurring at a mean of 2.9 years after surgery.

2.6.3 *Radiotherapy*

Radiotherapy involves the delivery of doses of ionizing radiation to a cancerous tumour, with the aim of causing DNA damage to the cancer cells preventing further growth and leading to cell death when cellular division is attempted. Developed more than 100 years ago following the discovery that x-rays had potential therapeutic properties (Sriprasad *et al.*, 2009), radiotherapy now provides a modality for treatment of patients with early stage disease confined to the prostate and those with advanced disease suffering from metastatic spread and increased pain.

Radical radiotherapy, used for the treatment of early stage prostate cancer, is performed using either external beam radiation therapy (EBRT) or internal radiation therapy (brachytherapy). EBRT is the most commonly used form of radical radiotherapy (Volpe and Watkins, 2006) with high-energy ionizing radiation beams delivered to the prostate gland over a course of therapy lasting 4-7 weeks. Radiation produced from a radioactive source or electromagnetic energy is delivered to target sites on the patient at external doses of 65 to 78 Gy, providing daily fractions of around 1.8-2.0 Gy per day. In addition to standard EBRT, conformal radiotherapy and intensity modulated radiotherapy are both available options that allow the shape and intensity of the radiation beam to be modified to optimise radioactive delivery to the tumour while minimising the exposure of surrounding tissues. Studies are on-going to investigate the most effective technique (Cancer Research UK, 2010b).

Brachytherapy is the implantation of radioactive 'seeds' into the prostate gland. Using ultrasound guidance, Iodine-125 or Palladium-103 radioisotopes

are inserted through a transperineal approach to pre-planned locations within the prostate (Hilaris *et al.*, 2000). Patients can receive between 80 and 100 seeds in an operation expected to last around an hour, with this rapid delivery of radiation considered one of the strengths of brachytherapy compared with the daily treatment schedules of up to seven weeks experienced with EBRT. Radiation doses delivered with brachytherapy depend on the positioning of the seeds inside the prostate gland. Use of peripheral loading allows radiation doses at the centre of the prostate to remain below twice the prescription dose lowering the incidence of urinary complications (Wallner, 2000).

Radical radiotherapy is performed with a curative intent, yet disease recurrence is not uncommon. Although studies investigating biochemical recurrence after radiotherapy have varied in the form of radiotherapy patients have been exposed to and duration of follow-up, disease recurrence in 20-50% of patients has been reported (Eastham *et al.*, 1997; Hanks *et al.*, 1997; D'Amico *et al.*, 2003; Alicikus *et al.*, 2010). Disease progression prior to treatment is evidently an important factor in determining the rates of disease recurrence (Hanks *et al.*, 1997; Alicikus *et al.*, 2010). In patients presenting with localised disease and PSA <10 $ng \cdot ml^{-1}$ disease-free survival was reported in around 80% of those treated with radical radiotherapy. Conversely, radiotherapy in patients with locally advanced disease and pre-treatment PSA >20 $ng \cdot ml^{-1}$ has been reported to be less effective and disease recurrence is evident in 40-50% of cases.

Side effects associated with radical radiotherapy have decreased from the considerable burden of the early techniques, however men undergoing EBRT and brachytherapy do still experience considerable treatment related morbidities. Erectile dysfunction, infertility and incontinence are reported by many patients after radiation treatment (Macmillan Cancer Support, 2010). Furthermore, patients can experience increased fatigue as a side effect of radiotherapy which has been associated with activation of the proinflammatory cytokine network during treatment (Bower *et al.*, 2009).

Radiotherapy in the treatment of advanced cancer is used to control secondary tumours and to relieve pain. In patients with specific areas of disease spread, EBRT delivered to secondary tumours can kill cancerous cells, shrinking the cancer and decreasing pain experienced at that site. In patients suffering pain from multiple sites of metastatic spread, palliative radiotherapy is offered. The injection of the radioisotope Strontium 89 allows radiation to circulate throughout the body providing pain relief and slowing the rate of metastatic growth (Cancer research UK, 2010a).

2.6.4 *Androgen deprivation therapy (ADT)*

ADT has developed from the early work of Huggins and Hodges (1941), who won the Nobel-prize for first describing the androgen dependence of prostate cancer cells. The primary objective of ADT is to deprive the prostate of androgens. In normal function 90-95% of testosterone is produced in the testes, with the remaining 5-10% synthesized by the adrenal glands. Stimulation of testosterone production at the testes comes via a hormone cascade initiated with the pulsatile release of luteinizing-hormone releasing hormone (LHRH) from the hypothalamus. LHRH binds to the anterior pituitary promoting luteinizing-hormone (LH) release into the bloodstream. Subsequently, LH acts to regulate the rate of testosterone synthesis from cholesterol which takes place in the Leydig cells of the testis.

Testosterone is converted to DHT by prostatic tissue through conversion by 5α-reductase isoforms, making DHT the predominant androgen within the prostate (in other tissues testosterone can be converted to oestradiol by aromatase). DHT binds androgen receptors resulting in changes in gene expression, and specifically, stimulation of the fibroblast growth factor gene in the human prostate cancer cell. Stimulation of this gene initiates cell development and cancer progression (Harris *et al.*, 2009; Pommerville and de Boer, 2010). Further promotion of the cancer cell growth also comes through the same metabolic pathway from follicle stimulating hormone (FSH). Produced by the anterior pituitary after the binding of LHRH, FSH stimulates

the Leydig cells to increase LH binding in addition to directly stimulating cancer cell growth through binding with receptors on the prostate.

Inhibition of this cascade of events at one or more stages is achieved using ADT. ADT aims to prevent hormone-sensitive tumour development, and preferably, decrease tumour size, with decreases in intracellular DHT of ≥80% needed to shrink the size of the tumour through cellular apoptosis (Kyprianou and Isaacs, 1987, as cited in Tammela, 2004). This process is not curative however, with many cancers eventually becoming hormone refractory (otherwise known as castration resistant), meaning continued evidence of cancer progression in-spite of castrate testosterone concentrations. It has been speculated that the progression to hormone-refractory prostate cancer could in-fact be reliant upon production of intratumoral androgens (Montgomery *et al.*, 2008). While systemic testosterone concentrations remain at castrate levels, activity of enzymes involved in steroidogenesis and androgen catabolism is maintained in the metastatic tumour allowing production of sufficient testosterone concentrations within the tumour to activate androgen-receptor target genes and maintain tumour cell survival.

Treatment with ADT can eliminate gonadal testosterone production using orchiectomy or LHRH-analogues, with serum total testosterone ≤50 $ng \cdot dl^{-1}$ (<1.74 $nmol \cdot l^{-1}$) the target for surgically or medically castrated patients (Harris *et al.*, 2009). Alternatively, administration of anti-androgens can block the action of existing testosterone (Tammela, 2004). Hormonal therapies available in the UK for medical castration are shown in Table 2.3.

Table 2.3, Hormonal therapies available in the UK.

LHRH Agonists	LHRH Antagonists	Anti-androgen
Leuprorelin	Abarelix	Bicalutamide
Goserelin	Cetrorelix	Flutamide
Buserelin	Degarelix	Cyproterone acetate
Triptorelin		Nilutamide

2.6.4.1 Orchiectomy

Orchiectomy is the surgical removal of the testicles which can be performed either as a complete removal or in a subcapsular fashion leaving the tunica albuginea (Mehta *et al.*, 2007). The irreversible nature of the operation makes orchiectomy an unattractive option to many men who choose to undergo medical castration instead. Surgical castration reduces testosterone to castrate levels within 12 hours resulting in a rapid decrease in tumour burden, glandular atrophy and involution of the prostate, with decreased cellular proliferation and increased cellular apoptosis also noted within 3 days (Harris *et al.*, 2009).

2.6.4.2 Luteinizing-hormone releasing hormone analogues

LHRH-analogues can be divided into LHRH-agonists and LHRH-antagonists. Agonists are the original chemical castration method first licensed in 1986 after evidence of their use as an effective therapeutic agent was first published in 1982 (Tolis *et al.*, 1982). Administered via injection or subcutaneous implant at 1-3 month intervals, agonists bind and stimulate LHRH-receptors resulting in chronic receptor stimulation desensitizing pituitary LH release through feedback inhibition of the hypothalamic-pituitary axis (Pommerville and de Boer, 2010). The result of this desensitization is decreased LH release, and thus a reduction in serum testosterone, with castrate levels often reached within 1-3 weeks of commencing treatment (Moreau *et al.,* 2006).

A side effect experienced by patients undergoing LHRH agonist treatment is 'tumour flare' in response to the increase in circulating testosterone found in the first 1-2 weeks of therapy, prior to receptor desensitization (Thompson, 2001). Tumour flare is often characterised by accelerated disease progression and, in patients with advanced cancer or bony metastases, can be of concern as severe pain and potential spinal cord compression can be experienced. The advent of the anti-androgen therapy (discussed in 2.6.4.3 Anti-androgens) has brought a solution to the issue however, with patients

commencing LHRH-agonist therapy simultaneously prescribed anti-androgens for the first 2 weeks (Pommerville and de Boer, 2010).

LHRH-antagonists act by blocking, but not stimulating, the LHRH-receptors resulting in an immediate fall in LH and testosterone and avoiding tumour flare (Pommerville and de Boer, 2010). Castrate levels of serum testosterone can be achieved within a single day of antagonist therapy which is similar to the decline in testosterone seen with orchiectomy (Tammela, 2004).

2.6.4.3 Anti-androgens

Anti-androgens prevent the action of androgens by binding to androgen receptors in the target tissue to prevent the binding of DHT and testosterone (Suzuki *et al.*, 2008). Unlike therapy with LHRH-analogues, anti-androgen therapy will maintain circulating androgens at normal or increased concentrations, decreasing the onset of side effects often seen with androgen depletion. Side effects with anti-androgens can still include hepatotoxicity and thromboembolic complications with long-term steroidal anti-androgen use, while gynecomastia is highly prevalent with both steroidal and non-steroidal therapy.

Anti-androgen use in the initial weeks of LHRH-agonist therapy can prevent tumour flare by preventing binding of circulating androgens. Anti-androgens are also increasingly being used as monotherapy, with Bicalutamide shown to provide similar survival benefits to castration therapy (Iversen *et al.*, 1998).

2.6.4.4 Maximum androgen blockade

First described in the early 1980's by Labrie *et al.* (1982), maximum androgen blockade, otherwise referred to as complete androgen blockade or combined androgen blockade, uses a combination of methods to both decrease testosterone production (orchiectomy or LHRH analogues) and prevent testosterone action (anti-androgen). The addition of an anti-androgen

inhibits both adrenal androgens and the small quantities produced by the testes during LHRH agonist treatment.

2.6.4.5 Neoadjuvant or adjuvant ADT

In addition to being used as a primary therapy, ADT is also often employed as part of a multi-modal approach, along with radiotherapy or prostatectomy, for treatment of localised or locally advanced prostate cancer. Hormonal therapy can be used either before (neoadjuvant hormonal therapy, NHT) or at the same time as (adjuvant hormonal therapy, AHT) the primary treatment option, with different benefits gained from the different treatment schedules.

NHT prior to radiotherapy is performed to decrease tumour volume, thus enabling optimal radiation doses to be delivered to the prostate, yet minimising the exposure to surrounding tissues. NHT prior to prostatectomy reduces margin positivity improving the coverage of the cancerous area by surgery and lowering the incidence of extracapsular disease (Lee *et al.*, 1999a).

Use of AHT is performed under the premise that while surgery or radiation will eradicate the primary tumour, the hormonal treatment will eliminate micro-metastases. The benefit of this greater systemic therapy is a reduction in both local disease recurrence and distant metastases (See, 2003).

In the Cochrane Review on NHT and AHT for localised and locally advanced prostate cancer the wide-ranging benefits of the different treatment options are described (Kumar *et al.*, 2009). Although NHT prior to prostatectomy was not associated with any overall survival advantage, there were reductions in positive surgical margins and pathological improvements including lymph node involvements, pathological staging and organ confined rates, showing evidence of reduced disease spread as a result of hormonal therapy. Considering NHT prior to radiotherapy, Kumar *et al.* (2009) found evidence of survival benefits for patients with Gleason score 2-6 cancer in one study (Pilepich *et al.*, 2001), although these results were contradicted by the

findings of others. Evidence of improvements in both clinical disease-free survival and biochemical disease-free survival were both consistently reported.

Three studies were included in the review for investigations into the benefits of AHT with prostatectomy (Messing *et al.*, 1999; Wirth *et al.*, 2004; McLoed *et al.*, 2005). Only Messing *et al.* (1999) reported improvements in overall survival with immediate receipt of AHT after prostatectomy compared to a control group who received hormones only after signs of disease progression were evident. All three studies reported improvements in disease-free and progression-free survival. Combined AHT and radiotherapy was reviewed in four studies (Zagars *et al.*, 1988; Bolla *et al.*, 2002; McLoed *et al.*, 2005; Pilepich *et al.*, 2005) with improvements in overall survival, disease-free survival and disease reoccurrence reported in all studies.

It should be noted that there are possible disadvantages to the use of ADT with radiation or surgery. In addition to increasing the toxicity of treatment and thus increasing the risk of side effects, there is also a rise in the cost of providing the therapy (Kumar *et al.*, 2009). Furthermore, the early use of ADT can lead to the possible emergence of resistant clones increasing the possibility of hormone refractory disease should the disease progress. Additionally, use of NHT can lead to a possible delay in definitive local treatment as a result of the pre-treatment with ADT (Lee *et al.*, 1999a).

2.6.4.6 Trends in ADT use

Since its inception, use of ADT has markedly increased making it now the mainstay treatment for men with advanced and metastatic prostate cancer. Nearly 50% of men diagnosed with prostate cancer will undergo ADT at some stage after diagnosis (Meng *et al.*, 2002). Originally performed using surgical castration and/or diethylstilbestrol, the advancement in depot formulations of LHRH-agonists have made these the primary form of ADT, replacing diethylstilbestrol and reducing the use of surgical castration (Perlmutter and Lepor, 2007). This is evident in the results reported by

Carson *et al.* (2010) for trends in treatment between 1991 and 1999 for patients with metastatic cancer on the Surveillance, Epidemiology and End Results (SEER) project. Use of surgical castration decreased from being used in 48.1% of patients in 1991 to only being accepted by 10% in 1999, while treatment with LHRH-agonists increased from 27.2% to 60.7% over the same time period.

Despite primarily being considered a form of therapy for patients with advanced disease there is also a trend for increased use of hormonal treatment using LHRH-agonists for patients with localised cancer. Further results from the SEER project support this data, showing that between 1991 and 1999 use of LHRH-agonists for treatment of men with localised disease increased from 11.5% of patients up to 41.1% of patients, while use of orchiectomy fell from 12% to 1.8% over the same time period (Shahinian *et al.*, 2005).

Data on the overall use of ADT in England and Wales is provided by Hussain *et al.* (2008). Between 1987 and 2004 use of LHRH analogues increased by 17,810 prescriptions per year (from 14.5 cases per 100,000 population per year to 1089.8 per 100,000), while between 1982 and 2004 anti-androgen therapy increased by 7,508 prescription per year (from 0 to 515.9 cases per 100,000). Orchiectomy shows a reverse of this trend however; between 1991 and 2004 surgical castration decreased from 28.07 cases per 100,000 to 2.45 cases per 100,000 in men aged 55-74 years, and fell from 106.58 per 100,000 to 15.17 per 100,000 over the same period in men aged ≥ 75 years.

2.6.4.7 ADT and prostate cancer mortality

Although it has been suggested that increasing use of ADT might be contributing to the reduction in prostate cancer mortality (Demers *et al.*, 2001; Damber, 2004) there is limited evidence to support a direct mortality benefit of ADT. Currently data is available describing improvements in disease-specific mortality when ADT is used as neoadjuvant or adjuvant treatment alongside surgery or radiotherapy, as was discussed in 2.6.4.5 Neoadjuvant

or adjuvant ADT. However, evidence from studies directly evaluating survival benefits from ADT by comparing ADT monotherapy against no treatment is sparse, primarily because as patients become symptomatic they start ADT to achieve palliation of symptoms. Hence, the studies evaluating the benefits of ADT have focussed on comparing immediate initiation of treatment against deferring treatment until symptomatic disease progression for overall survival advantage (Studer *et al.*, 2006; Keating *et al.*, 2008; DiBlasio *et al.*, 2009). Although results from these studies are still inconclusive on the best time to commence ADT, the recent review of the subject by Kunath *et al.* (2013) concluded that the best survival advantage was found in those with early initiation of ADT (Hazard ratio (HR) = 0.57; 95% CI, 0.37-0.90 for early compared to late ADT). Similarly, in the Cochrane review of early versus deferred treatment it was reported that improvements in survival were apparent at 1, 2, 5 and 10 years after diagnosis with early treatment, however, only the difference in survival between groups at 10 years achieved statistical significance (OR = 1.5; 95% CI, 1.04-2.16) (Wilt *et al.*, 2001).

Treatment with ADT has also been shown to be related to prolonging the time for cancer progression. In a comparison of men who received ADT (LHRH-agonists, anti-androgens or orchiectomy) or no ADT for 10 years after radical prostatectomy, Siddiqui *et al.* (2011) reported that ADT was protective against PSA failure and clinical recurrence. HR of 0.17, 0.29, 0.36 and 0.35 were reported for PSA failure, local recurrence, systemic progression and death from prostate cancer, respectively. In an additional analysis comparing disease progression between men receiving ADT in the form of LHRH-agonists against those who underwent orchiectomy, there was little difference between the groups except for lower PSA progression in men treated surgically.

2.7 Testosterone

Testosterone is a cholesterol-based steroid hormone which exerts numerous effects on the male body throughout the life cycle (Marieb and Hoehn, 2010).

Starting during foetal development, testosterone is responsible for the differentiation of the foetal genitourinary tract leading to the male foetus developing Leydig cells, which begin testosterone production and subsequently lead to the masculinisation of the external genitalia. After birth, testosterone is responsible for the development of secondary sexual characteristics and anabolic processes during puberty, including growth of body and facial hair, increased muscle mass, testicular growth and sperm production (Marieb and Hoehn, 2010). Once physical maturity is achieved testosterone still has important homeostatic functions including spermatogenesis, maintenance of muscle mass and aiding erectile function (Ganong, 2005).

As previously described (2.6.4 Androgen deprivation therapy), testosterone is predominantly produced in males by the testes. After production testosterone diffuses into the blood circulation where it can be found as bioavailable testosterone (accounts for 20-50% of serum testosterone) or biologically inactive testosterone (the remaining 50-80%) (Jones, 2013). Bioavailable testosterone is made up of testosterone bound to albumin (approximately 20-50% of total serum testosterone) and free testosterone (approximately 2-3% of total testosterone). Bioavailable testosterone is available for biological actions due to the weak binding with albumin or the unbound nature of free testosterone. Conversely, biologically inactive testosterone is not available for metabolism in tissues. This testosterone will be bound with SHBG, with the strength of the bind inhibiting its use in other biological actions (Jones, 2013).

Bioavailable testosterone can lead to changes in the behaviour of cells in different targets tissues with these actions often mediated through binding of androgen receptors (Kadi, 2008). Androgen receptors are ligand-responsive transcription regulators which, when bound to circulating androgens, will commence a signalling cascade resulting in the development and maintenance of the male phenotype and male reproductive function (Li and Al-Azzawi, 2009). After binding to testosterone or DHT the androgen receptor undergoes nuclear translocation, increased phosphorylation and interaction

with DNA, prior to the receptor binding to the androgen-response element within the target gene where the subsequent cellular actions will be initiated (Li and Al-Azzawi, 2009).

2.7.1 *Hypogonadism*

In men with low testosterone concentrations, hypogonadism can be diagnosed. Male hypogonadism is defined by The European Association of Urology as a clinical syndrome caused by androgen deficiency which may adversely affect multiple organ functions and quality of life (Dohle *et al.*, 2012). Hypogonadism can be classified as primary or secondary depending upon the clinical defects leading to its development.

Primary hypogonadism, otherwise known as hypergonadotropic hypogonadism, is caused by testicular failure resulting in low serum testosterone and high LH and FSH concentrations. Primary hypogonadism can develop from testicular injury, tumour or infection; genetic defects affecting testicular development (e.g. Klinefelter syndrome); alcohol abuse; or after treatment with chemotherapy or radiotherapy (Dandona and Rosenberg, 2010).

Secondary hypogonadism is a result of a defect at one or more levels of the hypothalamic-pituitary-gonadal axis. Secondary hypogonadism is association with low serum testosterone, in addition to normal or low FSH and LH concentrations. Hence, secondary hypogonadism is also known as hypogonadotropic hypogonadism. This form of hypogonadism can be caused by hypothalamic or pituitary disorders, hyperprolactinaemeia or Kallmann syndrome. Furthermore, certain medications and illnesses can also lead to development of secondary hypogonadism (Dandona and Rosenberg, 2010).

Hypogonadism is prevalent among middle and older aged men, although reported prevalence rates vary between studies. Approximately 39% of men in the Hypogonadism in Males (HIM) study were reported as hypogonadal (Mulligan *et al.*, 2006) but the rate of hypogonadism in the Massachusetts

Male Aging Study (MMAS) was found to be between 6% and 12%, with several men meeting criteria for hypogonadism on only 1 of the 2 assessment dates (Araujo *et al.*, 2004). The variation in findings could be the result of differences in the age groups of men in each study or use of different criteria to define hypogonadism. While the HIM study enrolled men aged ≥45 years and defined hypogonadism as total testosterone <300 $ng \cdot dl^{-1}$ or current androgen treatment, in the MMAS participants were aged 40-69 years and hypogonadism was diagnosed after the presence of hypogonadal symptoms and total testosterone <200 $ng \cdot dl^{-1}$.

Incidence of hypogonadism increases with age. In the Baltimore Longitudinal Study on aging hypogonadism (defined as total testosterone <325 $ng \cdot dl^{-1}$) was diagnosed in 12%, 19%, 28% and 49% of men in their 50's, 60's, 70's and 80's respectively (Harman *et al.*, 2001). Likewise, in the HIM study hypogonadism was reported in 34% of men aged 45-54 years and 50% of men aged ≥85 years, a patient's risk of hypogonadism increased by 17% for every 10 year increase in age (Mulligan *et al.*, 2006).

Differences between studies in defining the criteria for hypogonadism are wide-spread throughout the literature and can be often explained by whether a study is investigating biochemical hypogonadism or clinical hypogonadism. While biochemical hypogonadism can be reported in men with low testosterone concentrations, The Endocrine Society suggests clinical hypogonadism should only be diagnosed in patients who consistently show signs and symptoms of hypogonadism (discussed below) in addition to low testosterone levels (Bhasin *et al.*, 2010).

Further confusing matters in the reporting of hypogonadism is the concentration of testosterone considered low or inadequate. Although The Endocrine Society suggests 300 $ng \cdot dl^{-1}$ (10.4 $nmol \cdot l^{-1}$) is the lower limit of normal measures of total testosterone (Bhasin *et al.*, 2010), The American Association of Clinical Endocrinologists recommends 200 $ng \cdot dl^{-1}$ (6.9 $nmol \cdot l^{-1}$; Petak *et al.*, 2002). Conversely, the consensus statement of the International Society of Andrology, the International Society for the Study of Ageing Males, European Association of Urology, European Academy of Andrology and the

American Society of Andrology recommends that patients with serum total testosterone <230 $ng \cdot dl^{-1}$ (8 $nmol \cdot l^{-1}$) will usually benefit from testosterone treatment (Wang *et al.*, 2008).

Importantly, all authorities suggest that measures of testosterone should be performed on more than one occasion and should be standardised for time of day. Diurnal variations in testosterone concentrations have led to the recommendation that testosterone is measured in the morning, when it is considered highest and most reproducible (Brambilla *et al.*, 2009; Dohle *et al.*, 2012).

2.8 Sequelae of ADT

Treatment with ADT is designed to induce hypogonadotropic hypogonadal testosterone concentrations. As reported above (2.6.4 Androgen deprivation therapy), serum total testosterone levels ≤50 $ng \cdot dl^{-1}$ (<1.74 $nmol \cdot l^{-1}$) are the target for surgically or medically castrated patients (Harris *et al.*, 2009). Considering this rapid development of hypogonadal testosterone concentrations it is of no surprise that men on ADT experience many of the symptoms of hypogonadism. Reduced libido, erectile dysfunction, gynaecomastia, hot flushes, fatigue, changes in mood and decreased bone mineral content are all primary clinical symptoms of hypogonadism (Dohle *et al.*, 2012) and have all been side effects associated with ADT; which can lead to a reduction in patients' overall quality of life (Casey *et al.*, 2012).

2.8.1 *Sexual health*

Sexual health side effects are one of the most significant occurrences in men on ADT, with loss of sexual function rated as one of the biggest factors in determining decreased quality of life in this patient group (Walker and Robinson, 2010). Decreased sexual health is characterised by decreased libido and erectile dysfunction (Thompson *et al.*, 2003; Stempkowski, 2006; Mohile *et al.*, 2009). Androgens play a critical role in the development and

maintenance of erections in penile tissue, and thus ADT greatly inhibits this action, with these side effects usually presenting within 12 months of starting treatment (Mohile *et al.*, 2009). In a study of 395 men on ADT, DiBlasio *et al.* (2008) reported 57 patients (14.4%) presented with erectile dysfunction, of which 70% had new onset erectile dysfunction after starting hormone therapy. Moreover, only 2.5% of patients reported normal libido after the initiation of ADT. These results are supported by Basaria *et al.* (2002), who reported that men on ADT had lower scores on the Watts sexual function questionnaire, had a lower frequency of spontaneous early morning erections and had more difficulty in gaining and maintaining erections than control groups of men with prostate cancer not on ADT and healthy age-matched controls. Furthermore, Basaria *et al.* (2002) also reported that the duration of ADT was inversely related to sexual desire showing a deleterious effect of prolonged hormonal therapy.

2.8.2 *Vasomotor flushing*

Vasomotor flushing, often described as hot flushes, is one of the most widely experienced side effects of ADT. Characterised by the temporary onset of body warmth, reddening skin and profuse sweating, often in tandem with feelings of intense nausea, vasomotor flushing is described by some as the most bothersome side effect of hormonal therapy (Holzbeierlain *et al.*, 2003). Large variation can exist between individuals in the severity and frequency of these symptoms. While some men experience only occasional episodes lasting a few seconds, others will regularly experience hot flushes of up to an hour. Onset of symptoms can come as a result of changes in body position, ingestion of warm liquids, or changes in ambient temperature (Baum and Torti, 2007).

Prevalence rates of vasomotor flushing have been shown to be high in men treated with ADT. Studies have shown evidence of hot flushes to some degree in 60-80% of men within 3 months of initiating treatment (Schow *et al.*, 1998; Ulloa *et al.*, 2009). Although symptoms can abate over time, Karling *et*

al. (1994) reported that after 8 years of treatment more than 40% of men still experienced hot flushes. Furthermore, these researchers showed that in men discontinuing ADT hot flushes can persist, with 48% of men still experiencing symptoms 5 years after treatment cessation.

The underlying mechanisms behind vasomotor flushing are not fully understood. It is postulated that a disturbance of the hormonal feedback to the hypothalamus could be responsible. Decreased testosterone feedback is thought to diminish endogenous peptide secretion leading to an increase in catecholamine release. It is proposed that excess catecholamines stimulate the thermal neurons in the hypothalamus resulting in an unbalancing of the thermoregulatory capacity and subsequent sweating and vasodilator responses (Holzbeierlain *et al.*, 2003; Frisk, 2010).

2.8.3 *Gynaecomastia*

Gynaecomastia can be a physically painful and embarrassing side effect of ADT characterised by proliferation of the glandular component of the male breast as an effect of the increase in the estrogen-to-androgen ratio (McLeod and Iverson, 2000; Thompson *et al.*, 2003; Di Lorenzo *et al.*, 2005; Suzuki *et al.*, 2008). Generally starting within 12 months of androgen withdrawal, the effects are initially reversible; however, hyalinisation and fibrosis occurring after a year of gynaecomastia are irreversible (McLeod and Iverson, 2000). Reviewing the prevalence of gynaecomastia in men on ADT, McLeod and Iverson (2000) suggested that the form of ADT used can influence the rate of gynaecomastia onset. Gynaecomastia was reported in 7.6% of patients after orchiectomy, 28.6% of patients on LHRH-agonists, 43.7% of patients on non-steroidal anti-androgens (bicalutamide or flutamide), and 17% of patients on combined androgen blockade therapy (flutamide with orchiectomy or flutamide with LHRH-agonists).

2.8.4 *Anaemia*

ADT has been linked with anaemia in men with advanced prostate cancer (Nalesnik *et al.*, 2004). Strum *et al.* (1997) reported large declines in haemoglobin 1 month after initiating complete hormonal blockade, with the nadir occurring after approximately 6 months of treatment. At nadir, haemoglobin concentrations had fallen >10% from baseline in 90% of patients, and >25% in 13% of patients. Anaemia has been linked to the effects of castration, with testosterone required for enhancement of erythropoietin formation in the kidneys and the action of erythropoiesis in bone marrow. Furthermore, in patients who suffer bony metastases the replacement of bone marrow with cancer cells will contribute to the degree of anaemia suffered (Nalesnik *et al.*, 2004).

2.8.5 *Bone health*

The occurrence of bone loss with ADT has received increased attention since the link was initially described by Stěpán *et al.* (1989). Testosterone is influential in regulation of bone resorption, and thus under hypogonadal conditions increased resorption occurs without concomitant increases in bone formation leading to a net loss in bone mineral density (Eastham, 2007). In a small prospective study, Morote *et al.* (2003) found that osteoporosis was detected in 41.5% of patients on ADT, compared with 28.1% of men with prostate cancer but ADT naïve. Of the patients on ADT, similar rates of osteoporosis were noted in men treated with LHRH-agonists alone (41.7%) to those in receipt of LHRH-agonists and anti-androgens for maximal androgen blockade (41.4%). Furthermore, Morote and colleagues provided evidence that osteoporosis risk increased with duration on treatment. Osteoporosis was reported in 36.4% of patients treated for 12-36 months, increasing to 42.1% and 50% of patients on ADT for 36-60 months and >60 months, respectively. These results are supported by the work of others who have also reported ADT resulting in bone loss (Kiratli *et al.*, 2001; Preston *et al.*, 2002; Greenspan *et al.*, 2005; Panju *et al.*, 2009).

2.8.6 *Fatigue*

Increased fatigue is a well-established side effect of treatment with ADT (Herr and O'Sullivan, 2000; Stone *et al.*, 2000; Cherrier *et al.*, 2009). Stone *et al.* (2000) reported increased fatigue after 3 months of hormonal therapy in as many as 66% of patients, although this was higher than the prevalence of fatigue reported by Storey *et al.* (2012) who found 43% of men treated with ADT for at least 6 months described cancer-related fatigue. Although the precise cause of fatigue in this patient group remains unclear, the effects of anaemia, pain, inadequate nutrition, depression, anxiety, endocrine abnormalities and lack of sleep have all been considered potential contributors (Stempkowski, 2006). In the study by Storey *et al.* (2012) depression and pain were reported to be the only factors independently associated with patient fatigue (OR = 4.7; 95% CI, 1.6-14.0 and OR = 3.1; 95% CI, 1.0-8.9, respectively). Increased fatigue is one of a spectrum of psychological traits thought to be affected through ADT. Fatigue, together with depression, anxiety, malaise and memory difficulties, form what has been collectively termed the '*androgen deprivation syndrome*' (Shahinian *et al.*, 2006).

2.8.7 *Cardiovascular risk*

Just as ADT has been associated with many of the symptomatic side effects found with hypogonadism, there is evidence that men treated with ADT might also be at increased risk of cardiovascular events similar to that shown with hypogonadism because of the reduction in testosterone concentrations. Khaw *et al.* (2007) reported that endogenous testosterone concentrations were inversely related to mortality from all-causes, cardiovascular disease or cancer. Khaw *et al.* suggested that a 6 $nmol \cdot l^{-1}$ (173 $ng \cdot dl^{-1}$) increase in total testosterone was associated with a 14% decrease in risk of all-cause mortality (OR = 0.86; 95% CI, 0.79-0.94) and a 17% decrease in risk of cardiovascular mortality (OR = 0.83; 95% CI, 0.74-0.94). Moreover, Hak *et al.* (2002) reported that higher testosterone concentrations could be protective

against cardiovascular morbidity. Men with total testosterone in the highest tertile (>12.6 to ≤36.8 $nmol \cdot l^{-1}$) had a relative risk ratio of only 0.4 (95% CI, 0.1-1.0) for development of severe aortic atherosclerosis in comparison with men with testosterone in the lowest tertile (0 to ≤9.8 $nmol \cdot l^{-1}$).

There is evidence of similar findings in men on ADT with the incidence of cardiovascular morbidity and mortality reported to be increased within 6 months of treatment initiation. D'Amico *et al.* (2007) pooled data from 3 randomized trials (including a total of 1,372 men) to investigate the timing of fatal myocardial infarctions in men on ADT (LHRH-agonist alone or in combination with an anti-androgen). In men older than 65 years of age, 6 months of hormone therapy increased the incidence of fatal myocardial infarctions compared to age-matched men not treated using ADT. These findings are supported by others who also report increased cardiovascular events in androgen deprived men. Keating *et al.* (2010) calculated that in men treated with LHRH-agonists the risk of suffering coronary heart disease, myocardial infarction, sudden cardiac death or stroke increased by 19%, 28%, 35% and 21% respectively in comparison with a reference group of men not on ADT. Furthermore, Saigal *et al.* (2007) reported that men treated with ADT for at least 12 months had a 20% higher risk of serious cardiovascular morbidity in comparison with patients who were not treated with ADT.

It must be noted that others have reported no association between ADT and incidence of cardiovascular mortality (Efstathiou *et al.*, 2008; Roach *et al.*, 2008; Efstathiou *et al.*, 2009). Reviewing the association between treatment with ADT and cardiovascular mortality, Nguyen *et al.* (2011) reported no increase in risk in men on ADT. Incidence of cardiovascular mortality in men on ADT (n = 2200) was 11% (95% CI, 8.3%-14.5%) while among controls not currently receiving ADT (n = 1941) it was 11.2% (95% CI, 8.3%-15%). These data resulted in a risk ratio for cardiovascular mortality with ADT use of 0.93 (95% CI, 0.79-1.10) which did not achieve statistical significance ($P = 0.41$). However, more recently this data has been called into question by editorials highlighting methodological flaws which cast doubt over the conclusions (Blankfield, 2012; Froehner and Wirth, 2012). It has been shown that around

50% of the men included in the review only received relatively short-term ADT (<3 years) and so they cannot be considered indicative of the effects experienced by men on long-term treatment. Furthermore, ~25% of men in the control group of one of the largest studies included in the review were treated with ADT within 3 years of study enrolment, providing a clear contamination of results. Finally, it has also been reported that studies included in the review of Nguyen and colleagues did not stratify their findings for the presence of pre-existing cardiovascular disease, and hence it cannot be ascertained whether cardiovascular end-points reported are truly the effects of ADT.

In-spite of contradictory findings for cardiovascular mortality in men treated with ADT there is growing evidence suggesting increased prevalence of cardiovascular risk factors in men treated in this manner. Cardiovascular risk factors similar to those reported in other hypogonadal groups have been shown in men on ADT with the reduction in testosterone concentration highly implicated in there development. These findings might be of little surprise considering studies calculating cardiovascular risk using the Framingham risk score have reported an inverse association between total testosterone concentrations and 10-year cardiovascular risk (Miner *et al.*, 2011; Chock *et al.*, 2012).

2.8.7.1 Body composition

Negative changes in body mass and body composition have been reported in men treated with ADT (Smith *et al.*, 2002; Nishiyama *et al.*, 2005; Smith *et al.*, 2008a; van Londen *et al.*, 2008). In the review of body composition changes in men on ADT by Haseen *et al.* (2010) they included 16 studies with data on 573 patients. Increases in body mass were reported in all studies, mean percentage increase of 2.1% (range 0.6-5.4%) over treatment durations from 1 to 12 months. Seven studies used dual energy x-ray absorptiometry (DEXA) to investigate changes in fat mass with increases reported in all studies with

a mean gain of 7.7%. Conversely, lean body mass was investigated in 6 studies with a mean loss of 2.8%.

Rapid changes in body composition have been shown to occur on commencement on ADT. After 1 month of treatment using LHRH-agonists or orchiectomy losses in lean body mass and gains in total body mass and body fat mass were reported by Smith *et al.* (2001). These trends continued at 3 months with further losses in lean body mass reported. The longitudinal study by van Londen *et al.* (2008) further confirmed the rapid changes in body composition after the initiation of ADT. Data collected 6 month after initiation of ADT showed gains in body fat mass, and percentage body fat, as well as losses in percentage lean body mass. Importantly, van Londen *et al.* (2008) also showed that duration of hormone therapy was correlated with the extent of adverse changes in body fat and lean body mass. After 24 months of hormone therapy, increases in body fat mass (2.2 kg) and percentage body fat (2.1%), and decreases in lean body mass (1.8 kg) and percentage lean body mass (2.3%) were reported in comparison with baseline data.

These alterations can lead to sarcopenic obesity, characterised by excess body fat in combination with reduced muscle mass or strength (Zamboni *et al.*, 2008). In addition to exacerbating feelings of fatigue, decreasing physical function, contributing to emotional distress and further decreasing quality of life, the onset of obesity can increase the risk of cardiovascular events and mortality. Increased abdominal adiposity and BMI have been linked with increased risk of type II diabetes mellitus, ischaemic stroke, coronary heart disease and development of other cancers (Chan *et al.*, 1994; Bianchini *et al.*, 2002; Suk *et al.*, 2003; Canoy *et al.*, 2007). Moreover, excess gains in fat mass and central adiposity leading to an increase in BMI has been associated with increases in all-cause and cardiovascular mortality (Stevens *et al.*, 1998; Taylor *et al.*, 2010).

The decrease in serum testosterone concentrations experienced with ADT is potentially responsible for changes in lean body mass. Supplementation of supra-physiological doses of testosterone have been shown to increase muscle mass without exercise in healthy adults (Bhasin *et al.*, 1996).

Similarly, testosterone replacement in hypogonadal men using physiological doses led to significant increases in muscle size and fat free mass (Bhasin *et al.*, 1997). It has been elucidated that these effects are a result of testosterone acting on the hypothalamus to stimulate growth hormone release leading to increased protein synthesis and decreased protein degradation (Mudali and Dobs, 2004).

Testosterone concentrations have also been directly linked to changes in fat mass with low concentrations of total, free and bioavailable testosterone all associated with obesity. Testosterone stimulates lipolysis while concomitantly inhibiting lipid uptake, lipoprotein lipase activity and differentiation of adipocyte precursors cells (De Pergola, 2000). Accordingly, in men with low testosterone concentrations, the resultant non-lipolytic environment leads to accumulation of fat mass, as is evident through increases in visceral and subcutaneous fat found with the age-associated testosterone loss and in hypogonadal males (Katznelson *et al.*, 1998; Vermeulen, 2000). It is noted that androgen deficiency has been most prominently associated with increases in visceral fat (Bhasin, 2003). In an investigation of the effect of testosterone concentrations on body fat distribution, Tsai *et al.* (2000) reported that lower total testosterone was an independent predictor of intra-abdominal fat area but not significantly associated with subcutaneous fat area. These authors suggested that the inhibition of lipoprotein lipase activity by endogenous testosterone was greater in visceral fat than in subcutaneous fat resulting in greater accumulation of visceral fat under hypogonadal conditions. The increase in fat mass signals the start of a vicious cycle, as increased cytokine concentrations found with increased adiposity act as catabolic agents resulting in exacerbation of sarcopenia initiated through the decreased anabolism as previously described (Mudali and Dobs, 2004).

2.8.7.2 Metabolic changes

ADT has been linked to adverse metabolic alterations promoting increased cardiovascular risk (Shahani *et al.*, 2008; Saylor and Smith, 2009; Choong

and Basaria, 2010). Decreased insulin sensitivity has been widely reported in men on ADT (Dockery *et al.*, 2003a; Basaria *et al.*, 2006; Smith *et al.*, 2006; Smith *et al.*, 2008a). Negative changes in insulin sensitivity index and fasting plasma insulin concentrations have been noted within 3 months of commencing treatment (Smith *et al.*, 2008a), with the continued decline in insulin sensitivity directly related to the duration of ADT (Basaria *et al.*, 2006, as cited in Choong and Basaria, 2010).

Secreted from pancreatic β-cells in response to increases in circulating glucose and amino acids, insulin regulates glucose concentrations by reducing gluconeogenesis and glycogenolysis in the liver and increasing glucose uptake in skeletal muscle and adipose tissue (Sesti, 2006). Inadequate responses of these target tissues to circulating insulin are the primary impairment in the development of insulin resistance. Decreasing insulin sensitivity is characterised by depressed insulin-stimulated inhibition of hepatic glucose production, decreased stimulation of glucose uptake into skeletal muscle and an impaired effect of lipolysis inhibition in adipose tissue (Schenk *et al.*, 2008).

Insulin resistance is a major precursor in the development of impaired glucose tolerance and type II diabetes mellitus, as well as featuring highly in other medical conditions such as obesity, dyslipidemia and hypertension. Moreover, insulin resistance has been linked to the development of atherosclerosis and coronary artery disease (Howard *et al.*, 1996; Rewers *et al.*, 2004). Insulin resistance at the level of the fat cell leads to a decrease in free fatty acid (FFA) uptake and/or an increase in the release of FFA from the fat cell. The response of the liver to the increased lipid synthesis is rapid incorporation of lipids into very low-density lipoprotein cholesterol (VLDL-C) which is subsequently secreted back into the blood stream. Increased circulating VLDL-C promotes atherosclerotic plaque formation both directly, by entering the vessel wall, and indirectly, by reducing high-density lipoprotein cholesterol (HDL-C) concentrations (Ginsberg, 2000).

Changes in glucose concentrations have been reported with ADT, but are slower to arise than the alterations in insulin described above. After 3 months

of treatment, multiple studies have reported no changes in fasting glucose (Dockery *et al.*, 2003a; Smith *et al.*, 2006; Smith *et al.,* 2008a), however, in the cross sectional study by Basaria *et al.* (2006) in which men treated with ADT for a minimum of 12 months were compared against men with prostate cancer not on ADT and healthy age-matched controls, ADT was associated with increased fasting glucose even after adjustment for age and BMI. These findings are suggestive of hyperglycaemia being a longer-term adaptation to hormone therapy. The authors speculated that the development of hyperinsulinaemia with the rapid onset of insulin resistance at the initiation of ADT temporarily maintains glucose concentrations, but the eventual β-cell failure with prolonged hormone therapy leads to hyperglycaemia.

Increased lipoprotein concentrations have also been widely reported in men on hormone therapy (Smith *et al.*, 2002; Braga-Basaria *et al.*, 2006b; Smith *et al.*, 2008b). Similar to the time-scale for the deterioration in insulin sensitivity, increases in low-density lipoprotein cholesterol (LDL-C) and HDL-C have been reported within 3 months of commencing ADT (Smith *et al.*, 2008b). After 48 weeks of LHRH-agonist therapy serum levels of total cholesterol, HDL-C and LDL-C were shown to be increased by 9.0%, 11.3% and 7.3%, respectively (Smith *et al.*, 2002).

It should be noted that the relevance of the changes in lipid profile to cardiovascular risk is still somewhat unclear. It is accepted that elevated total cholesterol with reduced HDL-C is associated with increased cardiovascular risk (D'Agostino *et al.*, 2008), however, elevated HDL-C has been shown to have anti-atherogenic qualities (Gordon *et al.*, 1989). Furthermore, there is the question of LDL-C particle size, with some evidence suggesting the quantity of small, dense LDL-C particles is of greater relevance than total LDL-C content to increased cardiovascular risk (Rizzo and Berneis, 2006). With current data from men on ADT showing significant increases in HDL-C and no data on LDL-C particle size, the atherosclerotic nature of the described lipid profiles could be questionable. What might be of importance in interpreting these data however, is the ratio of total cholesterol/HDL-C which has been shown to be directly related to increased total risk of

mortality in older men (Chyou and Eaker, 2000). In a small cross-sectional study, total cholesterol/HDL-C ratios of 4.7, 4.4 and 3.8 were reported for men on ADT, men with prostate cancer not on ADT and age-matched healthy controls, respectively (Braga-Basaria *et al.*, 2006b). Furthermore, analysis of data presented by Smith *et al.* (2002) shows a marginally increased total cholesterol/HDL-C ratio after 48 weeks of hormone therapy. The non-significant nature of these figures means this link can only be speculated upon at this time with further work clearly warranted in this area.

The metabolic alterations reported above could all be associated with the decrease in male sex hormones found with ADT. Studies in healthy males and hypogonadal populations have reported total testosterone to be inversely associated with insulin, glucose, triglycerides, total cholesterol and LDL-C, but positively associated with HDL-C concentrations (Oppenheim *et al.*, 1989; Haffner *et al.*, 1993; Simon *et al.*, 1997). Moreover, improvements in fasting glucose, insulin sensitivity, total cholesterol and LDL-C have been shown in hypogonadal males after testosterone replacement therapy (Zgliczynski *et al.*, 1996; Boyanov *et al.*, 2003; Naharci *et al.*, 2007).

The increase in body fat mass with reduced testosterone concentration could be the precursor to these metabolic alterations. Body fat accumulation is a common side effect of a reduction in male sex hormones (reviewed in 2.8.7.1 Body composition) and it is widely acknowledged that increased adiposity can induce numerous adaptations to the metabolic profile (Bays *et al.*, 2008; de Ferranti and Mozaffarian, 2008). Excess body fat is associated with an increase in the release of FFA and triglycerides into the circulation leading to lipid accumulation in tissues of the liver, heart, skeletal muscle and pancreatic β-cells. Dysfunction of substrate storage in these targets tissues can bring about the development of insulin resistance as previously described. This can subsequently result in an attenuation of lipolysis of chylomicrons and triglycerides further increasing circulating FFA concentrations and thus adding to the dysfunctional cycle.

Increases in fat mass as a result of reduced testosterone concentrations might not be the single mediating factor resulting in metabolic alterations

however, as testosterone could also have a direct effect on metabolic function. Acute sex steroid withdrawal in young men with idiopathic hypogonadotropic hypogonadism has been shown to reduce insulin sensitivity with no changes in body composition (Yialamis *et al.*, 2007). Similarly, testosterone replacement therapy can lead to reductions in total cholesterol and LDL-C in hypogonadal men with no effect on BMI (Zgliczynski *et al.*, 1996). Although the specific mechanisms underlying such an association remain unproven, there is evidence to suggest that androgen withdrawal might cause abnormalities in the hypothalamic-pituitary-gonadal axis at the level of Leydig cell function resulting in changes in insulin sensitivity (Traish *et al.*, 2009a). Furthermore, studies in mice have shown early evidence that testosterone deficiency is associated with changes in expression of GLUT-4 and hexokinase 2, which could also influence insulin concentrations (McLaren *et al.*, 2012).

2.8.7.3 Diabetes

Men treated with ADT are at increased risk of developing diabetes (Keating *et al.*, 2006; Lage *et al.*, 2007; Alibhai *et al.*, 2009; Keating *et al.*, 2010). In the observational study by Keating *et al.* (2006) including 73,196 men with local or regional prostate cancer, the risk of developing diabetes was increased by 44% and 34% for men treated with LHRH agonists or orchiectomy, respectively, in comparison with a control group of men with prostate cancer on no treatment. Similarly, in a more recent article by the same research group, diabetes prevalence was assessed in a cohort of 37,443 men recruited from the Veterans Healthcare Administration (Keating *et al.*, 2010). After a median of 2.6 years, diabetes risk was found to be higher in men on hormone therapy compared with men with prostate cancer not on ADT. Risk was increased by 28% with LHRH agonists, 16% with orchiectomy, 17% with combined androgen blockade and 2% with oral anti-androgen therapy.

The alterations in body composition and metabolic profile in patients on hormone therapy are considered highly influential in the development of overt diabetes. Characterised by peripheral insulin resistance, impaired regulation of hepatic glucose and loss of β-cell function, overt diabetes is associated with loss of glycaemic control leading to macro- and microvascular complications (Mahler and Adler, 1999). In the presence of insulin resistance, compensatory insulin release from pancreatic β-cells prevents the development of hyperglycaemia, however under the influence of adipokines, increased FFA and inflammatory cytokines often found with excess adipositiy, β-cell dysfunction and apoptosis can develop. In the face of insulin resistance at the liver resulting in increased glucose production and decreased glucose utilisation, the loss of β-cell insulin secretion leads to the development of a hypoinsulinaemic state and increased hyperglycaemia (Virally *et al.,* 2007; Jones *et al.,* 2010). Further compounding these events can be increased glucagon production by pancreatic α-cells. In healthy individuals glucagon acts to stimulate glycogenolysis and gluconeogenesis in the liver during periods of low blood glucose, and as a result glucose consumption inhibits glucagon release. However, loss of α-cell responsiveness with diabetes leads to an impairment of glucose inhibition of glucagon release, and thus further increases hepatic glucose production contributing to the hyperglycaemic state (Jones *et al.,* 2010).

Patients with diabetes are at increased risk of suffering a multitude of complications that can include accelerated atheroma development, renal failure, retinopathy, neuropathy, susceptibility to infections, cataracts, diabetic ketoacidosis and diabetic coma (Underwood, 2007). Furthermore, individuals with diabetes are at increased cardiovascular risk with evidence of higher incidence of cardiovascular morbidity and mortality reported in diabetic patients (Casiglia *et al.,* 2000).

In males, low testosterone concentrations have been associated with an increased incidence of type II diabetes mellitus (Ding *et al.,* 2006). Body composition changes will contribute to this increased risk with excessive adiposity promoting insulin resistance, lipotoxicity and negative adipokine

responses (Day and Bailey, 2011). It is of note however that in the Third National Health and Nutrition survey low testosterone was associated with an increased incidence of diabetes independently of adiposity (Selvin *et al.,* 2007). This evidence adds further credence to the data reviewed above (2.8.7.2 Metabolic changes) describing a direct link between testosterone withdrawal and the development of an insulin resistant state.

2.8.7.4 Arterial stiffness

The ability of the artery to expand and recoil in response to the cardiac cycle is related to the elastic properties of the artery. This is determined to a large extent by the elastin and collagen content within the arterial walls (Laurent *et al.,* 2005; Zieman *et al.,* 2005; Anderson, 2006). These elastic qualities allow the artery to stretch to accommodate blood flow during systole, with the subsequent recoil during diastole promoting forward flow (Arnett *et al.,* 1994). When arterial compliance is reduced the cushioning of blood ejected during systole decreases and thus blood flow to the periphery occurs more rapidly under increased pressure, characterised by raised systolic pressure and decreased diastolic pressure (Noon, 2009).

Evidence has shown arterial stiffness can be increased by a multitude of factors including ageing (McEniery *et al.,* 2005), diet (Kesse-Guyot *et al.,* 2010), physical inactivity (Vaitkevicius *et al.,* 1993) smoking (Kim *et al.,* 2005), type I and type II diabetes (Wilkinson *et al.,* 2000; Schram *et al.,* 2004), end stage renal disease (Pannier *et al.,* 2007) and hypercholesterolaemia (Wilkinson *et al.,* 2002). The implications of these effects can be severe, with increased risk of coronary artery disease (Gatzka *et al.,* 1998; Mattace-Raso *et al.,* 2006), hypertension (Franklin, 2005), myocardial infarction (Hirai *et al.,* 1989) and total cardiovascular risk (Haluska *et al.,* 2010; Mitchell *et al.,* 2010) all reported as a result of increased arterial stiffness. Moreover, arterial stiffness has been positively associated with cardiovascular and all-cause mortality (Blacher *et al.,* 1998; Laurent *et al.,* 2001; Shoji *et al.,* 2001). An increase in carotid-femoral pulse wave velocity (PWV) (a measure of transit

time directly related to arterial stiffness) of 1 standard deviation relates to a 48% increase in the risk of a first major cardiovascular event (Mitchell *et al.,* 2010). Furthermore, an increase of 1 $m \cdot s^{-1}$ in PWV has been shown to produce risk ratios of 1.69 (95% CI, 1.35-2.11) for cardiovascular events and 2.41 (95% CI, 1.81-3.2) for all-cause mortality (Khoshdel *et al.,* 2007).

Structural changes are evident in the pathophysiology of arterial stiffness. Progressive stiffening of the arteries found with normal ageing is the result of degeneration of elastic fibres within the arterial wall with concomitant increases in collagenous material (Laurent *et al.,* 2005; Anderson, 2006). Inflammation can also lead to dysregulation of the elastin-collagen balance promoting abnormal collagen deposition and diminished elastin content. The production of catabolic matrix metalloproteases (MMP) by inflammatory stimuli such as macrophages, oxidant radical formation, and vascular adhesion molecules is key in this process. MMP exert collagenolytic and elastinolytic effects resulting in this degradation of the extracellular matrix (Zieman *et al.,* 2005).

The work by Dockery *et al.* (2000) was the first to report increased arterial stiffness in men on ADT. In a small cross-sectional study comparing androgen deprived men against healthy age-matched controls they reported higher central PWV in men on ADT. The same group confirmed these results in a further cross-sectional study in which systemic arterial compliance was also reported to be increased in men on ADT (Dockery *et al.,* 2002). Stiffening of the arteries has been shown to be evident within as little as 3 months of commencing hormone therapy (Smith *et al.,* 2001; Dockery *et al.,* 2003a).

Further work by Dockery and colleagues highlights the impact of testosterone on arterial stiffness (Dockery *et al.*, 2009). Investigating the effects of different forms of ADT on arterial compliance they randomised 43 men to receive LHRH-agonist or anti-androgen therapy for 24 weeks. Although central and peripheral PWV were increased after 12 weeks with both forms of ADT, after 24 weeks differences between groups were evident. Arterial stiffness continued to increase between weeks 12-24 in men treated with

LHRH agonists, but in men on anti-androgens there was an improvement in arterial compliance resulting in no statistical difference in PWV between baseline and 24 weeks for patients in the anti-androgen group. Although it is unclear from these findings whether or not differences between groups for testosterone concentrations directly influenced arterial compliance, it is apparent that no other outcome measures demonstrated statistically significant changes at week 24.

This possible finding of a link between arterial stiffness and testosterone concentration would be in agreement with data previously presented demonstrating reduced arterial compliance in men with low testosterone (Dockery *et al.,* 2003b; Hougaku *et al.,* 2006; Yaron *et al.,* 2009). Dockery *et al.* (2003b) and Hougaku *et al.* (2006) both reported the findings of observational studies in groups of elderly men showing negative correlation between testosterone concentrations and arterial stiffness. These data are further supported by the work of Yaron *et al.* (2009) who demonstrated increased PWV in hypogonadal males in comparison with age-matched eugonadal controls.

2.8.7.5 Endothelial function

Considering the evidence reviewed above describing the development of a pro-atherogenic environment, it could be hypothesised that treatment with ADT would lead to the development of endothelial dysfunction. Endothelial dysfunction incorporates an array of disruptions to normal endothelial function. However, this term is most commonly defined as an abnormality in the regulation of the vessel lumen (Grover-Páez and Zavalza-Gómez, 2009). This state is characterised by impaired vascular reactivity, in addition to being proinflammatory and prothrombotic. Endothelial dysfunction is now widely regarded as an important initial event in the development of atherosclerosis which can precede plaque and fatty streak formation (Celermajer, 1997), and as such, endothelial function is considered by some to be a barometer of cardiovascular risk (Vita and Keaney, 2002).

The vascular endothelium is a single layer of cells located between the lumen and the vascular smooth muscle. Responding to changes in hemodynamic forces or blood-borne stimuli, the normal vascular endothelium regulates arterial tone, platelet and leukocyte interactions, coagulation, fibrinolysis and vascular growth through the synthesis and release of a plethora of vasoactive and thromboregulatory molecules and growth factors such as nitric oxide (NO), endothelins, prostacyclin and endothelial cell growth factors (Celermajer, 1997). Of these substances, one of the most important for maintenance of vascular homeostasis is NO. NO is a gaseous lipophilic free radical generated in the endothelium by endothelial NO synthase (Chatterjee and Catravas, 2008) and is the primary endothelium-derived relaxing factor responsible for maintaining vascular smooth muscle tone and opposing the actions of endothelial-derived contracting factors.

In the presence of risk factors including hypercholesterolaemia, hypertension, diabetes and smoking, decreased expression and loss of function of endothelial NO synthase causes a decline in NO synthesis, while elevated reactive oxygen species formation leads to accelerated NO degradation as superoxide anions inactivate available NO (Cai and Harrison, 2000; Hirata *et al.*, 2010). With the development of this pro-atherogenic state NO suppression of endothelial-derived contracting factors is lost leading to increased expression of vasoconstrictors such as endothelin-1 and angiotensin-II. Consequently, increases in vascular inflammation and oxidative stress further promote NO degradation, while increased expression of adhesion molecules on the surface of endothelial cells lead to binding of leukocytes and early atheroma formation (Grover-Páez and Zavalza-Gómez, 2009).

These descriptions of mechanisms involved in endothelial dysfunction are supported by evidence from studies in different populations where endothelial function has been shown to be impaired. Patients presenting with insulin resistance (Shinozaki *et al.,* 2001), hypercholesterolaemia (Perrault *et al.,* 2000; Vladimirova-Kitova *et al.*, 2009) and obesity (Al Suwiadi *et al.*, 2001) have all been shown to suffer endothelial impairment further strengthening

the hypothesis of endothelial dysfunction in men on ADT in whom, as previously described, the risk of developing these cardiovascular risk factors is increased. Moreover, evidence of reduced arterial compliance in men on ADT also strengthens this hypothesis as arterial stiffness has been shown to correlate with endothelial function (Nigam *et al.,* 2003; Wang, 2007). Endothelial-derived NO has a role in modulation of arterial compliance (Kinlay *et al.*, 2001), with long-term NO deficiency thought to lead to increased arterial stiffness as a result of vascular remodelling (Wang, 2007).

2.8.7.5.1 *Measurement of endothelial function*

Although there are several methods by which endothelial function can be both directly or indirectly measured (Al-Qaisi *et al.,* 2008), use of high resolution ultrasound to detect flow-mediated dilatation (FMD) in the brachial artery has become increasingly popular. First described by Celermajer *et al.* (1992), FMD allows a non-invasive assessment of endothelial-dependent vasodilatation. The inflation and release of an occluding cuff results in changes in arterial diameter in response to the subsequent reactive hyperaemia. Increased blood flow into the previously occluded vascular bed distal to the cuff position induces an increase in shear stress at the level of the endothelial cells lining the artery. This stimulates the release of endothelial-derived relaxing factors that diffuse into the smooth muscle cells of the arterial wall leading to a signalling cascade which results in a lowering of calcium concentrations and vasorelaxation (Thijssen *et al.*, 2011).

The relaxing factors responsible for arterial dilatation will differ depending upon the position of the occluding cuff. FMD measured using a cuff positioned in the traditional location distal to the position of arterial imaging will be primarily NO-dependent (Joannides *et al.,* 1995; Mullen *et al.*, 2001). However, use of a proximal cuff results in arterial dilatation only partially mediated by NO and more dependent upon other vasoactive substances (Doshi *et al.,* 2001). Although these data clearly suggest that different markers are being measured using a proximal or distal cuff position, FMD

measured both ways has been linked to the risk of cardiovascular events (Green *et al.,* 2011). Reanalysing data originally presented by Inaba *et al.* (2010), Green and colleagues reported that with 1% increase in FMD with a distal cuff the relative risk for future cardiovascular events was 0.91 (95% CI, 0.87-0.96), but with a 1% increase in FMD with a proximal cuff relative risk was 0.83 (95% CI, 0.78-0.88). Thus, for a 1% decrease in FMD measured with a distal cuff risk of future cardiovascular events increases by 9%, while a 1% decrease in FMD using a proximal cuff increases the risk by 17%. Proximal cuff assessments remain less common as a result of greater difficulty in achieving data of sufficient quality as cuff inflation and deflation can collapse or distort the distal arterial segment being imaged (Charakida *et al.*, 2010).

FMD provides a measure of cardiovascular health exceeding that given by traditional risk factors for cardiovascular disease. As previously described, there is evidence that cardiovascular risk factors such as insulin resistance and increase blood lipid profile can influence endothelial function (Shinozaki *et al.,* 2001; Vladimirova-Kitova *et al.*, 2009), however, it has also been shown that changes in such traditional risk factors (plasma lipids, blood pressure, blood glucose, waist-to-hip ratio, BMI) do not fully account for alterations in FMD (Green *et al.*, 2003). Although no studies have conclusively described other factors influencing this measure of endothelial dilatation, there is evidence to suggest that changes in endothelial progenitor cells (Liao *et al.*, 2010) and dietary antioxidant content (Franzini *et al.*, 2012) could also be important.

2.8.7.5.2 *Endothelial function and hypogonadism*

Evidence from trials investigating the effects of hypogonadism on endothelial function further supports the hypothesis of endothelial impairment with ADT. Clinical studies in humans have provided evidence of dysfunctional endothelia in other hypogonadal populations with these data strongly supported by evidence from pre-clinical studies using animal models.

Investigations by Yilmaz *et al.* (2011) and Akishita *et al.* (2007) reported on the effects of testosterone concentrations on endothelial function in patients with chronic kidney disease and men with coronary risk factors, respectively. Both studies described a positive association between total and free testosterone concentrations and endothelial function, with Akishita *et al.* reporting that endothelial-dependent arterial dilatation in men in the highest quartile of free testosterone was 170% of that found in men in the lowest quartile. These results are supported by the baseline data of Bernini *et al.* (2006) who describes reduced vascular reactivity in hypogonadal men in comparison with a eugonadal control group. Notably however, Bernini *et al.* (2006) also reported that 6 months of testosterone therapy in the hypogonadal group further reduced endothelial function. This finding is in agreement with data presented in other studies describing reduced arterial reactivity in hypogonadal men after treatment with testosterone replacement therapy (Zitzmann *et al.,* 2002; Sader *et al.,* 2003). Taken together the data above suggests that while low physiological testosterone concentrations can impair endothelial function, use of exogenous testosterone supplementation can have further deleterious effects.

Mechanisms underlying endothelial impairment with low testosterone concentrations are as yet incompletely understood with different opinions available in the current literature. While there is evidence supporting a direct effect of reduced testosterone concentrations on the endothelial cell (Foresta *et al.,* 2006; Lu *et al.,* 2007; Milardi *et al.*, 2012), others consider the increase in metabolic risk factors with hypogonadism to be responsible for endothelial damage (Traish *et al.,* 2009b).

Considering the wealth of evidence supporting a hypothesis of endothelial dysfunction in men treated with ADT it is interesting that this has only been investigated by a single study that, rather counter-intuitively, reported enhanced endothelial function in men on ADT (Herman *et al.,* 1997). Herman and colleagues compared FMD results of 10 men with prostate cancer treated with ADT (orchiectomy or maximal anti-androgen therapy for ≥6 months), to a control group of men in remission after non-prostate

malignancies, and a group of healthy age-matched controls. FMD for men on ADT was 6.2%, while for men with non-prostate malignancies and healthy controls FMD was measured as 2% and 2.7%, respectively. No differences between groups were reported for arterial responses to glyceryl trinitrate (GTN).

The findings of Herman *et al.* (1997) could be considered to contradict the evidence reviewed above describing increased development of cardiovascular risk factors in men treated with ADT and the evidence of endothelial dysfunction in other hypogonadal populations. Accumulation of body fat, changes in blood lipid profile and increases in insulin resistance have all been associated with endothelial dysfunction in other patient groups (Grover-Páez and Zavalza-Gómez, 2009), and as such it seems intuitive that the development of these cardiovascular risk factors in men on ADT would be indicative of a reduction in endothelial function. Furthermore, the evidence of decreased arterial compliance in men on ADT could be considered to be symptomatic of endothelial dysfunction in consideration of the inverse relationship between arterial stiffness and endothelial function previously described (Wang, 2007). Hence, it must be questioned whether Herman and colleagues have reported data with a type I error. It is possible that insufficient sample size, recruitment of a sample unrealistic of men usually found in this patient group or errors in data collection during FMD assessments (Black *et al.*, 2008) could have all influenced the results described. Further research is clearly warranted to investigate whether the findings of Herman *et al.* (1997) can be supported or challenged.

2.9 Study 1. The effects of treatment of prostate cancer with androgen deprivation therapy on endothelial function

Study research question, aims and hypotheses

In consideration of the evidence reviewed above the following research question was developed along with study aims and hypotheses.

Research question

Is there a difference in endothelial function between men with prostate cancer treated with ADT and age-matched controls who have no history of prostate cancer or androgen treatment?

Study aims

To investigate if there is a difference in endothelial function between men treated with ADT for prostate cancer and age-matched controls who have no history of prostate cancer or androgen treatment.

Null hypothesis

There is no difference in endothelial function between men treated with ADT for prostate cancer and age-matched controls who have no history of prostate cancer or androgen treatment.

Experimental hypothesis

Endothelial function is different in men treated with ADT for prostate cancer compared with age-matched controls who have no history of prostate cancer or androgen treatment.

3.0 METHODS: Study 1

3.1 Study design

The study used a cross sectional design with two groups; men on ADT for prostate cancer and community dwelling, physically inactive, age-matched controls who had no history of prostate cancer or androgen treatment. Data for these independent groups were collected and compared for between group differences.

3.2 Ethics

Institutional ethics approval was granted for this study by the Research Ethics Committee of the Faculty of Health and Wellbeing, Sheffield Hallam University (appendix 1). This approval allowed the recruitment of a group of men to act as a control group. Ethics approval for recruitment of men with prostate cancer was granted by the NHS Yorkshire and Humber Research Ethics Committee as part of a larger lifestyle intervention study (appendix 2). All procedures conformed to the Declaration of Helsinki.

3.3 Sample size calculation

This study used a case-control design with 20 men recruited to both the ADT and control groups. This number of participants was calculated based upon a previous investigation of the effects of testosterone concentrations on FMD (Akishita *et al.*, 2007) assuming a similar absolute difference between groups of 2.3 ± 2.4% for arterial dilatation. Sample size was determined using the nQuery statistical software (nQuery Advisor 6.01, nQuery Statistical Solution, USA) using 80% power at an alpha level of 0.05.

3.4 Participant recruitment

Data for men with prostate cancer treated with ADT was taken from the baseline assessments of men recruited for a lifestyle intervention study. The 20 men included in this cross-sectional evaluation were the first twenty recruited for the lifestyle intervention study fitting all inclusion and exclusion criteria for this study. A consort diagram for recruitment of men for the intervention study is presented in the methods for study 2 in this thesis (Figure 7.2).

Controls were recruited from within the local community. Organisations considered likely to have men aged 60 years or older were approached either in person, over the phone or by email and asked to display a recruitment poster to their members (copy of poster provide in appendix 3). In total 34 organisations were approached, of which 17 agreed to display the information. Men interested in participating were asked to contact the research team, at which time they were screened for inclusion/exclusion criteria (see 3.5 Inclusion and exclusion criteria). Those considered eligible were sent further information about the study (copy of participant information sheet in appendix 4) and given a minimum of 5 days to consider whether they chose to participate. Men still interested in taking part after the cooling off-period were invited to meet a study researcher at which time they completed a medical questionnaire and provided informed consent (appendix 5 and 6, respectively). These men were also asked to quantify the volume and intensity of physical activity they completed in their leisure time using the Godin Leisure Score Index (Godin LSI; Godin and Shephard, 1985; appendix 7). Participants were asked to report the number of times they performed more than 15 minutes of strenuous, moderate and mild exercise in an average week. The total leisure activity score was subsequently calculated using the equation:

Total leisure activity score = (9 x number of strenuous sessions) + (5 x number of moderate sessions) + (3 x number of mild sessions)

A consort diagram for the recruitment of controls is provided in Figure 3.1. In total 47% of men requesting further information about the study maintained their interest and were willing to participate. The twenty men included in the study constituted 32% of those initially showing interest in participating.

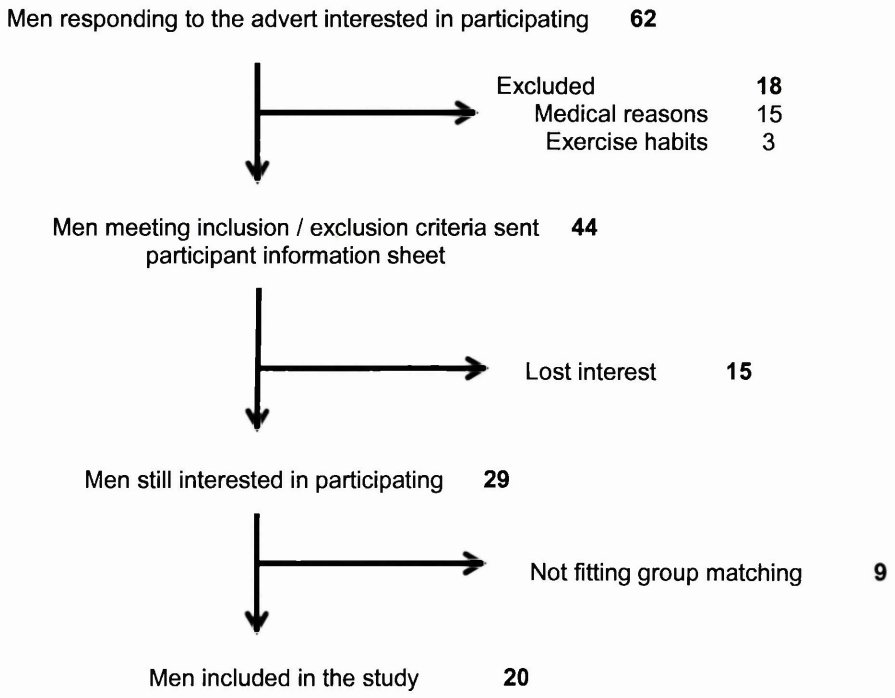


Figure 3.1. Consort diagram for the recruitment of controls

3.5 Inclusion and exclusion criteria

Criteria for prostate cancer patients being included in the study:

- Histologically confirmed advanced prostate cancer, at least stage T3 N0 M0
- Been in receipt of ADT for a minimum of 6 months and due to receive for at least the next 6 months
- Current stable disease; defined as PSA <5 $ng.ml^{-1}$ or three consecutive decreasing PSA readings

- Able to provide signed informed consent

Criteria for prostate cancer patients being excluded from the study:

- Unable or unwilling to complete assessments
- Current participation in regular physical activity meeting the minimum guidelines for older adults described by the American College of Sports Medicine (2009), defined as moderate-intensity physical activity for 30 minutes at least 3 times per week, or vigorous physical activity for 20 minutes at least 3 times per week for the last 6 months
- Painful bony metastases
- Less than 12 months since completion of radiotherapy
- Having ever received chemotherapy
- Less than 2 months post surgical treatment
- Unstable angina, uncontrolled hypertension, recent myocardial infarction or pacemaker
- History of sudden onset shortness of breath, blurred vision or fainting spells
- Any physical or mental impairment that would limit the ability to understand and complete the study and make consent unethical

Criteria for men being included in the control group:

- Aged 60 years or older
- Able to provide signed informed consent

Criteria for men being excluded from the control group:

- Current participation in regular physical activity meeting the minimum guidelines for older adults described by the American College of Sports Medicine (2009), defined as moderate-intensity physical activity for 30 minutes at least 3 times per week, or vigorous physical activity for 20 minutes at least 3 times per week for the last 6 months
- Current infection or clinically significant illness in the 2 weeks prior to enrolment
- A previous diagnosis of prostate cancer
- Taking any medication that would affect androgen concentrations
- Any medical conditions that would affect androgen concentrations
- Having ever received chemotherapy
- Unstable angina, uncontrolled hypertension, recent myocardial infarction or pacemaker
- History of sudden-onset shortness of breath, blurred vision or fainting spells
- Any physical or mental impairment that would limit the ability to understand and complete the study and make consent unethical

3.6 Outcome measures

Assessments were completed in the exercise physiology laboratories of the Centre for Sport and Exercise Science, Sheffield Hallam University. Participants were asked to attend the assessment session in the fasted state, having refrained from the consumption of food or beverages (except water) for at least 8 hours, and having avoided tobacco products for at least 12 hours. These sessions were undertaken in the morning to minimise the impact of fasting on participants daily routine. Participants were asked to

refrain from taking part in any strenuous physical activity for at least 12 hours prior to attending the assessment. Where possible, participants were asked to refrain from taking any vasoactive medications for at least 12 hours prior to attending the assessment session.

3.6.1 *Assessment of vascular function*

Vascular function assessments were conducted in accordance with the guidelines described by Thijssen *et al.* (2011). All assessments took place in a quiet, dimly-lit and temperature-controlled room with the participant resting supine. Prior to commencing ultrasound assessments participants rested quietly for a minimum of 15 minutes with their right arm extended and supported in a position approximately 80° from the torso where it stayed for the duration of vascular function assessments. Resting blood pressure and heart rate were assessed in the contra-lateral arm with an automated sphygmomanometer (Dinamap, Dash 2500, GE Healthcare, Waukesha, WI, USA). Ultrasound assessments of the right brachial artery were performed in the distal third of the upper arm using a 7-mHz linear array transducer attached to a high-frequency ultrasound system (Terason T3000, Teratech Corporation, Burlington, MA, USA). Once a suitable longitudinal B-mode view of the artery had been located the probe was held stable and image optimisation was performed by manipulation of depth and gain settings to allow clear visualisation of the near and far arterial walls and the lumen. Doppler assessment of blood velocity was performed throughout all assessments. The angle of insonation was set at ≤60° to the artery walls with greater angles of insonation previously shown to overestimate blood velocity (Harris *et al.*, 2010). Where necessary 'heel-toe' adjustments of the probe and manipulation of the doppler steering angle were performed to achieve an insonation of 60°.

3.6.1.1 Endothelial-dependent dilatation

Endothelial-dependent dilatation was assessed using the FMD technique as originally described by Celermajer *et al.* (1992). A pneumatic rapid inflation/deflation cuff (Hokanson E20 rapid cuff inflator with Hokanson AG101 cuff inflator air source, D.E. Hokanson Inc, Bellevue, WA, USA) was placed distal to the olecranon process on the right arm prior to commencing the ultrasound assessment (set-up for FMD scan shown in Figure 3.2). The cuff was subsequently inflated to a pressure 50 mm Hg above systolic blood pressure, with occlusion maintained for 5 minutes. Baseline recordings of vessel diameter and blood velocity were performed for 1 minute prior to cuff inflation. Recordings were restarted 30 seconds prior to cuff release and continued for a further 3 minutes thereafter. Continuous recording throughout the duration of the 3-minute, post-deflation period was considered sufficient to ensure peak vessel diameter had been recorded (Black *et al.*, 2008).

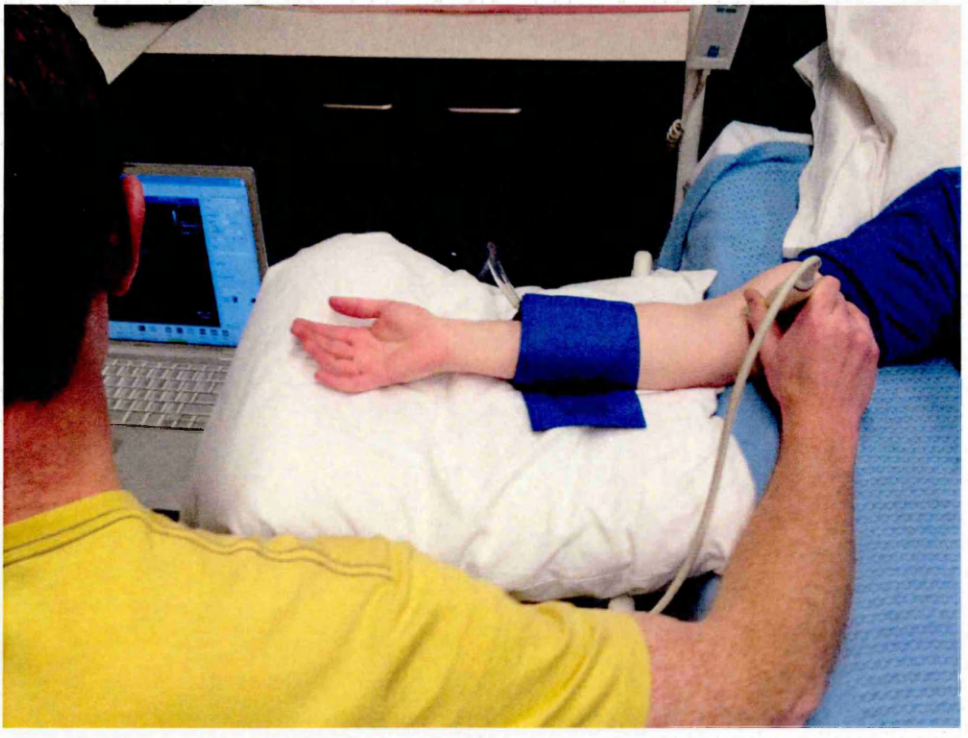


Figure 3.2. Position of ultrasound probe and rapid inflation cuff for assessments of endothelial-dependent dilatation of the brachial artery using a distal cuff placement.

3.6.1.2 Endothelial-independent dilatation

Endothelial-independent arterial dilatation was assessed as the arterial response to a single dose (0.4 mg) of GTN. Participants rested quietly for 15 minutes after completion of endothelial-dependent assessments to ensure recovery of baseline arterial diameter prior to commencing image acquisition. GTN was administered sublingually by an exercise physiologist external to the research team. Arterial imaging was performed for 1 minute prior to GTN administration and continued for a further 6 minutes thereafter with recording maintained throughout. Continual recording for 6 minutes post-GTN administration was considered sufficient to detect maximal arterial dilatation, which Corretti *et al.* (2002) suggested should occur within 3-4 minutes. Furthermore, 6 minutes exceeded the time for GTN-mediated dilatation during pilot testing in a group of 6 men of similar age to those to be involved in the study (age = 64 ± 6 years, time to peak dilatation 253 ± 36 seconds). An example of the pattern of arterial dilatation post-GTN is displayed in Figure 3.3. Participants' blood pressure was measured in the contra-lateral arm using an automated sphygmomanometer (Dinamap, Dash 2500, GE Healthcare, Waukesha, WI, USA) prior to, and then every 2 minutes after, GTN administration. Blood pressure measures were repeated until blood pressure returned to baseline values.

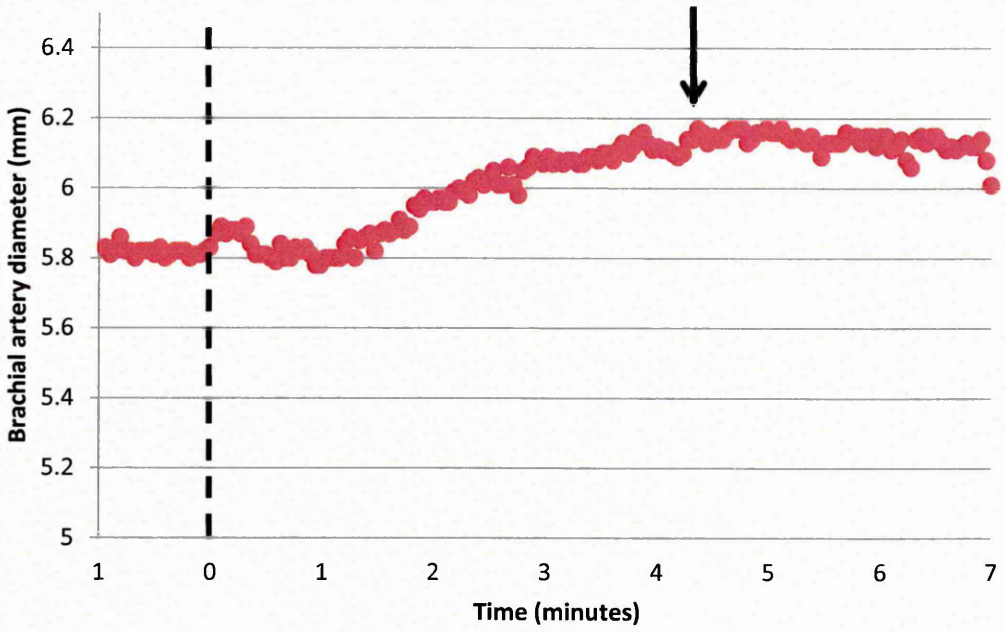


Figure 3.3. Arterial diameter during assessment of endothelial-independent dilatation. GTN delivered at 0 minutes (represented by dashed line). Arterial diameter before dashed line represents diameter during baseline minute. Peak arterial diameter represented by arrow (occurs 4 minutes 21 seconds after GTN delivery).

3.6.1.3 Ultrasound analysis

Throughout vascular assessments the ultrasound on-screen display was recorded at a rate of 15 frames per second using Camtasia Studio software (v5.0.0, TechSmith Corporation, Okemos, MI, USA). Recorded files were subsequently converted to an audio video interleave (avi) format prior to analysis using the Brachial Analyser for Research software package (v5.6.19, Medical Imaging Applications, Iowa, USA). A screenshot of arterial analysis in this manner is provided in Figure 3.4. This software allows vessel diameter measurement by using automated electronic callipers to track movement of the vessel walls within a selected region of interest for each frame of the video file. Changes in blood velocity throughout FMD scans were assessed using the same software. A region of interest was drawn around the blood-flow waveform in which the peak of the blood velocity waveform was

automatically detected. Calibration of the analyser software was performed prior to both arterial diameter and blood flow analyses using the in-built calibration tools.

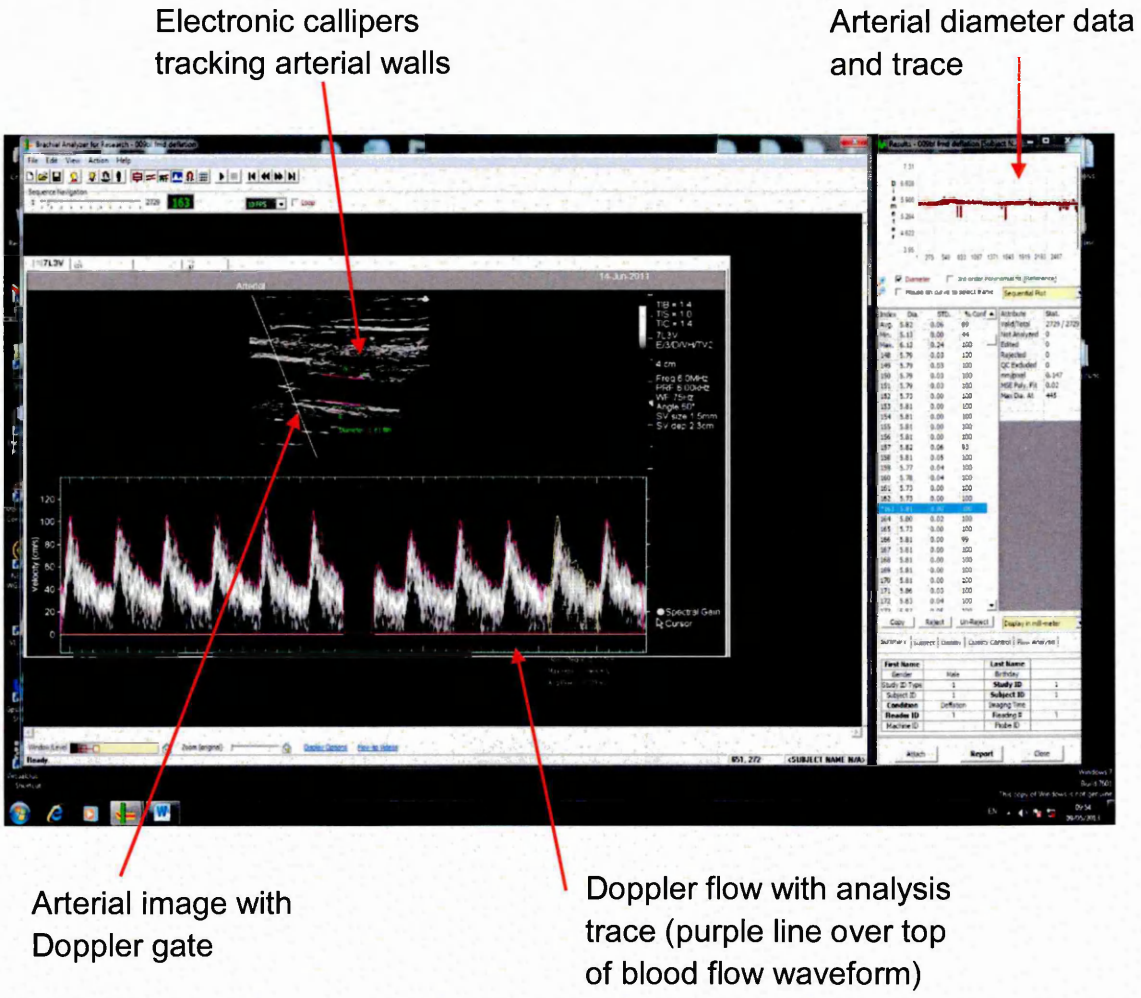


Figure 3.4. Screen shot of analysis of arterial scan using Brachial Analyser for Research. Annotated to highlight key aspects of analysis.

Arterial shear rate (SR) was calculated for endothelial-dependent scans to quantify the stimulus eliciting changes in vessel diameter following cuff release. Arterial shear was calculated using the equation:

$$SR = 4*V/D$$

where *V* is Doppler velocity and *D* is vessel diameter (Parker *et al.*, 2009). SR area under the curve (SR AUC) was calculated as the sum of arterial shear from cuff release through to peak vessel diameter.

Raw data for arterial diameter were smoothed prior to calculation of the magnitude of arterial dilatation. This smoothing technique calculates the median diameter of 50 consecutive frames (3.3 seconds of data) with each 50 frame bracket sharing a 20% overlap with the preceding bracket. As there is no accepted consensus on the best method by which to smooth arterial diameter data, this method was selected being amongst the most widely used in current research (Black *et al.*, 2008; Tinken *et al.*, 2008). An example of smoothed and unsmoothed data is provided in Figure 3.5.

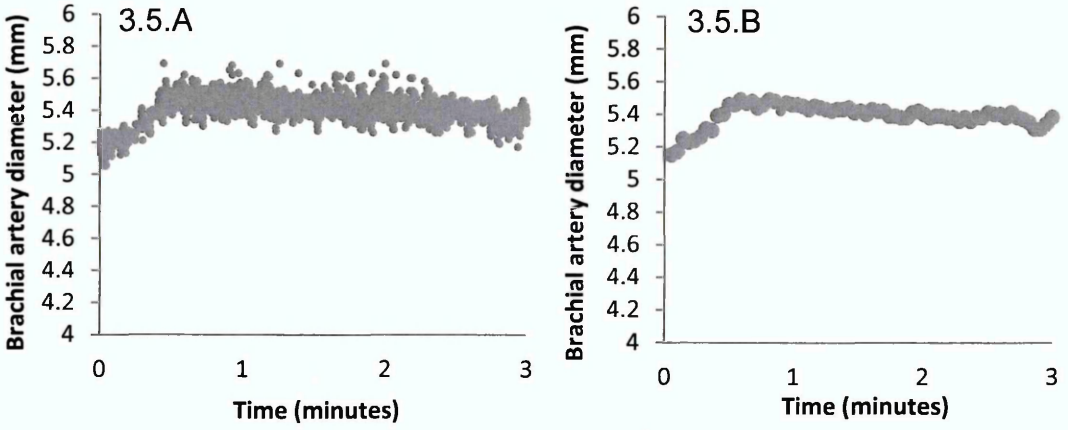


Figure 3.5. Post-analysis smoothing of FMD scan. 3.5.A unsmoothed data, 3.5.B smoothed data.

Baseline arterial diameter was calculated as the mean of data acquired through the minute prior to cuff inflation or GTN administration. Peak diameter was considered the highest data point following cuff release or GTN administration. Absolute change in arterial diameter was calculated as:

Absolute arterial dilatation = Peak diameter - Baseline diameter

Additionally, the relative change in arterial diameter was calculated as a percentage increase from baseline using the equation:

$$\text{Percentage arterial dilatation} = [(\text{Peak diameter} - \text{Baseline diameter}) / \text{Baseline diameter}] * 100$$

Allometrically-scaled data were also presented for all arterial dilatation assessments in accordance with the guidelines presented by Atkinson *et al.* (2013) to account for differences between groups in baseline arterial diameter. Data for baseline and peak arterial diameter were transformed using a natural log ($\log_n$) prior to the difference in arterial diameter between time points being calculated using the equation:

$$\text{Allometrically-scaled arterial diameter change} = \log_n \text{peak diameter} - \log_n \text{baseline diameter}$$

The difference between groups for the $\log_n$ transformed diameter change was subsequently analysed with the $\log_n$ of baseline diameter included as a covariate. Data presented in the results show the antilog of mean values of $\log_n$ transformed data, which has subsequently been converted to a percentage using the equation:

$$\text{Percentage allometrically scaled dilatation} = (\text{Antilog of scaled diameter difference} - 1) * 100$$

Exponents for scaling of baseline data were calculated using linear regression, with $\log_n$ peak diameter included as the dependent variable, while group and $\log_n$ baseline diameter were included as independent variables. A variable of group*$\log_n$ baseline diameter was also created and included as an independent variable in an initial regression analysis to examine whether there was an interaction between group and $\log_n$ baseline diameter which would necessitate the need for separate exponents for the different groups. To show the spread in data 95% CI of the exponent were also reported. The between group analysis for allometrically scaled arterial diameter change was re-run including body fat mass, cardiovascular disease drugs (antihypertensive medications, aspirin, nitrates and statins) and $\log_n$ baseline

diameter as covariants to estimate the additional confounding effects of fat mass and concomitant medications on arterial diameter change.

To avoid researcher bias, all video files were re-coded prior to analysis to ensure the researcher was blinded to the participant's group.

3.6.2 *Anthropometry*

Participant's stature (Holtain Stadiometer, Holtain Ltd, Pembrokeshire, UK) and body mass (Weylux Beam Balance Scales, Weylux, UK) were measured using standard laboratory techniques. BMI was subsequently calculated using the equation:

$$BMI = \text{body mass} / \text{stature}^2$$

Body composition was assessed via bioelectrical impedance using the Inbody 720 (Biospace, Seoul, South Korea). The Inbody 720 performs multi-frequency bioelectrical impedance at 1, 5, 50, 250, 500 and 1000 KHz to calculate segmental muscle and fat mass through measurement of intracellular and extracellular water. The Inbody 720 uses eight contact electrodes positioned on the palm and thumb of both hands and anterior and posterior aspects on the sole of both feet. Skin surfaces to make contact with the electrodes were cleaned with disinfectant wipes prior to test commencement as per the manufacturer instructions. During the test participants were asked to stand as still as possible with arms fully extended and abducted laterally to approximately 20 degrees.

3.6.3 *Blood markers*

Capillary and venous bloods were taken from all participants. Capillary blood was collected from a finger-prick performed on the middle finger of the left hand for immediate assessment of haemoglobin concentrations. Blood samples (10 µL) were collected on microcuvettes (B-Hemoglobin microcuvettes, HemoCue, Ängelholm, Sweden) prior to analysis using a

Haemoglobin Photometer (HemoCue, Ängelholm, Sweden). A check of photometer calibration was performed at each assessment using a known standard.

Venous blood (20 ml) was drawn from the antecubital vein using standard phlebotomy techniques. Serum and plasma were separated from whole blood samples prior to freezing at - 80°C (Sanyo VIP-series Ultra Low Temperature Freezer, Sanyo Biomedical, Wood Dale, IL, USA). Batch analysis of samples was carried out in the Department of Clinical Chemistry at the Royal Hallamshire Hospital, Sheffield, UK. Samples were analysed for male sex hormones (testosterone and SHBG) and lipid profile (total cholesterol, HDL-C, LDL-C and triglycerides) using the Cobas 8000 Modular Analyser (Roche Diagnostics, Basel, Switzerland).

3.7 Statistical analyses

Data are presented as mean ± standard deviation (SD) unless stated. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) for Windows (v 19.0.0, IBM inc, NY, USA). Variation in frequency distribution for demographic data was examined using Pearson's Chi squared test. Outcome data was analysed for standard descriptive statistics, with normality of distribution assessed using the Shapiro-Wilk test. Differences between groups for outcome measures were assessed using independent *t*-tests or the non-parametric equivalent (Mann Whitney-U) with all tests performed two-sided. Statistical significance was set as $P < 0.05$. Additionally, outcome measures were assessed for effect sizes using Cohens-*d*, with thresholds set at 0.2 for a small effect, 0.5 for a medium effect and 0.8 for a large effect (Cohen, 1992). Effect sizes were calculated using the equation:

$$\text{Effect size} = (\text{mean}^{\text{group1}} - \text{mean}^{\text{group2}}) / \text{SD}^{\text{pooled}}$$

Where $mean^{group1}$ is the mean of group 1, $mean^{group2}$ is the mean of group 2, and SD^{pooled} is the pooled standard deviation. Pooled standard deviation was calculated using the equation:

$$SD^{pooled} = \sqrt{[((n^{group1}-1) * (SD^{group1})^2 + (n^{group2}-1) * (SD^{group2})^2) / n^{group1} + n^{group2}]}$$

Where n^{group1} is the number of participants in group 1, n^{group2} is the number of participants in group 2, SD^{group1} is the standard deviation of group 1 and SD^{group2} is the standard deviation of group 2.

Relationships between variables were examined using tests of correlation. Duration of ADT and testosterone concentrations were correlated against measures of body composition, blood pressure, baseline arterial diameter and arterial dilatation. Additionally, variables associated with magnitude of arterial dilatation were assessed with duration of ADT, PSA, body composition and blood pressure included in the analysis. In cases where both variables were normally distributed, Pearsons bivariate correlation coefficient was used; however, if one or more variables did not achieve normal distribution, Spearmans rank correlation was employed. Correlation coefficients <0.35 were considered weak, 0.36-0.67 moderate, 0.68-0.89 high and ≥0.9 very high (Taylor, 1990). To examine covariates influencing the association between variables partial correlations were performed with covariates included as controlled variables.

3.8 Reliability of measures

Reliability of measurement techniques was assessed to allow quantification of the technological and biological variability inherent in all physiological techniques. Ten men (n = 6 ADT patients and n = 4 controls) aged 69 ± 6 years completed a second assessment within 7 days of the initial assessment session, with the testing procedures standardised between the two trials. To limit the circadian variation in outcome measures, participants were asked to attend this additional session at the same time of day as they had completed the initial assessment. Furthermore, participants were asked

to prepare for the assessments in the same manner in accordance with the guidelines for vascular function assessment (Thijssen *et al.*, 2011).

Standard error of measurement (SEM), intraclass correlation coefficient (ICC), relative technical error of measurement (rTEM) and coefficient of variation (CV) were calculated in accordance with suggestions of reliability tests in sports medicine (Atkinson and Nevill, 1998; Hopkins *et al.*, 2009). The ICC was selected based upon the work of Weir (2005). Results of reliability tests are presented in Table 3.1.

Table 3.1. Reliability statistics for main outcome measures.

Outcome measure	Trial 1	Trial 2	SEM	rTEM (%)	CV (%)	ICC
Body mass (kg)	87.1 (18.2)	87.0 (18.5)	0.45	0.19	0.39	1.00
Skeletal muscle mass (kg)	37.6 (4.7)	37.8 (5.0)	0.45	0.69	0.94	0.99
Body fat mass (kg)	20.6 (14.9)	20.5 (14.6)	0.72	1.60	2.37	1.00
Body fat percentage (%)	22.0 (11.6)	21.8 (11.6)	0.70	1.29	2.23	1.00
Visceral fat area (cm^2)	119.9 (71.6)	121.6 (69.6)	4.25	2.91	2.80	1.00
Systolic blood pressure (mm Hg)	142 (11)	146 (15)	5.47	5.01	3.73	0.76
Diastolic blood pressure (mm Hg)	80 (8)	81 (8)	4.39	1.59	4.40	0.67
MAP (mm Hg)	105 (6)	105 (8)	4.06	0.61	3.97	0.51
Resting heart rate ($beats \cdot min^{-1}$)	57 (5)	61 (7)	2.77	13.73	5.78	0.71
Baseline arterial diameter (mm)	5.2 (0.6)	5.2 (0.6)	0.15	0.54	2.00	0.94
Peak arterial diameter (mm)	5.5 (0.4)	5.5 (0.4)	0.17	1.27	1.96	0.86
FMD (mm)	0.32 (0.21)	0.29 (0.20)	0.04	15.48	12.48	0.96
FMD (%)	6.5 (5.2)	6.1 (5.0)	0.80	11.52	10.97	0.98

Abbreviations. CV: Coefficient of variation, FMD: Flow-mediated dilatation, ICC: Intraclass correlation coefficient, MAP: Mean arterial pressure, rTEM: Relative technical error of measurement, SEM: Standard error of measurement. Data for trials stated as mean (SD).

Considering the reproducibility results presented above against the standards described by Cicchetti, (2000) for levels of ICC (<0.4 = poor, 0.4-0.59 = fair, 0.6-0.74 = good, ≥0.75 = excellent) suggests our findings are excellent for body composition and ultrasound data, and good for blood pressure measurements. Our results demonstrate CV of body composition measurements is comparable to those reported in studies investigating the reliability of DEXA (Guo *et al.*, 2004).

There is no conventionally accepted level of reproducibility for ultrasound assessments of FMD, and current available data from assessments of FMD reliability vary greatly in their findings, at least partly as a result of variations between centres for FMD techniques (Charakida *et al.*, 2010). However, reliability of baseline arterial diameter and FMD response found in the current assessment are of similar magnitude to those previously reported by studies using the same method for FMD assessment (Welsch *et al.*, 2002; Donald *et al.*, 2008). Donald *et al.* (2008) found CV of 2.6% and 10.6% for the difference in baseline arterial diameter and FMD response, respectively. Similarly, Welsch *et al.* (2002) reported ICC and SEM of 0.92 and 1.53%, respectively, for the difference in FMD response between days.

4.0 RESULTS: Study 1

4.1 Demographic details and patient characteristics

Groups were well-matched for age, current smoking status and history of cardiovascular disease (Table 4.1). More men in the control group were previous smokers, however the difference between groups did not achieve statistical significance (P = 0.053). There were no marked differences between groups for daily physical activity measured using the Godin LSI (18 ± 13 points and 19 ± 13 points for ADT and control groups, respectively; P = 0.878).

Table 4.1. Cohort demographic details, given as count within cohort (% of group) unless otherwise stated

	ADT patients n = 20	Controls n = 20	*P*
Age- yr: Mean (SD)	69 (7)	69 (5)	0.779
Lifestyle			
Current smokers	1 (5)	1 (5)	1.000
Previous smoker	9 (45)	15 (75)	0.053
Currently employed	4 (20)	1 (5)	0.151
Health history			
History of cardiovascular disease	12 (60)	10 (50)	0.525
Diagnosed hypertension	12 (60)	8 (40)	0.342
Diagnosed diabetes	1 (5)	1 (5)	1.000
Previous myocardial infarction	3 (15)	2 (10)	0.292
Medications			
Any anti-hypertensive medication	13 (65)	9 (45)	0.110
Statin therapy	9 (45)	11 (55)	0.527
Beta-blockers	6 (30)	1 (5)	0.037
Aspirin	8 (40)	5 (25)	0.311
ACE-inhibitors	10 (50)	2 (10)	0.006
Diuretics	4 (20)	3 (15)	0.677
Angiotensin II receptor antagonists	0	3 (15)	0.072
Calcium channel blockers	8 (40)	5 (25)	0.311
Anti-coagulants	1 (5)	2 (10)	0.548

Abbreviations. ADT: Androgen deprivation therapy, ACE: Angiotensin converting enzyme

Median duration of ADT was 22 months (range 6-133 months). All ADT patients were treated with LHRH-analogue injections alone (n = 18) or in addition to the anti-androgen Bicalutamide (n = 2). PSA for men on ADT was 1.74 ± 2.96 $ng \cdot ml^{-1}$. Five men in the ADT group had previously received radiotherapy (median duration since treatment completion 18 months, range 12-58 months). Serum testosterone concentrations were lower in men on ADT (0.4 ± 0.2 $nmol \cdot L^{-1}$) than in controls (18.5 ± 7.1 $nmol \cdot L^{-1}$; P <0.001) but

SHBG was similar between groups (48 ± 24 nmol·L^{-1} and 53.4 ± 17.2 nmol·L^{-1} for ADT and controls, respectively; $P = 0.3$).

4.2 Vascular function assessments

Data for ultrasound assessments are given in Table 4.2. Baseline and peak arterial diameter for FMD assessments were similar between groups ($P > 0.05$). The FMD response was lower in men on ADT than in controls for all three methods of data presentation ($P < 0.05$; mean difference for relative FMD = 2.1%; 95% CI, 0.1 to 4.0). After adjustment for body fat mass and concomitant-medications, the difference in FMD remained significant ($P = 0.029$), with the magnitude of difference in mean FMD between groups altered marginally from 2.1% (95% CI, 0.3 to 4.0) for FMD scaled to baseline arterial diameter, to 2.4% (95% CI, 0.3 to 4.5). There were no substantial differences between groups for blood flow at baseline or at peak velocity after cuff release ($P > 0.05$). SR AUC was similar between groups ($P > 0.05$).

Table 4.2. Ultrasound assessment data, mean (SD)

	ADT patients	Controls	*P*	*d*
Baseline diameter (mm)	4.90 (0.56)	5.10 (0.73)	0.338	0.04
Peak diameter (mm)	5.09 (0.58)	5.39 (0.71)	0.150	0.06
FMD (mm)	0.19 (0.10)	0.29 (0.18)	0.034	0.02
FMD (%)	3.9 (2.1)	5.9 (3.8)	0.047	0.33
Allometrically-scaled FMD (%)	3.7 (2.7)	6.0 (2.7)	0.023	0.39
Time to peak diameter (sec)	54.3 (29.2)	60.6 (29.7)	0.401	0.15
Resting flow ($ml \cdot min^{-1}$)	123 (51)	126 (81)	0.607	0.03
Peak flow ($ml \cdot min^{-1}$)	1510 (484)	1808 (587)	0.094	0.40
SR AUC	38811 (18298)	38064 (16537)	0.893	0.03
GTN baseline diameter (mm)	5.17 (0.54)	5.06 (0.47)	0.497	0.02
GTN diameter peak (mm)	5.80 (0.60)	5.80 (0.53)	0.985	0.00
GTN-mediated dilatation (mm)	0.63 (0.21)	0.74 (0.27)	0.152	0.02
GTN-mediated dilatation (%)	12.2 (4.2)	14.8 (5.7)	0.113	0.31
Allometrically-scaled GTN (%)	12.3 (4.6)	14.4 (4.6)	0.163	0.28

Abbreviations. ADT: Androgen deprivation therapy, FMD: Flow-mediated dilatation, GTN: Glyceryl trinitrate, SR AUC: Shear rate area under the curve

Arterial diameter prior to GTN assessments and peak arterial diameter after GTN administration showed no substantial differences between groups (P >0.05). GTN-mediated change in arterial diameter was similar between groups for all methods of data presentation (P >0.05).

Linear regression lines for log-transformed baseline and peak diameter for FMD assessments for ADT and control men are shown in Figure 4.1. The exponent for allometric-scaling of FMD assessments were calculated as 0.93 (95% CI, 0.83-1.00). Similarly, for GTN-mediated dilatation an exponent of 0.87 (95% CI, 0.73-1.01) was found.

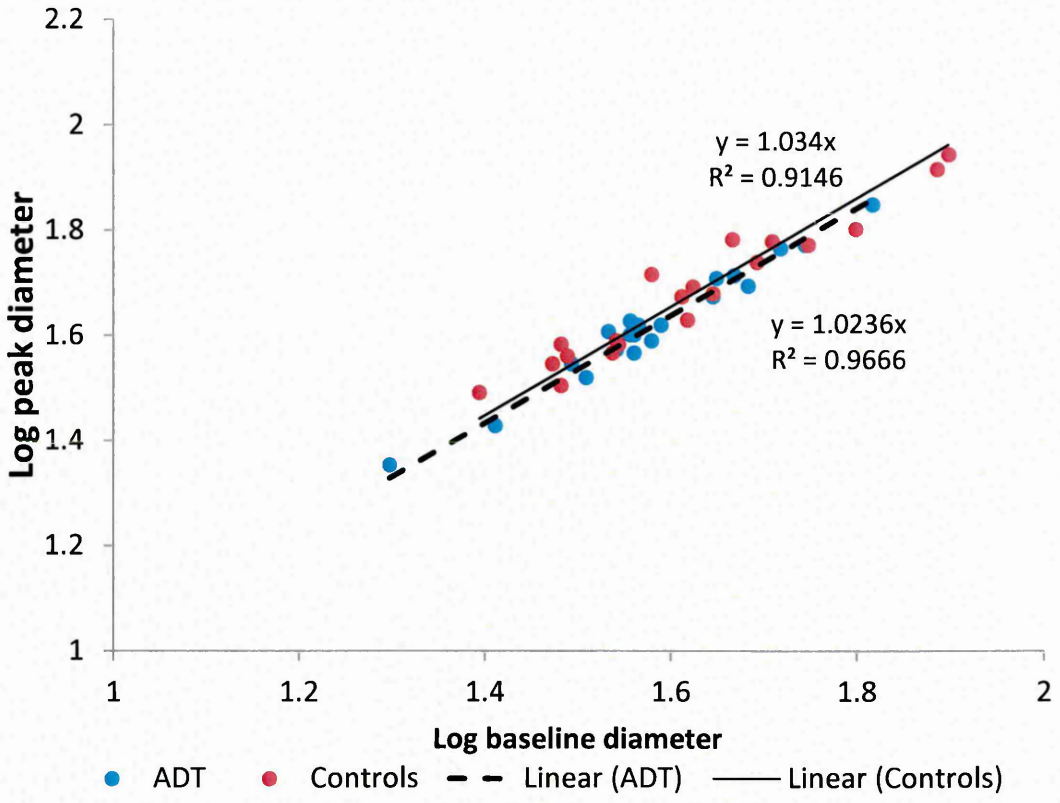


Figure 4.1. Linear regression of log baseline diameter and log peak diameter for FMD assessments in men on ADT (●) and controls (●).

4.3 Secondary outcomes

Table 4.3 shows body composition and blood pressure data. Groups were well-matched for body mass and BMI (P >0.05), however differences between groups were evident with body composition. Body fat mass and body fat percentage were both higher in men on ADT than in controls (P <0.05). There were no substantial differences between groups for skeletal muscle mass or visceral fat area (P >0.05).

Groups did not differ for systolic blood pressure, diastolic blood pressure, mean arterial pressure or pulse pressure (P >0.05). Resting heart rate was higher in men treated with ADT than in controls (P = 0.032).

Table 4.3. Blood pressure and body composition data, mean (SD)

	ADT patients	Controls	*P*	*d*
Systolic blood pressure (mm Hg)	145 (16)	139 (12)	0.167	0.31
Diastolic blood pressure (mm Hg)	79 (8)	79 (9)	0.843	0.04
Mean arterial pressure (mm Hg)	105 (10)	103 (9)	0.390	0.19
Pulse pressure (mm Hg)	66 (15)	59 (9)	0.940	0.38
Resting heart rate (beats·min^{-1})	66 (12)	58 (9)	0.032	0.49
Body composition				
Body mass (kg)	90.5 (12.1)	89.0 (14.4)	0.718	0.08
BMI (kg·m^{-2})	29.6 (3.3)	28.4 (3.8)	0.273	0.19
Skeletal muscle mass (kg)	32 (5.1)	34.4 (5.2)	0.152	0.28
Body fat mass (kg)	32.5 (8.2)	27.4 (7.6)	0.035†	0.43
Body fat (%)	35.8 (6.2)	30.5 (4.6)	0.004	0.60
Visceral fat area (cm^2)	179 (30)	168 (25)	0.216	0.29

Abbreviation. BMI: Body mass index. (†) denotes assessed using Mann Whitney U test

Results of bloods analysis are displayed in Table 4.4. HDL-C, LDL-C, total cholesterol and total cholesterol / HDL-C ratio were all similar between groups (P >0.05). Triglycerides were higher in men on ADT than controls (P = 0.001). Haemoglobin concentrations were lower in men on ADT (P = 0.006).

Table 4.4. Blood analysis, mean (SD)

	ADT patients	Controls	*P*	*d*
HDL-C (mmol·l^{-1})	1.35 (0.39)	1.49 (0.39)	0.213†	0.03
LDL-C (mmol·l^{-1})	2.81 (1.14)	2.88 (1.07)	0.841	0.01
Total cholesterol (mmol·l^{-1})	5.08 (1.22)	4.92 (1.17)	0.766†	0.04
Total cholesterol/HDL-C ratio	3.97 (1.18)	3.45 (0.99)	0.143	0.11
Triglycerides (mmol·l^{-1})	2.03 (0.9)	1.22 (0.52)	0.001	0.18
Haemoglobin (g·l^{-1})	131 (15)	146 (15)	0.006	0.65

Abbreviations. HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol. (†) denotes assessed using Mann Whitney U test

4.4 Correlations

Relationships between outcome measures and duration of ADT were assessed using non-parametric tests as a result of data for ADT duration being non-normally distributed. ADT duration was positively correlated with body fat mass (*rs* = 0.416, *P* = 0.068) and body fat percentage (*rs* = 0.386, *P* = 0.092), however, neither achieved statistical significance (both *P* >0.05). ADT duration demonstrated a statistically significant relationship with visceral fat area (*rs* = 0.519, *P* = 0.019; Figure 4.2). Adjusting correlations for age resulted in strengthening of the association of ADT duration to body fat mass (r = 0.582, *P* = 0.009), body fat percentage (r = 0.486, *P* = 0.069) and visceral fat area (r = 0.661, *P* = 0.002).

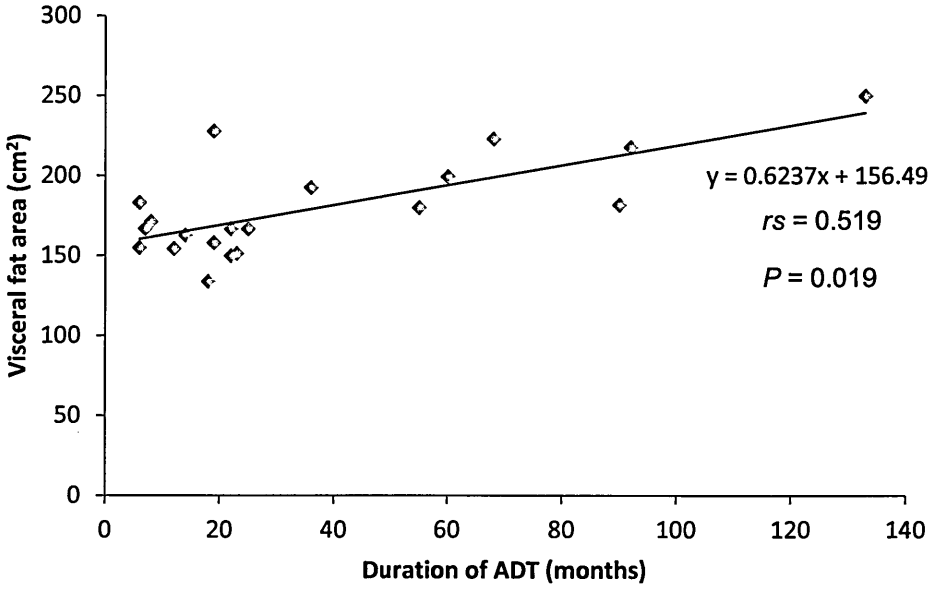


Figure 4.2. Relationship between duration of treatment with ADT and visceral fat area. Black line represents line of best fit for data.

Relationships between testosterone concentrations and other outcome measures were assessed for the two groups separately due to the wide variation between groups in testosterone caused by castration in men on ADT. Scatterplots for the relationship between testosterone and systolic

blood pressure, body fat mass, BMI and baseline arterial diameter for men in the control group are presented in Figure 4.3. For men in the control group testosterone concentrations were negatively correlated with body fat mass (*rs* = -0.448, *P* = 0.048) and BMI (r = -0.421, *P* = 0.064). After controlling for age the association with both fat mass and BMI were strengthened (r = -0.467, *P* = 0.044 and r = -0.492, *P* = 0.032, respectively). Testosterone also showed a strong negative correlation with skeletal muscle mass (r = -0.710, *P* <0.001); however the significance of this finding was lost when skeletal muscle mass was assessed as a percentage of total body mass (r = -0.056, *P* = 0.813).

Serum testosterone concentrations showed a negative correlation with systolic blood pressure (r = -0.495, *P* = 0.026) and baseline arterial diameter (r = -0.441, *P* = 0.052). Controlling for body fat mass resulted in a loss of the significance of the association between testosterone and systolic blood pressure (r = -0.444, *P* = 0.057). Adjustment of the correlation between testosterone and baseline arterial diameter for systolic blood pressure resulted in a weakening of the association (r = -0.320, *P* = 0.182), but controlling for body fat mass made the correlation stronger (r = -0.509, *P* = 0.026).

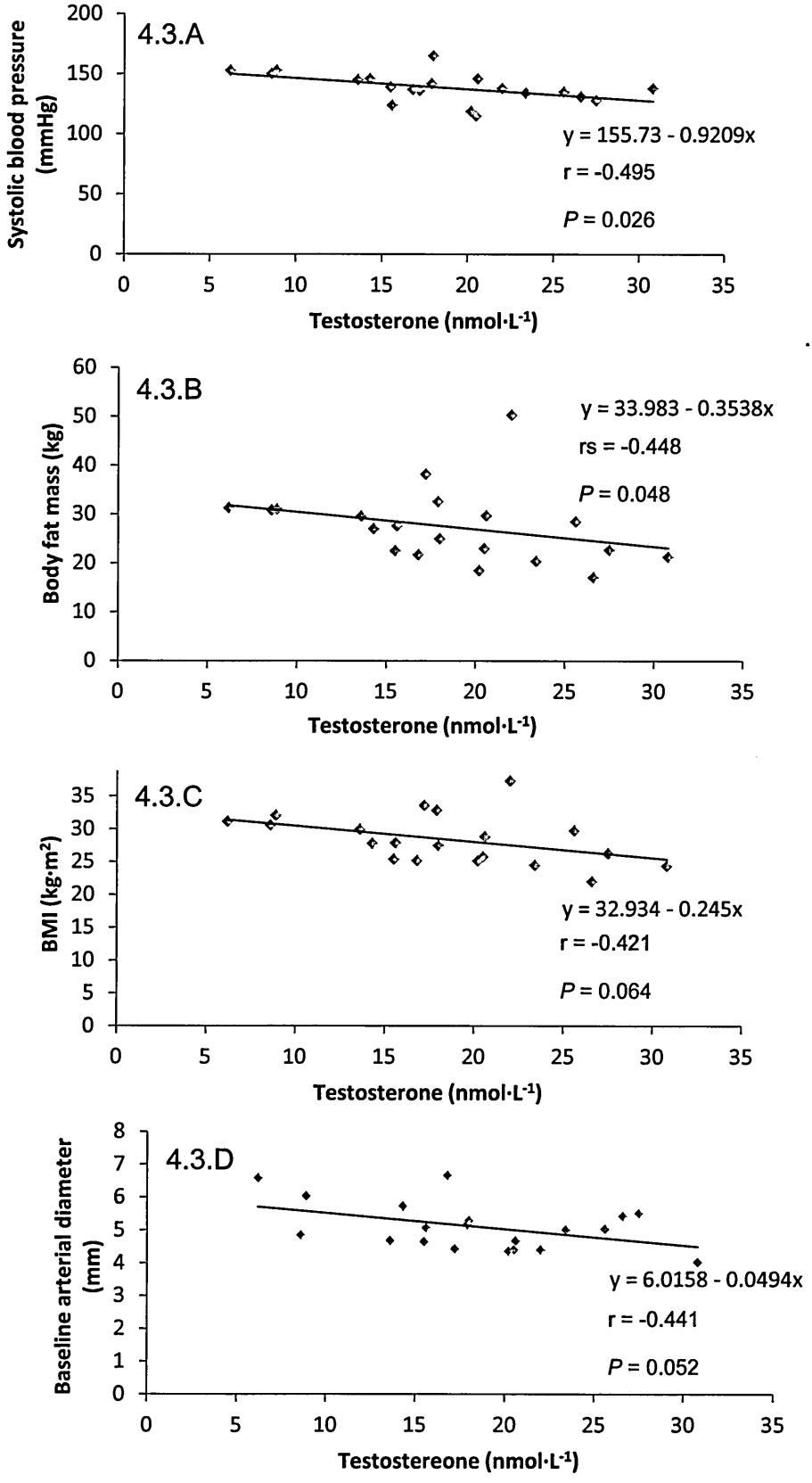


Figure 4.3. Relationship between testosterone concentrations and systolic blood pressure (4.3.A), body fat mass (4.3.B), BMI (4.3.C) and baseline arterial diameter (4.3.D) for men in the control group. Black lines denote line of best fit for each data set.

There was no relationship between serum testosterone concentrations and any measures in men treated with ADT (P >0.05).

In men on ADT percentage body fat was weakly correlated with change in arterial diameter when expressed as both relative diameter change (r = -0.365, P = 0.113) or as the ratio of peak arterial diameter to allometrically-scaled baseline diameter (r = -0.369, P = 0.110). This relationship was not evident in men in the control group (r = 0.069, P = 0.773 for relationship with percent FMD and r = 0.032, P = 0.892 for relationship with scaled ratio).

FMD was not correlated to any other variables in either group (data not presented, all P >0.05). When data for both groups were combined, no associations were evident between arterial dilatation calculated using any method and any other variables.

4.5 ADT compared to eugonadal controls

Table 4.5 presents data for main outcomes after the exclusion of men in the control group with biochemical hypogonadism (n = 3). Differences between groups were evident for FMD for all methods of data presentation (P <0.05). In addition, differences between groups were observed for body fat mass, body fat percentage and triglyceride concentrations (P <0.05). Exclusion of hypogonadal controls also led to a trend for higher systolic blood pressure in men treated with ADT, although this did not achieve statistical significance (P = 0.071).

Table 4.5. Comparison of ADT patients against eugonadal controls for main outcomes, mean (SD)

	ADT patients (n = 20)	Eugonadal controls (n = 17)	*P*	*d*
Body mass (kg)	90.5 (12.1)	86.1 (13.4)	0.297	0.24
BMI ($kg \cdot m^2$)	29.6 (3.3)	27.9 (3.9)	0.146	0.26
Skeletal muscle mass (kg)	32.0 (5.1)	33.1 (4.2)	0.494	0.14
Body fat mass (kg)	32.5 (8.2)	26.8 (8.1)	0.012	0.47
Body fat (%)	35.8 (6.2)	30.7 (4.9)	0.010	0.57
Visceral fat area (cm^2)	179 (30)	166 (26)	0.157	0.35
Systolic blood pressure (mmHg)	145 (16)	136 (12)	0.071	0.44
Diastolic blood pressure (mmHg)	79 (8)	77 (8)	0.521	0.14
Mean arterial pressure (mmHg	105 (10)	101 (8)	0.107	0.37
FMD (mm)	0.19 (0.10)	0.29 (0.15)	0.022	0.02
FMD (%)	3.9 (2.1)	5.9 (3.2)	0.028	0.34
Allometrically-scaled FMD (%)	3.8 (2.7)	5.9 (2.5)	0.024	0.38
Serum testosterone ($nmol \cdot l^{-1}$)	0.4 (0.0)	20.4 (5.0)	<0.001	3.02
HDL-C ($mmol \cdot l^{-1}$)	1.35 (0.09)	1.47 (0.39)	0.314	0.03
LDL-C ($mmol \cdot l^{-1}$)	2.81 (0.25)	2.83 (1.15)	0.843	0.01
Total cholesterol ($mmol \cdot l^{-1}$)	5.08 (0.27)	4.86 (1.23)	0.593	0.05
Triglycerides ($mmol \cdot l^{-1}$)	2.03 (0.20)	1.22 (0.55)	0.002	0.18

5.0 DISCUSSION: Study 1

The primary finding of this study is that of reduced FMD of the brachial artery in physically-inactive men treated with ADT for prostate cancer in comparison with a group of controls matched for age, activity levels and comorbidity. These findings suggest that the function of the vascular endothelium is impaired in men treated with ADT for prostate cancer (Deanfield *et al.*, 2007). As endothelial function is linked to vascular health, the findings provide evidence in support of epidemiological data showing increased cardiovascular risk in men with prostate cancer treated in this manner (Keating *et al.*, 2010; Levine *et al.*, 2010; Bourke *et al.*, 2012).

ADT has been associated with the development of cardiovascular risk factors (Smith *et al.*, 2001; Mohamedali *et al.*, 2011) and an increased incidence of adverse cardiovascular events and mortality (D'Amico *et al.*, 2007; Keating *et al.*, 2010): as such it is intuitive for ADT to also be associated with endothelial dysfunction. Disruption of normal endothelial function is an important event in the development of atherosclerosis (Celermajer, 1997). In the presence of cardiovascular risk factors, evidence of endothelial dysfunction can be detected before any angiographic evidence of disease or increased intima-media ratio (Werns *et al.*, 1989). The effect of cardiovascular risk factors on the endothelium can lead to increased expression of the vasoconstrictor endothelin-1 and reduced expression of endothelial NO synthase, increasing vascular inflammation. Under these conditions increased expression of adhesion molecules (e.g. vascular cell adhesion molecule-1) on the surface of the endothelia increases binding of leukocytes found in early atheroma formation (monocytes and T-lymphocytes). Once adherent to the endothelium, leukocytes penetrate into the intima where they perpetuate a local inflammatory response which can result in macrophages displaying scavenging receptors for lipoproteins and ingesting lipids. This process leads to the development of foam cells and the earliest signs of fatty streak formation on the arterial wall (Grover-Páez and Zavalza-Gómez, 2009).

The decreased expression of endothelial NO synthase is a key event in this process of atheroma formation as this results in reduced production of NO. In addition to being a potent vasodilator, NO also exerts a number of other vasoprotective and anti-atherosclerotic properties (Naseem, 2005). In a review of the role of NO in cardiovascular disease, Naseem (2005) describes how NO inhibits cell adhesion molecule expression, platelet-leukocyte interactions, LDL-C oxidation and vascular smooth muscle cell proliferation limiting atheroma development. These findings are of particular importance for the results of the current study due to the NO-dependence of FMD assessed using an occlusive cuff placed distal to the location of arterial imaging (Joannides *et al.*, 1995). It is consistent with this evidence to assume that our findings suggest treatment of prostate cancer with ADT decreases NO availability and thus increases the risk of atheroma formation compared to a group of matched controls.

The finding of reduced endothelial function in this study is strengthened by the use of allometric-scaling in the calculation of FMD. Although FMD calculated as an absolute or relative measure has been shown to be related to endothelial function and cardiovascular risk (Yeboah *et al.*, 2009; Inaba *et al.*, 2010), the recent article by Atkinson *et al.* (2013) describes the importance of scaling FMD for baseline arterial diameter. FMD response has been shown to be greater in smaller diameter arteries (Celermajer *et al.*, 1992) and hence, allometric-scaling of the FMD response ensures that differences reported between groups can be attributed to variations in endothelial function instead of being the result of different magnitudes of response from different calibre arteries. In the current study the increased difference in FMD response between groups after allometric-scaling is therefore suggestive of endothelial dysfunction in men on ADT for prostate cancer. In addition, with the on-going development of this new technique for FMD analysis it can be noted that the exponent for allometric-scaling calculated for FMD results for our data (0.93) is similar to those previously reported for this technique (Atkinson *et al.*, 2013; Atkinson and Batterham, 2013).

Although the mechanisms underlying a reduction in FMD in men treated with ADT for prostate cancer cannot be fully explained from this study, the reduction in serum testosterone with ADT could directly influence vascular function. Evidence from both animal and human studies suggests a direct vasodilatory effect of testosterone. In vivo studies in dogs and pigs have demonstrated dose-response increases in arterial dilatation with testosterone infusion (Chou *et al.*, 1996; Molinari *et al.*, 2002). This evidence is supported by the findings from studies in men with coronary artery disease where arterial infusion of testosterone has been shown to cause dilatation of the coronary artery and can reduce exercise-induced myocardial ischemia (Rosano *et al.*, 1999; Webb *et al.*, 1999). It has been reported that this direct vasodilatory action of testosterone is independent of the androgen receptor, aromatase and the vascular endothelium, but is associated with inactivation of L-type calcium channels and/or activation of potassium channels (Jones and Saad, 2009). In a review of the mechanisms behind the vasodilatory properties of testosterone, Jones *et al.* (2003) concluded that the majority of studies supported a calcium antagonistic action of testosterone leading to vasodilatation.

Testosterone withdrawal may also indirectly affect endothelial function through the development of cardiovascular risk factors. Negative changes in insulin sensitivity, blood lipid profile and body composition have all been shown in men treated with long-term ADT (Braga-Basaria *et al.*, 2006b; Derweesh *et al.*, 2007; van Londen *et al.*, 2008) and these changes can be associated with the reduction in circulating testosterone (Jones & Saad, 2009). In other populations the presence of such cardiovascular risk factors has been independently linked to endothelial dysfunction (Perrault *et al.*, 2000; Al Suwaidi *et al.*, 2001; Kim *et al.*, 2006), and as such, the evidence of increased fat mass and triglyceride concentrations in men on ADT in the current study could have an impact on the finding of endothelial dysfunction. Although there is evidence both supporting and contradicting an effect of triglycerides on endothelial function (Schnell *et al.*, 1999; Capell *et al.*, 2003) excess body fat has been strongly linked to increased endothelial dysfunction

(Al Suwaidi *et al.*, 2001; Perticone *et al.*, 2001; Arkin *et al.*, 2008). Increases in insulin concentrations, circulating fatty acids and vascular inflammation are all associated with excess adiposity and each of these outcomes has been linked to reductions in endothelial function (Barton *et al.*, 2012; Campia *et al.*, 2012).

In addition, low testosterone concentrations have been associated with other changes that could affect vascular function. It must be noted however that whether or not these effects are a direct result of the reduction in testosterone or an outcome of the increase in cardiovascular risk factors with hypogonadism cannot be determined from these studies. Endothelial progenitor cells have been shown to be important for maintenance of vascular health (Shantsila *et al.*, 2007) but are thought to be reduced in hypogonadal men (Foresta *et al.*, 2006). Foresta *et al.* (2006) reported that endothelial progenitor cells were around 60% lower in a group of men with hypogonadotropic hypogonadism compared with a group of age-matched controls, however, after 6 months of treatment with testosterone replacement therapy endothelial progenitor cell concentrations increased in the hypogonadal men to exceed that found in the controls (nearly 70% greater). Similarly, testosterone concentrations have been inversely linked to levels of endothelin-1 which, as described above, is a potent vasoconstrictor that can increase vascular inflammation. Higher endothelin-1 concentrations have been reported in hypogonadal patients compared with age-matched, healthy controls (Kumanov *et al.*, 2002; Kumanov *et al.*, 2007), but this difference between groups was removed by 6 months of testosterone replacement therapy (Kumanov *et al.*, 2007). Although it was beyond the scope of the current study to perform measurements of endothelial progenitor cells or endothelin-1, it would be of interest for future studies to further investigate if these biomarkers are altered in ADT patients and subsequently to examine whether or not endothelial function of men on ADT is influenced by their concentrations.

The findings of the current study are in agreement with evidence of endothelial dysfunction in other hypogonadal populations (Akishita *et al.*,

2007; Yilmaz *et al.*, 2011). Moreover, the magnitude of the FMD results in our study are comparable with those reported in these previous investigations. Yilmaz *et al.*, (2011) reported slightly higher FMD values (median (range) FMD responses for the lowest and highest groups 5.2% (4.0 - 7.2) and 8.4% (7.2 - 9.7), respectively) than were found in the current study, however their groups were younger, had lower BMI and less history of cardiovascular disease. In comparison, the study by Akishita *et al.*, (2007) reported FMD responses very similar to those found in our study (mean FMD in lowest and highest quartiles of testosterone approximately 3.4% and 5.7%, respectively).

Although as suggested above the results of the current study are in agreement with evidence of endothelial dysfunction in other hypogonadal groups, they are in contrast to the results published in the only other study investigating endothelial function in men treated with ADT (Herman *et al.*, 1997). Herman and colleagues reported superior endothelial function in 10 men treated with ADT for prostate cancer compared with a group of 10 healthy controls and a group of 10 men in remission from a non-prostatic malignancy (arterial dilatation of 6.2 ± 3%, 2.7 ± 2% and 2.0 ± 1.9% for each group, respectively). There are a number of potential reasons for these apparently conflicting findings.

Firstly, differences in the samples recruited might be an important factor. Men in the study by Herman and colleagues were all free from any history of cardiovascular disease. This contrasts with the current study in which at least 50% of men in both groups had some form of pre-existing cardiovascular comorbidity, which could be considered more representative of the health of an elderly population in a developed country where >60% of men aged 60-79 years have been reported to have a history of cardiovascular disease (American Heart Association, 2013). Our findings therefore suggest ADT has deleterious effects on endothelial function in men with pre-existing cardiovascular disease, and hence ADT could represent an independent risk factor in this high risk group. This is in agreement with the findings of increased risk of myocardial infarction or diabetes in men on ADT with cardiovascular comorbidities (Keating *et al.*, 2012).

Secondly, technical factors in the assessment of FMD may also be involved in the variation between the two studies. In the study by Herman and colleagues arterial diameter measured 50-60 seconds post-deflation was reported as peak diameter, yet more recently this duration has been shown to be insufficient to detect the full dilatory response in some people (Black *et al.*, 2008). In an investigation of the time to peak arterial diameter following 5 minutes of forearm ischaemia, 25% of elderly inactive participants achieved their full dilatory response within a time frame of 50-70 seconds following cuff release, and only 58% achieved maximal dilatation in the first 90 seconds. Consequently Herman and colleagues might have missed the true peak arterial diameter in participants in each of their three groups. It is of interest in this context that, in the current study, 85**%** of participants had a peak diameter response occurring outside the 50-60 second window. Furthermore, in the study by Herman *et al.* changes in arterial diameter were not scaled for differences in baseline arterial diameter in accordance with the suggestions of Atkinson *et al.* (2013). Thus, differences reported between groups in FMD could be mediated by differences in arterial size instead of endothelial function. Although data presented by Herman and colleagues suggests baseline diameter was similar between groups, this does not eradicate the influence of baseline diameter on estimates of endothelial function reported using the traditional approach to FMD (Senn *et al.*, 1994).

Thirdly, duration of treatment with ADT may also be an important variation between studies. Men on ADT in the work of Herman *et al.* had been medically castrated for a mean of 18 ± 4 months (range 6-33 months), in comparison with mean treatment duration of 37 ± 35 months (range 6-133 months) in our study. Although increases in body fat percentage and insulin resistance have been demonstrated within the first 3 months following initiation of ADT (Smith *et al.*, 2006), hyperglycaemia has only been reported in patients treated with ADT for a minimum of 12 months (Basaria *et al.*, 2006; Mohamedali *et al.*, 2011) suggesting an on-going effect of prolonged androgen deprivation. Thus, it could be speculated that long-term hypogonadism may lead to the development of endothelial dysfunction.

Although there was no correlation between duration of ADT exposure and magnitude of FMD in the current study, this would warrant further investigation in a larger sample.

Analysis of correlations between variables demonstrates that the samples included in the current study are representative of the wider population. The positive correlation between duration of ADT and measures of body fat are in agreement with data presented by Haseen *et al.* (2010) who reported that duration of ADT was an independent predictor of increasing fat mass. Similarly, van Londen *et al.* (2008) reported increasing fat mass over a 2-year prospective study in groups of patients on acute ADT (treated for <6 months at study enrolment) and those on chronic ADT (treated for >6 months at study enrolment). Although rapid increases in body fat seen over the first 12 months of treatment were not maintained, statistically significant increases in body fat mass and body fat percentage were still evident over the course of the study in patients established on ADT suggesting an on-going effect of treatment on fat mass accumulation.

In addition, correlation between serum testosterone and body fat mass in the control group agrees with previous evidence (Mudali and Dobs, 2004; Matsumoto, 2005; Dandona and Rosenberg, 2010; Mammi *et al.*, 2012). Testosterone has been shown to impact adipose tissue accumulation by regulating lipolysis and adipogenesis (Mudali and Dobs, 2004) and hence increased body fat is an established side effect of low testosterone concentrations (Mammi *et al.*, 2012) and is widely reported in male hypogonadism (Matsumoto, 2005; Dandona and Rosenberg, 2010). It is of interest that in our sample skeletal muscle mass did not show a positive correlation with serum testosterone concentrations in the control group as previous research has demonstrated the anabolic actions of testosterone (Bhasin *et al.*, 2001) and there is evidence of a positive relationship between testosterone concentrations and muscle mass in elderly men (LeBlanc *et al.*, 2011). Although our finding may be a sampling issue, the strong inverse nature of this relationship was lost when skeletal muscle mass was assessed as a percentage of total body mass suggesting that this finding may also be

explained, at least in part, by participants with higher levels of body fat developing increased skeletal muscle as a result.

Serum testosterone concentrations were also found to be negatively correlated to systolic blood pressure in men in the control group, which again is in agreement with previous data showing low testosterone concentrations are associated with hypertension (Khaw and Barrett-Connor, 1988; Svartberg *et al.*, 2004). Khaw and Barrett-Connor (1988) described a decrease in both systolic and diastolic blood pressure for each quartile increase in testosterone in a sample of 1132 men aged 30-79 years. Moreover, Zitzmann and Nieschlag (2007) reported that treating hypogonadal men with long-term intramuscular testosterone injections resulted in statistically significant reductions in both systolic and diastolic blood pressure. It is noted however that these previous studies suggest this association between testosterone and blood pressure is at least partially mediated by the effects of testosterone on body composition. Adjustment of findings for BMI or body fat mass has been shown to weaken the association between testosterone and blood pressure (Khaw and Barrett-Connor, 1988; Svartberg *et al.*, 2004; Zitzmann and Nieschlag, 2007). These findings are in agreement with our data where adjustment for body fat mass removed the statistical significance of the association between testosterone and systolic blood pressure.

It is of interest that our findings also demonstrate a trend for an inverse correlation between serum testosterone concentrations and baseline brachial arterial diameter, because to the best of our knowledge such an association has not been previously reported. It is postulated that the increase in blood pressure with reduced testosterone concentrations might mediate this effect on arterial diameter. Previous studies have provided data demonstrating that higher blood pressure is linked to increased internal artery diameter for the carotid and radial arteries, which is thought to be the result of arterial distension and remodelling under increased pressure (Khder *et al.*, 1997; Boutouyrie *et al.*, 1999). These findings would support our data showing a weakened correlation between testosterone and arterial diameter after controlling for systolic blood pressure. In addition, body size could also

influence baseline arterial diameter. There is evidence of a positive association between arterial diameter and body size (Sandgren *et al.*, 1999), and hence, it could have been expected that the negative correlation between testosterone and body fat mass could also influence the association between testosterone and arterial diameter in the current study as it would be expected that increased fat mass would be found in individuals with larger overall body size. However, including body fat mass as a control variable in the association between testosterone and arterial diameter in the current study only served to strengthen the association.

Although the current study examines the differences between a drastically hypogonadal population and a control group, the results cannot be generalised to a comparison of hypogonadal against eugonadal individuals because of the presence of men with biochemical hypogonadism in the control group. Three men in the control group (15% of the group) were found to have serum testosterone concentrations below the lower limit of normal measures suggested by the Endocrine Society (total testosterone 300 $ng \cdot dl^{-1}$ or 10.4 $nmol \cdot l^{-1}$; Bhasin *et al.*, 2010). Although retrospective exclusion of these men would have allowed greater generalisation of results, their inclusion makes our control group more representative of the wider population of elderly men (Harman *et al.*, 2001). Harman *et al.* (2001) reported the incidence of hypogonadism (defined as total testosterone <325 $ng \cdot dl^{-1}$ or 11.3 $nmol \cdot l^{-1}$) among men aged 60-69 years was 19%, which compares very closely to our finding from a group with a mean age of 69 years. It should be noted that reanalysis of data after the exclusion of these men increased the statistical significance of the difference between groups for absolute and relative FMD, but had little effect on FMD allometrically scaled for baseline diameter. Furthermore, removal of hypogonadal men from the control group increased the differences between groups for measures of body fat mass, visceral fat area and systolic blood pressure. These changes from the original analysis are all congruent with the expected effects of hypogonadism on these markers (Svartberg *et al.*, 2004; Dandona and Rosenberg, 2010).

The finding of increased use of anti-hypertensive medication, specifically ACE-inhibitors and beta-blockers, in men on ADT could be considered indicative of the increased endothelial dysfunction with ADT use. Such treatments have been shown to improve endothelial function (Rajagopalan and Harrison, 1996), and as such, the difference between groups for use of these medications could be expected to have resulted in no difference, or improved endothelial function in men on ADT. The fact that endothelial function was still found to be impaired in men on ADT could therefore be suggestive of good compliance with the pre-assessment instructions to, where possible, avoid medication use on the morning of the assessment, thus allowing the activity of the treatment to be minimised (Brown and Vaughan, 1998). Conversely, if participants did not truthfully report compliance with pre-assessment preparations and had taken their medication, the difference between groups could be expected to be greater than was observed in the current findings should the effects of treatment be removed from the observed results for vascular function.

In conclusion, NO-mediated endothelial function measured using FMD is reduced in men treated with ADT for prostate cancer in comparison with community-dwelling, physically-inactive men matched for age and history of cardiovascular disease. These data support previous research on endothelial function in other hypogonadal populations, but contradict the findings of the single previous investigation of endothelial function measured in this manner in men on ADT (Herman *et al.*, 1997). These results show that the effect of ADT on endothelial function in men with prostate cancer is concordant with data on other markers of cardiovascular risk in this population. Measures of endothelial function with FMD therefore provide a quantitative means by which changes in cardiovascular health could be assessed in men on ADT for prostate cancer, and thus would be a suitable method to examine longitudinal changes in cardiovascular risk in such men.

6.0 REVIEW OF LITERATURE: Study 2

6.1 Lifestyle interventions

In an editorial on the on-going needs of cancer survivors and the remit of the NCSI, Richards *et al.* (2011) describe the importance of strategies to improve patients' health and wellbeing after cancer treatment. The authors consider the physical and mental consequences of living beyond a cancer diagnosis and highlight the need for interventions to enhance health outcomes.

Lifestyle interventions encouraging patients to increase physical activity and undertake dietary modifications provide one possible method that could lead to such benefits. While convincing evidence has been presented showing wide-spread benefits of this form of intervention among disease-free individuals and individuals with other morbidities (Lichtenstein *et al.*, 2006; Blair and Morris, 2009; O'Donovan *et al.*, 2010), the role of nutrition and exercise in the aftercare of cancer survivors is still being defined (Davies *et al.*, 2011). This is the case for men with prostate cancer being treated with ADT. Such lifestyle interventions have been shown to be feasible and can lead to benefits in overall well-being in this patient group (Segal *et al.*, 2003; Galvão *et al.*, 2010; Bourke *et al.*, 2011), however, many of the physical effects of diet and exercise remain largely unstudied in this population. In consideration of the plethora of evidence describing the physical burden of treatment in this manner (reviewed in Study 1), further investigations into the benefits that can be accrued through diet and exercise in men on ADT are clearly warranted.

6.1.1 *Physical activity*

Caspersen *et al.* (1985) provide definitions of physical activity and exercise. It is important to define these terms as although they are often used interchangeably they refer to different concepts. *Physical activity* is defined

as any bodily movement produced by skeletal muscles that results in energy expenditure. This differs from *exercise* which is defined as planned, structured, and repetitive bodily movement done to improve or maintain one or more components of physical fitness. As an addition, it must also be noted that exercise can also include isometric muscular activity (Winter and Fowler, 2009), although this is not included in this definition.

Increasing physical activity has been shown to result in benefits to both physical and mental well-being. Studies in healthy individuals and various patient groups have shown that exercise can help to prevent and manage a wide range of pathologies and can lower the risk of mortality from all causes (Warburton *et al.,* 2006).

6.1.1.1 Physical activity and the risk of disease and mortality

An inverse, dose-response relationship has been reported between the volume of physical activity performed and the risk of mortality from all causes (Lee and Skerrett, 2001). This conclusion is in agreement with data presented by Myers *et al.* (2004) showing a reduction in mortality risk with increasing amounts of physical activity (HR = 0.38; 95% CI, 0.19-0.73 for risk of all-cause mortality for individuals in highest quartile of physical activity compared to those in lowest quartile).

Similarly, volume of physical activity has also been associated with cardiovascular mortality risk; Hamer *et al.* (2012) reported that participation in three sessions per week of moderate to vigorous activity led to a reduction in cardiovascular mortality risk of nearly 40% (HR = 0.61; 95% CI, 0.38-0.98). In addition, there is evidence of a reduction in the incidence of cardiovascular events with increasing physical activity. Studies have shown decreased incidence of myocardial infarction (Lakka *et al.*, 1994), ischemic stroke (Sacco *et al.*, 1998), coronary heart disease (Tanasescu *et al.*, 2002) and diabetes (Manson *et al.*, 1992) with greater volumes of physical activity.

Moreover, physical fitness has also been associated with cardiovascular risk, with Lee *et al.* (1999b) showing that men who were lean and unfit had more than three times the risk of cardiovascular mortality of men who were lean but fit (HR = 3.16; 95% CI, 1.12-8.92). In fact, Blair *et al.* (1996) reported that the increase in cardiovascular risk incurred by low fitness can exceed that of established cardiovascular disease risk factors. Men with a fitness score in the lowest 20% had a relative risk (RR) of 1.70 (95% CI, 1.28-2.25) for cardiovascular disease, which is higher than the risk accrued by cigarette smoking (RR = 1.57; 95% CI, 1.18-2.10), hypercholesterolaemia (RR = 1.65; 95% CI, 1.26-2.15), high systolic blood pressure (RR = 1.34; 95% CI, 1.00-1.80), family history of mortality due to coronary heart disease (RR = 1.18; 95% CI, 0.89-1.57) or BMI ≥27 $kg \cdot m^{-2}$ (RR = 1.20; 95% CI, 0.91-1.58).

6.1.1.2 Mechanisms for exercise decreasing cardiovascular disease risk

It has been established that regular exercise training can decrease cardiovascular risk because of its effects on traditional markers of cardiovascular health such as lipid profile, blood pressure, insulin sensitivity and body composition (Paffenbarger *et al.*, 1983; Myers, 2003; Kokkinos and Myers, 2010). Exercise has been shown to have comparable benefits in treating hypercholesterolaemia, hypertension and diabetes to drug therapies often used for management of these conditions (Joyner and Green, 2009).

The benefit of increased physical activity on these traditional markers does not fully account for the reduction in cardiovascular risk shown with exercise training, suggesting that exercise might also exert independent effects to lower cardiovascular risk. Mora *et al.* (2007) described that the effects of exercise training on markers of cardiovascular risk (blood lipids, inflammatory and hemostatic biomarkers, BMI, blood pressure and diabetes) only accounted for 59% of the reduction in cardiovascular disease risk, suggesting that 41% of risk reduction is mediated through other changes.

6.1.1.2.1 *Exercise and body composition*

Exercise has been comprehensively shown to promote positive changes in body composition. Increased lean body mass and decreased fat mass are both widely reported outcomes associated with increasing physical activity in previously sedentary individuals (Fentem, 1994; Pollock *et al.*, 2000; Warburton *et al.*, 2006).

Skeletal muscle hypertrophy is a commonly recognised effect of exercise training. Increased protein synthesis in response to an overload stimulus results in the growth of new muscle tissue (Schoenfeld, 2010). Stimulation of satellite cells located between the lamina and sarcolemma play a key role in this process providing a pool from which myonuclei and myogenic regulatory factors are drawn. The donation of additional nuclei from the satellite cells into the exercised muscle fibre allows increased protein synthesis and the subsequent formation of further myofibrils. Furthermore, the stimulation of gene expression leads to the binding of DNA responsible for the generation of muscular repair, regeneration and growth leading to further myogenesis (Cornelison and Wold, 1997). Although satellite cell number and myogenic capacity is reduced with normal aging potentially inhibiting this process of muscle development, exercise has been shown to prevent and reverse this satellite cell decline maintaining the myogenic capacity (Shefer *et al.*, 2010). Increases in satellite cells have been reported for up to 48-72 hours after acute bouts of exercise performed at an intensity sufficient to induce muscle damage. Long-term increases in satellite cell numbers have been reported with chronic exercise training (Martin and Lewis, 2012).

Changes in the rate of lipid breakdown and utilization occurring during exercise promote increased fat oxidation for several hours after acute bouts of exercise or chronically following prolonged exercise training (Thompson *et al.*, 2012). Concomitant decreases in antilipolytic activity and increases in lipid oxidation rates have been shown to occur in subcutaneous adipose tissue following participation in aerobic exercise (de Glisezinski *et al.*, 2003). Catecholamines binding to β-adrenergic receptors on the surface of the fat cell stimulate increases in lipolytic rate through activation of hormone

sensitive lipase which initiates lipolysis within the fat cell. Moreover, the exercise-induced increase in mitochondrial density in the trained muscle allows greater capacity for fat oxidation at the level of the muscle preventing FFA being reesterified in tissues such as skeletal muscle or the liver (Horowitz, 2001).

Improvements in body composition have been shown in exercise studies across a wide-range of age groups. Although a reduction in muscle mass and an increase in adiposity are accepted outcomes of normal aging, elderly people can still achieve gains in lean body mass and loss of fat mass by increasing daily physical activity (Evans and Campbell, 1993). Raguso *et al.* (2006) demonstrated that men and women above the age of 65 years performing greater amounts of daily moderate or intense physical activity (defined as activity above 4-6 metabolic equivalents (METs)) benefited from greater fat-free soft tissue in comparison with their less active peers. Furthermore, the amount of physical activity an individual performed was positively correlated with muscle mass and negatively correlated with whole body and abdominal fat accumulation. These results are in agreement with the results of training studies showing body composition changes after exercise training regimes. Stewart *et al.* (2005) reported a 3.5% decrease in body fat mass and a 3.5% increase in lean mass after 6 months of training with a mixture of aerobic and resistance exercises in men and women aged 55-75 years. Similarly, Campbell *et al.* (1994) reported that 12 weeks of resistance training resulted in a 1.8 kg decrease in fat mass and 1.4 kg increase in fat-free mass in previously sedentary men and women aged 56-80 years.

6.1.1.2.2 *Exercise and blood pressure*

Physical activity is recommended in both the prevention and treatment of hypertension by the World Health Organisation (World Health Organization, 2003), the European Society of Hypertension (European Society of Hypertension, 2003), and the Joint National Committee on Prevention,

Detection, Evaluation and Treatment of High Blood Pressure (Chobanian *et al.*, 2003). Meta-analyses of the training-mediated changes in blood pressure have consistently reported hypotensive effects of exercise. Examining the results of 54 randomized controlled trials (RCT's) investigating the effects of aerobic exercise training on blood pressure (range of intervention duration 3 weeks to 2 years), Whelton *et al.* (2002) reported decreased systolic blood pressure in 44 trials (mean reduction 4 mm Hg) and diastolic pressure in 42 trials (mean reduction 3 mm Hg). These findings were in agreement with Halbert *et al.* (1997) who analysed 29 RCT's using exercise interventions of 4 weeks or longer (range of intervention duration 6-52 weeks) including a total of 1533 normotensive and hypertensive participants. They found a mean reduction in systolic and diastolic pressure of 5 mm Hg and 3 mm Hg, respectively, after training in the 26 studies using aerobic exercises.

It should be noted that although both of these meta-analyses only reported beneficial changes from aerobic exercise more recent studies have demonstrated improvements in blood pressure with resistance training. In the meta-analysis by Cornelisson and Fagard, (2005) it was reported that moderate intensity resistance exercise resulted in reductions in blood pressure comparable to those achieved with aerobic training.

Structural adaptations and changes in vascular responsiveness to vasoactive substances occurring with increasing physical activity have been identified as possible mechanisms behind exercise induced improvements in blood pressure (Pescatello *et al.*, 2004). Decreases in endothelin-1 have been reported after exercise training (Maeda *et al.*, 2001) while there is speculation that sympathetic nervous system activity may also be reduced with exercise training leading to a decrease in norepinephrine concentrations (Mueller, 2007), although clinical evidence of this effect is limited. Both substances act as potent vasoconstrictors, and thus, such exercise-induced decreases promote reductions in vascular resistance. Similarly, improvements in vasodilatory function occur as an outcome of increased NO expression promoting reductions in vascular tone and improvements in arterial compliance (Green *et al.*, 2004). In addition, exercise training induces

structural changes of the arterial system resulting in a reduction in vascular resistance. Evidence from training studies show structural adaptations occurring in response to repeated bouts of exercise (Dinenno *et al.*, 2001; Tinken *et al.*, 2008), while conversely, decreases in arterial diameter and functional capacity have been shown with physical inactivity (Thijssen *et al.*, 2010).

6.1.1.2.3 *Exercise and metabolic changes*

Acute bouts of exercise increase glucose uptake and metabolism in skeletal muscle. Activation of intramyocellular signalling events within the skeletal muscle cell lead to translocation of the glucose transporter GLUT-4 to the plasma membrane, mediating an insulin-independent increase in glucose uptake (Kennedy *et al.*, 1999). Furthermore, exercise promotes an increase in insulin-mediated uptake of glucose into the skeletal muscle with this insulin-sensitizing action reported to last up to 48 hours after exercise completion (Hawley and Lessard, 2008). This response has been reported in both healthy humans and individuals with type 2 diabetes (Kennedy *et al.*, 1999). Increases in glucose uptake after an acute bout of activity have been shown with both aerobic and resistance exercise (Kraniou *et al.*, 2005; Black *et al.*, 2010). Activities combining aerobic and resistance exercises might have the greatest benefit on blood glucose uptake by maximising the ability of the muscle to take on glucose through both insulin-dependent and independent pathways (Colberg *et al.*, 2010).

Exercise induced improvements in glucose tolerance and insulin action are mediated by several mechanisms. Increases in GLUT-4 mRNA and protein expression have been associated with improved glucose uptake and metabolism while adaptations in the expression and activity of proteins for insulin signal transduction, including insulin receptor substrate isoforms (IRS-1 and IRS-2) and phosphatidylinositol 3-kinase (PI3K), lead to an increased rate and efficiency in insulin-mediated glucose clearance (Zeirath, 2002; Hawley and Lessard, 2008). Enhanced PI3K activity has been considered

especially important in achieving improvements in glucose transport with chronic exercise. PI3K activity is higher in fitter individuals and has been positively correlated with glucose disposal rate and aerobic capacity (Kirwan *et al.*, 2000).

Exercise induced changes in FFA uptake and oxidation in the skeletal muscle can be important factors determining these changes in insulin sensitivity. In insulin resistant individuals FFA uptake by skeletal muscle cells will be increased yet FFA oxidation will be reduced leading to higher fat concentrations within the muscle cell which can inhibit activation of IRS-1 and PI3K, thus decreasing insulin-stimulated glucose transport (Yu *et al.*, 2002).. Exercise training results in an increase in oxidation of FFA in the muscle cell which has been shown to lead to improvements in insulin action (Solomon *et al.*, 2008).

Because body fat mass will influence plasma FFA concentrations and thus FFA uptake by the skeletal muscle, it was concluded in early studies investigating changes in insulin sensitivity with exercise that improvements in insulin action must be mediated by exercise-induced reductions in body fat mass (Segal *et al.*, 1991). These findings have been contradicted by more recent studies that have shown that periods of prolonged training of moderate intensity can improve insulin sensitivity independently of changes in BMI, waist circumference or fasting lipids (Duncan *et al.*, 2003) providing evidence that exercise training can directing influence substrate metabolism within the muscle cell.

Aerobic exercise has been the most widely studied form of activity for benefits to insulin action. Improvements in whole-body insulin sensitivity have been reported after only 1 week of aerobic training in obese adults with type 2 diabetes (Winnick *et al.*, 2008). Resistance training can also lead to benefits in insulin response (Dunstan *et al.*, 2002). It has been shown that training with combined aerobic and resistance exercise can result in greater improvements in glucose disposal than would be found with either exercise form individually (Cuff *et al.*, 2003).

Tambalis *et al.* (2009) reviewed the benefits of training using different forms of exercise on cholesterol and triglyceride concentrations in 84 studies (duration range 8 weeks to 1 year). In the 28 studies using moderate intensity aerobic exercise (defined as activity ≤60% maximal oxygen consumption or ≤60% maximal heart rate) the most marked benefits were found in HDL-C (statistically significant increase in 21.4% of studies) while only 7% of studies showed improvements in LDL-C, total cholesterol and triglycerides. High-intensity aerobic exercise (defined as activity >60% maximal oxygen consumption or >60% maximal heart rate) was used in 37 of the studies reviewed and resulted in more consistent benefits to HDL-C (improved in 60% of studies) although the magnitude of change was similar to those found with moderate intensity exercise (HDL-C increase of 3-20%). Similarly, reductions in LDL-C, total cholesterol and triglycerides were reported more consistently in high intensity aerobic training studies (20%, 34% and 22% of studies, respectively) but the magnitude of improvement was again no different from that reported with moderate intensity aerobic exercise. Data was also presented for 23 studies using resistance exercise alone or in combination with aerobic training. The most notable effect of including resistance training was marked reductions in LDL-C, with 39% of trials reporting statistically significant improvements although the magnitude of change was similar between exercise forms (6-21% reduction in LDL-C with aerobic training alone, 5-23% reduction with resistance exercise alone). Reductions in total cholesterol and triglycerides were reported in 23% and 13% of studies including resistance exercise, respectively. Resistance exercise was less effective in increasing HDL-C than training with aerobic exercise as improvements were only reported in 17% of studies (range from 6-14% increase in HDL-C).

Although the joint position stand from the American College of Sports Medicine and the American Diabetes Association suggests that changes in lipid profiles are mainly affected by weight loss (Colberg *et al.*, 2010), changes in plasma lipase activity with training can also result in improvements in blood lipid profile. Increases in lipase activity with training

can influence cholesterol concentrations without any changes in total body mass or fat mass (Duncan *et al.*, 2003).

6.1.1.2.4 *Exercise and the vascular endothelium*

The ability of exercise to influence changes in the vascular endothelium provides a potential target whereby cardiovascular risk could be reduced, with or without concomitant alterations of traditional cardiovascular risk factors (Di Francescomarino *et al.*, 2009). Although exercise-induced changes in traditional cardiovascular risk factors have a profound effect on endothelial function, it has been proposed that exercise also mediates functional improvements through independent mechanisms (Green *et al.*, 2003). Higashi and Yoshizumi (2004) suggested that in response to the stimulus of increased arterial shear stress brought about during bouts of exercise, NO bioavailability is increased by up-regulation of endothelial NO synthase gene expression and a reduction in oxidative stress. This leads to a decline in NO inactivation. This evidence is supported by Tuttle *et al.* (2001) who describe the functional and structural changes occurring in the arterial wall in response to increased shear stress. Using mesenteric arteries in rats, Tuttle *et al.* (2001) performed arterial ligation to manipulate the rate of perfusion to 50%, 200% or 400% of that found in control animals. After 2 days lumen diameter decreased in arteries with 50% perfusion, but increased by 17% and 33% in arteries with 200% and 400% of normal perfusion rates, respectively. Increases in arterial shear stress experienced with higher perfusion rates were considered to be highly involved in this arterial remodelling with expression of endothelial NO synthase found to be positively correlated to the level of shear stress. The lack of further changes in lumen diameter found 7 days following the intervention led the authors to suggest that structural changes take place rapidly following initiation of periods of prolonged arterial shear stress, but diminish as shear rate decreases with lumen expansion.

6.1.1.3 Physical activity after cancer diagnosis

Physical activity provides a non-pharmacological means of treating some of the physical and psychological challenges experienced by cancer survivors. In addition to reducing some of the negative side-effects associated with the disease and its treatments, there is also evidence of improvements in recurrence-free survival and disease-specific mortality in individuals taking part in greater volumes of physical activity (Schmitz *et al.*, 2010; Sabiston and Brunet, 2012).

6.1.1.3.1 *Cancer-related fatigue*

Exercise has been shown to reduce cancer-related fatigue (McMillan and Newhouse, 2011; Cramp and Byron-Daniel, 2012). In the recent Cochrane review of exercise for the management of cancer-related fatigue, Cramp and Byron-Daniels (2012) reported on the findings of 56 studies including 4068 participants, with the majority (28 studies) carried out in breast cancer patients. They describe how exercise can reduce fatigue, with greater benefits accrued through aerobic exercise training compared to resistance exercise or low-intensity mind-body exercise (e.g. yoga, qigong). It has been suggested that exercise induced improvements in fitness and muscular development can directly reduce fatigue, while in addition, the benefits of exercise on symptom clusters such as depression and anxiety can also have beneficial effects (McMillan and Newhouse, 2011).

6.1.1.3.2 *Body size and body composition*

Physical activity can help to manage the changes in body size and body composition that can occur with treatments for numerous cancers. Increasing body mass as a result of body fat accumulation is a widely reported outcome of certain cancer treatments such as ADT for prostate cancer (2.8.7.1 Body composition) and adjuvant chemotherapy for breast cancer (Sheean *et al.*, 2012), and can promote the development of further comorbidities in addition

to increasing the risk of development of secondary cancers. While structured physical activity can help decrease or prevent the gain in fat mass it can also reduce the loss of lean muscle mass that is also associated with these forms of treatment (McDonald *et al.*, 2011).

In contrast, patients with cancers of the head and neck, oesophagus and stomach can often be underweight or lose weight as a result of their treatment and again increasing physical activity can be beneficial. Activity regimes improving aerobic fitness and muscular strength can promote maintenance of a healthy body composition.

6.1.1.3.3 *Immune function*

There is early evidence that immune function could be improved in cancer survivors who take part in physical activity. Increases in natural killer cell activity were shown in post-menopausal breast cancer survivors randomised to receive 15 weeks of supervised exercise training (n = 25) compared to those in a non-exercise control group (n = 28, Fairey *et al.*, 2005). Similarly, 2 weeks of cycling exercise following curative resection of a stomach cancer resulted in higher natural killer cell activity than was found over the same duration in controls (Na *et al.*, 2000).

These findings are contradicted by Nieman *et al.* (1995) who reported no difference in natural killer cell activity in breast cancer survivors after an 8 week exercise training programme. However, only 12 of the 16 patients enrolled in this study were available for follow-up assessment and differences in age, BMI and natural killer cell activity were reported between groups at baseline.

6.1.1.3.4 *Disease recurrence and mortality*

Physical activity after a diagnosis of breast or colon-rectal cancer can decrease the risk of disease recurrence, cancer-specific or all-cause mortality.

Studies have shown benefits can be accrued in a dose-response fashion with individuals participating in greater volumes and intensities of activity having the greatest reduction in risk. Furthermore, there is some evidence that disease progression in prostate cancer survivors can be influenced by the volume of vigorous activity after diagnosis and the patients history of physical activity.

The benefits of physical activity after a cancer diagnosis have been most extensively examined in women with breast cancer, with improvements in disease-specific and all-cause mortality reported in several studies (Holmes *et al.*, 2005; Holick *et al.*, 2008; Irwin *et al.*, 2008; Sternfeld *et al.*, 2009) although others have reported no effect (Enger and Bernstein, 2004). In one of the largest studies of physical activity and survival after breast cancer diagnosis, Holick *et al.* (2008) reported that compared to women expending <2.8 METs·h·wk^{-1} in physical activity, women engaging in 2.8-7.9 METs·h·wk^{-1} had a HR for dying from breast cancer of 0.65 (95% CI, 0.39-1.08) while women expending 8.0-20.9 METs·h·wk^{-1} had a HR of 0.59 (95% CI, 0.35-1.01) and women expending ≥21.0 METs·h·wk^{-1} had a HR of 0.51 (95% CI, 0.29-0.89). Moreover, Irwin *et al.* (2008) described how changing physical activity habits at diagnosis could influence mortality risk. They found that women who decreased activity at diagnosis had an almost four-fold increase in risk compared to women who were inactive before and after diagnosis (HR = 3.95; 95% CI, 1.45-10.50). Conversely, women who increased activity almost halved the risk of mortality compared to the continually inactive group (HR = 0.55; 95% CI, 0.22-1.38).

Similarly, physical activity has been shown to reduce the risk of disease recurrence and total and disease-specific mortality in patients with colorectal cancer (Meyerhardt *et al.*, 2006a; Meyerhardt *et al.*, 2006b; Wolin *et al.*, 2010). Meyerhardt *et al.* (2006a) reported that patients completing ≥18 METs·h·wk^{-1} of physical activity had a 61% reduction in risk of disease-specific mortality (HR = 0.39; 95% CI, 0.18-0.82) and a 57% decrease in risk of all-cause mortality (HR = 0.43; 95% CI, 0.25-0.74) compared to patients participating in <3 METs·h·wk^{-1}. They also showed the importance of

increasing physical activity upon cancer diagnosis with those who made the greatest increase in activity having the greatest reduction in mortality risk.

The evidence of benefits of physical activity after a prostate cancer diagnosis are limited to the findings of Richman *et al.* (2011) which reported that the risk of disease progression was inversely associated with walking pace. In a prospective study of physical activity after diagnosis in 1,455 men with localised prostate cancer, men who walked ≥3 hours per week at a brisk pace (≥3 mph) had their risk of disease progression reduced by 57% in comparison with men walking <3 hours per week at a less than brisk pace (<2 mph) independent of age, BMI and PSA at diagnosis (HR = 0.43; 95% CI, 0.21-0.91). No association was found between total walking duration or volume of non-vigorous activity and disease progression.

Furthermore, an individual's history of physical activity has been reported to influence prostate cancer mortality, although evidence supporting this association remains sparse. Reporting on data from 2,705 men in the Health Professional Follow-Up Study diagnosed with non-metastatic prostate cancer, Kenfield *et al.* (2011) showed that total physical activity was inversely associated with all-cause mortality in a dose-response fashion. Compared to men engaging in <3 METs·h·wk^{-1} of activity, they found HR of 0.8 (95% CI, 0.61-1.06) for 3 - <9 METs·h·wk^{-1}, 0.69 (95% CI, 0.53-0.90) for 9 - <24 METs·h·wk^{-1}, 0.65 (95% CI, 0.49-0.86) for 24 - <48 METs·h·wk^{-1} and 0.38 (95% CI, 0.27-0.53) for ≥48 METs·h·wk^{-1}. Furthermore, Kenfield *et al.* (2011) reported that prostate cancer specific mortality was associated with total physical activity. Durations of both non-vigorous and vigorous intensity activity were inversely linked to all-cause mortality, but only the amount of vigorous activity showed a statistically significant association with prostate cancer mortality (HR = 0.39; 95% CI, 0.18-0.84 for ≥3 h·wk^{-1} of vigorous activity compared to <1 h·wk^{-1}).

The findings of Kenfield *et al.* (2011) are supported by evidence from other studies which also reported a positive association between history of activity and prostate cancer progression or mortality (Giovannucci *et al.*, 2005; Giovannucci *et al.*, 2007), however, these authors were also drawing data

from men in the Health Professional Follow-Up Study and hence, these findings add little to the data presented by Kenfield and colleagues. Studies in other samples have reported no effect of physical activity on prostate cancer mortality (Crespo *et al.*, 2008).

6.1.1.4 Exercise studies in men on ADT

The evidence reviewed above shows the benefits that can be accrued through participation in regular physical activity. These data describe how increased physical activity can promote physical and mental benefits in disease-free populations and those with cardiovascular morbidities, in addition to leading to symptomatic benefits in cancer survivors. Furthermore, regular exercise has been shown to have an inverse, dose-response relationship to the risk of cardiovascular events or mortality for cancer-free individuals, while in cancer survivors, there is early evidence for benefits to disease recurrence or disease-specific mortality.

Considering the evidence reviewed above in the context of exercise training for men with prostate cancer on ADT has led to authors hypothesizing that in addition to providing the symptomatic relief for cancer survivors, exercise might also be able to reduce the burden of cardiovascular risk associated with treatment (Galvão *et al.*, 2009). This hypothesis currently remains largely unstudied however, with exercise studies completed in this population to-date (shown in Table 6.1) not using cardiovascular outcomes as primary end-points. Accordingly, this remains an area where further research is warranted.

Table 6.1, Exercise interventions in men with prostate cancer on androgen deprivation therapy

Researcher	Participants	Study design	Duration	Intervention	Main findings
Segal *et al.* (2003)	135 men on ADT (Duration ADT ≥3 months)	Randomized to RT (n = 74) or control (n = 61)	12 weeks	Training 3 x week with 9 exercises performed for 2 sets of 8-12 reps at 60-70% 1 RM. Resistance increased by 2.26 kg when > 12 reps can be performed.	Reduction in fatigue, increase in QoL and increas in upper and lower body muscular fitness with RT No changes in body composition.
Galvão *et al.* (2006)	10 men on ADT (Duration ADT ≥2 months)	Single group, repeated measures.	20 weeks	Progressive high intensity RT 2 x per week under supervision in groups of 1-4 people. Programme of 10-12 concentric and isotonic resistance exercises progressing from 2 sets at 12 RM to 4 sets at 6 RM.	Increase in muscular strength and endurance, functional capacity and quadriceps muscle thickness. No change in body fat mass or lean body mass.
Culos-Reed *et al.* (2007)	31 men on ADT	Single group, repeated measures.	12 weeks	Activity program including light RT and low intensity AT. Performed at home 3-5 x per week. Additional group based support every 2 weeks with 1 hour exercise session and behaviour change training to aid lifestyle intervention including goal setting, overcoming barriers, and relapse prevention.	Increase in leisure time physical activity, walk tes distance and post-test heart rate and RPE recovery. Improvements in QoL and fatigue. Increase in body mass and BMI at end-point.
Segal *et al.* (2009)	121 men on radiotherapy. 74 radiotherapy + ADT. 47 radiotherapy alone.	Randomized to RT (n = 40), AT (n = 40) or UC (n = 41).	24 weeks	RT: 3 x per week, 10 exercises at 60-70% 1 RM. AT: exercise on cycle ergometer, treadmill or elliptical 3 x per week at 50-75% VO_{2peak}.	Fatigue improved with RT and AT versus UC. Greater increase in body fat percentage with UC

Abbreviations. RT: Resistance training; AT: Aerobic training; UC: Usual care; RM: Repetition maximum (maximal amount lifted in specified number of repititions); VO_{2peak}: peak oxygen consumption; QoL: Quality of life

Table 6.1 continued....

Researcher	Participants	Study design	Duration	Intervention	Main findings
Galvão *et al.* (2010)	57 men on ADT (Duration ADT ≥2 months)	Randomized to exercise group (n = 29) or UC (n = 28).	12 weeks	Progressive RT and AT 2 x per week under supervision in groups of up to 5 people. RT progressed from 2-4 sets at 12 RM to 2-4 sets at 6 RM. AT included 15-20 minutes at 65-80% HR_{max}.	Training group had increase in lean mass, muscle strength, and physical function an improvements in QoL, fatigue and feelings of wellbeing. Decrease in C-reactive protein also found in exercise group. No change in body mass or body fat mass.
Culos-Reed *et al.* (2010)	100 men on ADT (Duration ADT ≥ 6 months)	Randomized to exercise group (n = 53) or UC (n = 47).	16 weeks	Activity program including light RT and low intensity AT. Performed at home 3-5 x per week and in group sessions 1 x per week. Behaviour change training to aid lifestyle intervention including goal setting, overcoming barriers, and role of nutrition.	Increase in leisure time activity score. Difference in neck and waist girth at end-point . No change in fatigue, QoL, or physical function.
Bourke *et al.* (2011)	50 men on ADT (Duration ADT ≥ 6 months)	Randomized to exercise group (n = 25) or UC (n = 25)	12 weeks	Three exercise sessions per week. Weeks 1-6: 2 supervised sessions and 1 home-based session per week. Weeks 7-12: 1 supervised session and 2 home-based sessions per week. Progressive AT and RT. Fortnightly dietary advice also given.	Improvement in walking capacity, lower limb muscular strength, exercise behaviou and fatigue . No change in QoL, body mas or BMI.
Nobes *et al.* (2012)	40 men starting ADT	Randomized to exercise plus metformin (n = 20) or usual care (n = 20)	6 months	Home based exercise plan to increase aerobic activity. Metformin dose of 850 mg per day, increased to 850 mg twice daily after two weeks.	Improvements in body mass, BMI and systolic blood pressure in intervention group.

Abbreviations. RT: Resistance training; AT: Aerobic training; UC: Usual care; RM: Repetition maximum (maximal amount lifted in specified number o repititions); VO_{2peak}: peak oxygen consumption; QoL: Quality of life

6.1.1.4.1 *Effects of exercise on fatigue and quality of life in men on ADT*

Reductions in fatigue have been reported after interventions using resistance training alone (Segal *et al.*, 2003), or in combination with aerobic training (Galvão *et al.*, 2010; Bourke *et al.*, 2011). In a randomized-controlled trial in which 155 men were assigned to receive 12 weeks of resistance exercise training three times per week (n = 82), or 12 weeks of usual care (n = 73), Segal *et al.* (2003) reported statistically significant improvements in fatigue in the exercise group. Similarly, Bourke *et al.* (2011) also reported improvements in fatigue over a 12 week intervention, with the magnitude of change exceeding that shown by Segal *et al.* (2003); studies can be compared due to use of the same measurement tool for fatigue. Using an exercise intervention including a mixture of aerobic and resistance exercises, in addition to providing dietary advice, Bourke *et al.* (2011) reported improvements in fatigue for the exercise group in comparison to little change for the men in the control group, with the difference between groups at the end of the intervention exceeding that required to be considered of clinical importance (Cella *et al.*, 2002).

Both Segal *et al.* (2003) and Bourke *et al.* (2011) also reported improvements in health related quality of life. Segal and colleagues reported a statistically significant difference between groups for quality of life measures with improvements in quality of life seen in men in the intervention group, while in the controls quality of life decreased. This pattern of change was similar to that shown by Bourke *et al.* (2011), who found small improvements in quality of life in the intervention group compared to a marked reduction in the controls, although in this study the difference between groups after the intervention was not found to be statistically significant.

It is worth noting that the study by Bourke *et al.* (2011) included a follow-up assessment 3 months after completion of the exercise intervention. Data for this assessment demonstrates that perceptions of both quality of life and fatigue got worse after cessation of the supervision, with follow-up values similar to those observed at baseline. Although the continued increase in perceptions of fatigue in the control group meant that the statistical

significance for the difference between groups was still observed, the mean difference in change between groups was markedly reduced.

6.1.1.4.2 *Effects of exercise on physical performance and functional capacity in men on ADT*

Measures of physical performance and functional capacity have consistently been shown to improve in men on ADT taking part in exercise training. Although comparison between studies is difficult because of the different measurement techniques employed to assess performance, improvements in walking test duration were shown in studies using predominantly gym based exercise (Galvão *et al.,* 2006; Galvão *et al.*, 2010; Bourke *et al.*, 2011) and those using mainly home-based exercise (Culos-Reed *et al.*, 2007). Moreover, there is evidence of improvements in muscular strength and muscular endurance in studies using resistance exercise alone (Segal *et al.,* 2003; Galvão *et al.,* 2006), or in combination with aerobic exercise training (Galvão *et al.*, 2010).

6.1.1.4.3 *Effects of exercise on body composition in men on ADT*

Positive changes in body composition (reduction in body fat mass and increased skeletal muscle mass) are a widely acknowledged effect of increasing exercise in healthy humans, however, there is little evidence of such changes in exercise studies with men on ADT. Segmental body composition analysis and girth measurements have identified small increases in upper and lower limb lean mass with exercise training using combined aerobic and resistance exercise (Galvão *et al.*, 2010) or resistance exercise alone (Galvão *et al.*, 2006), although no positive changes in body mass or BMI were reported. Benefits to both body mass and BMI were reported in the work of Nobes *et al.* (2012), however this study combined exercise training with Metformin and thus the benefits of increased activity cannot be distinguished from those resulting from Metformin therapy.

This evidence suggests that the negative effects of ADT on body composition cannot be easily overcome by increasing physical activity, however, regular exercise might reduce the increase in fat mass and reduction in muscle mass patients would have otherwise experienced. This is evident in the data presented by Culos-Reed *et al.* (2010), in which statistically significant changes in neck and waist girth were reported after 16 weeks of home and gym based exercises despite minimal improvement in these measures in the exercising group (intervention group change in neck girth = -0.36 ± 1.81 cm, change in waist girth = -0.53 ± 4.68 cm). Continued weight gain in the control group over the duration of the study was the primary factor accounting for the greater difference between groups at follow-up assessment (control group change in neck girth = 0.71 ± 1.77 cm, change in waist girth = 2.06 ± 4.84 cm).

6.1.1.4.4 *Exercise and cardiovascular health in men on ADT*

In addition to the data reviewed above there is little further evidence for a beneficial effect of exercise on cardiovascular health or markers of cardiovascular disease from exercise studies in men on ADT. The effects of exercise on blood pressure in this population have been under-reported, with only 2 study reporting pre and post intervention values (Culos-Reed *et al.*, 2010; Nobes *et al.*, 2012). Culos-Reed *et al.* (2010) did find a reduction in blood pressure in men taking part in the intervention, however this was of similar magnitude to the reduction in blood pressure observed in the control group, and hence no statistically significant difference between groups was found. Conversely, Nobes *et al.* (2012) found differences between groups from systolic blood pressure, but because participants were given Metformin with exercise the benefits of activity cannot be deduced.

Investigations of the effects of exercise on biomarkers for cardiovascular disease have shown little further benefit. No changes in insulin, glucose, HDL-C, LDL-C or triglycerides have been reported in exercise studies in men on ADT (Galvão *et al.*, 2010; Bourke *et al.*, 2011). It is noted however that the

finding of a statistically significant change in C-reactive protein (CRP) over the 12 week intervention of Galvão *et al.* (2010) provides encouraging evidence of improvements in cardiovascular health with exercise in this population. For men in the exercise group CRP decreased from 2.7 $mg \cdot l^{-1}$ at baseline to 1.8 $mg \cdot l^{-1}$ after 12 weeks, while the control group showed an increase from 2.3 $mg \cdot l^{-1}$ to 4.5 $mg \cdot l^{-1}$. As a marker of systemic inflammation, CRP concentrations have been regarded as a novel marker of cardiovascular health (Ridker, 2007), and as such, this finding is encouraging evidence of a beneficial effect of exercise training on cardiovascular health in men treated with ADT.

6.1.1.4.5 *Summary of exercise studies in men on ADT*

The evidence reviewed above describes how exercise studies in men on ADT have found improvements in physical performance and patient well-being, but little meaningful change in primary markers of cardiovascular risk. To-date cardiovascular health outcomes have not been primary outcome measures of any studies in this patient group however, and limited attention has been paid to the lack of change found in these measures. Currently, only one study has stated that participants were sedentary at baseline (Bourke *et al.*, 2011) meaning that the possible changes in cardiovascular health outcomes in other studies could have been diluted by the effects of the participants exercise history. Furthermore, although current evidence has not shown changes in traditional markers of cardiovascular risk, the effects of exercise training on novel markers, such as endothelial function, remain unstudied.

6.1.1.5 Exercise monitoring and prescription

For studies investigating the effects of physical activity, or those encouraging participants to increase their activity, being able to effectively monitor current

activity levels and prescribe safe and effective training regimes is very important.

6.1.1.5.1 *Exercise monitoring*

Assessment of the volume of activity individuals are participating in outside of a structured, supervised environment (e.g. home-based exercise) can provide a challenge for studies of current activity habits. Although there are a number of methods of measuring physical activity and energy expenditure, many of these can be limited by the need for technical or expensive equipment (Vanhees *et al.*, 2005). Vanhees *et al.* (2005) suggest that methods for assessment of physical activity can be grouped into three categories; criterion methods, objective methods and subjective methods. Criterion methods include doubly labelled water, indirect calorimetry and direct observations. These are considered the most accurate methods of activity measurement; however, they are limited by being inpractical, expensive and are demanding of the participant. Objective methods for physical activity assessment include activity monitors (e.g. pedometers, accelereometers) or heart rate monitoring. The data collected from such assessments can permit subsequent calculation of daily activity and energy expenditure with the measurements having the benefit of not being unduely obstrusive to the participant. Limitations of these methods can include the wide variation in heart rate due to confounding factors and the fact that basic accelerometers will not be able to distinguish between exercise intensities. Subjective techniques use physical activity activity questionnaires for activity assessment. These methods are quick and inexpensive to use, and tend to be the most popular method in large-scale studies (LaPorte *et al.*, 1985), however they can be limited by the participants interpretations of the questions and their perceptions of their activity.

6.1.1.5.2 *Exercise prescription*

In all exercise training studies the volume of activity participants undertake should be tailored to the individual, with consideration given to the aim of the training, the health status and phsyical abilities of the participant and the available equipment or facilities. The outcomes of such considerations can then be included in the use of the FITT principle for exercise training, which considers the frequency, intensity, time (or duration) and type (or mode) of exercise being prescribed. Guidelines have now been developed by different international bodies (e.g. American College of Sports Medicine (ACSM), British Association of Sports and Exercise Science, etc) to cater for manipulating these training principles to the needs of different populations (e.g. children, healthy adults, older adults, different diseased populations) (American College of Sports Medicine, 2013; British Association of Sport and Exercise Science, 2013; Exercise and Sports Science Australia, 2013), however the applications of such guidelines will still be dependent upon the individual needs and abilities of the participant.

The type, or mode, of exercise being prescribed will be dependent upon the aims of the training, the abilities of individual and the equipment available. For elderly populations, aerobic activities that do not impose undue orthopaedic stress are recommended in addition to resistance activities using weight training or weight bearing activities that will strengthen the major muscle groups (American College of Sports Medicine, 2009).

The American College of Sports Medicine (2009) suggest that the frequency and time (or duration) of aerobic activities prescribed will both be dependent upon the intensity of the activity, with lower frequency and duration recommended with higher intensity activity. When moderate intensity activity (defined as 3-6 METs) is being performed a minimum of 5 sessions per week are recommended, with activity performed for 30-60 minutes per day in bouts of at least 10 minutes to accumlate 150-300 minutes per week. For vigorous activity (>6 METs), a minimum of 3 sessions per week are suggested with exercise performed for 20-30 minutes per day to accumulate 75-100 minutes

per week. In addition, the same ACSM guidelines recommend resistance exercise should be performed on at least 2 days per week.

The American College of Sports Medicine (2009) define the intensity of activity prescribed for older adults on a 0-10 scale for rating of perceived exertion (RPE), stating that moderate activity would be considered an RPE of 5-6 while vigorous activity would be an RPE of 7-8. It must be noted however that RPE is only one of a number of metrics of intensity, with alternatives including percentages of maximal heart rate or heart rate reserve, percentages of maximal oxygen consumption or metabolic equivalent workloads (METs). Selection of the correct intensity metric is important as not all of these measures are suitable for all patient groups. In the case of a population of elderly men with established cardiovascular risk factors, such as men on ADT, limitations exist in some of these measures. Use of maximal testing is limited by the high physiological strain placed upon the participant increasing the risk of adverse events, and hence, measurement of maximal outcomes is unsuitable in such a population outside of a clinical setting (Gibbons *et al.*, 1997). Furthermore, the use of predicted maximal heart rates or heart rate zones can be limited by the widespread use of medications that will influence heart rate (e.g. Beta-blockers) (Herman *et al.*, 2009). Moreover, use of of METs to prescibe or predict exercise intensity has been shown to be limited by the assumption that resting metabolic rate will be the same for all individuals at a rate of oxygen consumption of 3.5 $ml \cdot kg^{-1} \cdot min^{-1}$. This figure, derived from the measurement of 1 man aged 40 years and weighing 70 kg, has been shown to not apply to all individuals (Byrne *et al.*, 2005), and thus predicting exercise intensity based upon this assumption is flawed. RPE can therefore provide a suitable measure for monitoring exercise intensity in this population which can avoid such physiological limitations and can be used during home-based activity when other methods for monitoring intensity maybe unavailable (Herman *et al.*, 2006).

6.1.2 *Diet*

As an adjunct to increasing physical activity, men on ADT should be encouraged to make modifications to their diet to achieve greater health benefits. While there is suggestion that diet might influence prostate cancer progression there is stronger evidence supporting the role for dietary manipulation in promoting improvements in cardiovascular health.

6.1.2.1 Diet and prostate cancer

Just as diet is thought to have a role in the development of prostate cancer (reviewed in 2.3.1 Prostate cancer risk factors), there is evidence that nutrients consumed post-diagnosis can affect the rate of disease progression. Lycopene has been possibly the most widely researched nutrient for its effects on prostate cancer. An antioxidant found most abundantly in tomatoes, lycopene consumption has been shown to be inversely related to disease progression with studies reporting lower PSA, reduced prostatic DNA damage and improved surgical outcomes in men consuming higher quantities of lycopene after diagnosis (Chen *et al.*, 2001; Kucuk *et al.*, 2002; Chan *et al.*, 2006). Evidence of similar effects with other nutrients is still sparse however. Although there are reports of lower rates of progression with low fat diets or diets high in fish or soy (Hussain *et al.*, 2003; Demark-Wahnefried *et al.*, 2004; Chan *et al.*, 2006) these studies have all been contradicted by others who describe no benefit from these diets (Lloyd *et al.*, 2010; Bosland *et al.*, 2013).

Similarly, evidence of nutrients increasing the risk of disease progression is equally limited. Prospective studies investigating diet post-diagnosis have reported negative effects of milk eggs and poultry with skin (Chan *et al.*, 2006; Richman *et al.*, 2010), however these findings are as yet unconfirmed. It is clear that further research is warranted in this area.

6.1.2.2 Diet and cardiovascular risk

Diet is an important modifiable risk factor for the development of cardiovascular disease. The nutrients contained within foods consumed can strongly influence glucose and cholesterol concentrations, blood pressure and obesity, and as such can be critical in the development of atherosclerotic lesions and the incidence of cardiovascular events.

Considering the important role of diet in the reduction of cardiovascular disease the latest American Heart Association guidelines on diet and lifestyle recommend a diet high in fruits and vegetables, whole-grains and high-fibre foods but with limited consumption of saturated fats and high sugar products (Table 6.2, Lichtenstein *et al.*, 2006). These recommendations of a healthy, well balanced diet still cover the main dietary components required for the maintenance of general health and the reduction of cardiovascular disease, and as such are in agreement with the dietary guidelines of the British Dietetic Association (Mead *et al.*, 2006).

Importantly, dietary guidelines recommend increased consumption of fruit and vegetables providing vital sources of antioxidants that are thought to be beneficial for reducing vascular inflammation. Acutely, consumption of foods high in antioxidants as part of a meal has been shown to prevent the negative effect dietary fats would have on the vascular endothelia (Esposito *et al.*, 2003). Chronic consumption of a diet high in antioxidants is considered to have further benefits as has been shown by positive health outcome achieved using a Mediterranean-style diet high in antioxidants, polyunsaturated fatty-acids and fibre. Benefits including improvements in body composition, vascular inflammation, insulin resistance and endothelial function have all been shown in patients following a Mediterranean style diet (Esposito *et al.*, 2010). Moreover, there is evidence of reduced risk of cardiovascular events and all-cause mortality in individuals maintaining a Mediterranean style diet (de Lorgeril *et al.*, 1999; Trichopoulou *et al.*, 2003). Although the exact mechanisms underlying these benefits remain incompletely understood it is thought the cumulative effect of improved body

composition, reduced cholesterol consumption and increased antioxidants are all involved.

Table 6.2. American Heart Association dietary recommendations for cardiovascular disease risk reduction. Taken from Lichtenstein *et al.* (2006).

- Balance calorie intake and physical activity to achieve or maintain healthy body weight
- Consume a diet rich in vegetables and fruits
- Chose whole-grain, high-fibre foods
- Consume fish, especially oily fish, at least twice a week
- Limit your intake of saturated fat to <7% of energy, trans fat to <1% of energy, and cholesterol to <300 mg per day by
    - choosing lean meats and vegetable alternatives
    - selecting fat-free, 1% fat and low-fat dairy products
    - minimizing intake of partially hydrogenated fats
- Minimize your intake of beverages and foods with added sugars
- Choose and prepare foods with little or no salt
- If you consume alcohol, do so with moderation

6.1.2.3 Dietary monitoring

Although it is widely accepted that dietary content is an important aspect of a healthy lifestyle (Lichtenstein *et al.*, 2006), there is little consensus opinion on the most appropriate methods for monitoring an individual's current diet. Available methods include food records (diet diaries), 24 hour or multiple pass recalls, food frequency questionnaires and household food surveys. Inherent in these techniques are weaknesses however, as bias in recording good and bad foods, detail on portion size and detail on food composition can be limitations to all methods.

The most appropriate method for use in a study can be dependent on the participant group being researched and the desired information required from the analysis (e.g. level of accuracy needed, food consumption of an individual or a household, time period of interest). In the case of working with an elderly population living in the community such issues are of importance and must be considered to ensure the most appropriate measures are used. In such a situation, the recall methods and

food frequency questionnaires are limited by the reliance on memory of foods previously consumed. Additionally, in an analysis of an individual participant's diet, the household food surveys are inappropriate due to not easily distinguishing the foods consumed by a specific individual in a household of multiple people (Thompson and Subar, 2013).

Accordingly, use of diet diaries can be considered one of the most appropriate methods for working with this population. Food diaries can provide detailed and relatively accurate data. Moreover, diet diaries can provide information on food consumption frequency which can be beneficial in intervention studies when assessment of eating habits is required (Thompson and Subar, 2013). This information can exceed that gained through food frequency questionnaires which can be limited by the number of foods listed and the lack of detail on the methods of food preparation or the timing of food consumption. Furthermore, dietary records can be more appropriate for monitoring diets over a longer period than can be achieved through recall. Previous studies have demonstrated that the results of food diaries are comparable to those achieved with other diet analysis techniques (Block, 1982; Brunner *et al.*, 2001).

6.2 Summary of data on lifestyle interventions

These data highlight the effects that physical activity and diet can have on cardiovascular health in the general population and on disease-specific end-points in men with prostate cancer. Although the evidence supporting a positive effect of exercise and diet on the general well-being of men treated with ADT continues to grow, as yet the consequences of such changes in lifestyle on cardiovascular health remain largely unstudied. Hence, further research investigating the effects of structured exercise training and dietary improvements on markers of cardiovascular health in men treated with ADT is clearly warranted. With the treatment of cardiovascular comorbidities of ADT estimated to have cost the NHS between £700 million and £2 billion from 2004-2007 (Bourke *et al.*, 2012), such lifestyle interventions could provide a cost-effective means of decreasing the financial burden that can only be expected to grow as the number of men living with prostate cancer continues to increase.

6.3 Study 2. The effects of supervised exercise training and dietary advice on markers of cardiovascular risk in men treated with androgen deprivation therapy for prostate cancer

Study research question, aims and hypotheses

In consideration of the evidence reviewed above the following research question was developed, along with the study aims and hypotheses.

Research question

Does a lifestyle intervention, including supervised exercise training and dietary advice, have benefits on markers of cardiovascular risk in men with prostate cancer treated with ADT?

Study aims

To examine if 12 weeks of supervised exercise training and dietary advice can have a benefit on markers of cardiovascular risk in men with prostate cancer treated with ADT.

To examine if 12 weeks of supervised exercise training and dietary advice can improve physical fitness and general well-being in men with prostate cancer treated with ADT

To examine if any changes made over 12 weeks of supervised exercise training and dietary advice are maintained over a 12 week period after the supervision is completed.

Null hypotheses

There is no difference in markers of cardiovascular risk in men with prostate cancer treated with ADT after 12 weeks of supervised exercise training and dietary advice compared with 12 weeks of usual care

There is no difference in physical fitness and general well-being in men with prostate cancer treated with ADT after 12 weeks of supervised exercise training and dietary advice compared with 12 weeks of usual care

Twelve weeks after removal of supervision there will be no difference in measures of cardiovascular risk, physical fitness or general well-being in comparison with those observed after 12 weeks of supervised exercise training

Experimental hypotheses

There is a difference in markers of cardiovascular risk in men with prostate cancer treated with ADT after 12 weeks of supervised exercise training and dietary advice compared with 12 weeks of usual care

There is difference in physical fitness and general well-being in men with prostate cancer treated with ADT after 12 weeks of supervised exercise training and dietary advice compared with 12 weeks of usual care

Twelve weeks after removal of supervision there will be differences in measures of cardiovascular risk, physical fitness or general well-being in comparison with those observed after 12 weeks of supervised exercise training

7.0 METHODS: Study 2

7.1 Study design

This study used a mixed design with participants randomly allocated to receive either 12 weeks of exercise training and dietary advice, or 12 weeks of usual care. Repeat assessments were performed after 6 weeks (mid-point assessment) and 12 weeks of the intervention (end-point assessment) and at a follow-up 12 weeks after the end-point assessment (follow-up assessment). The patient pathway through the study is shown in Figure 7.1.

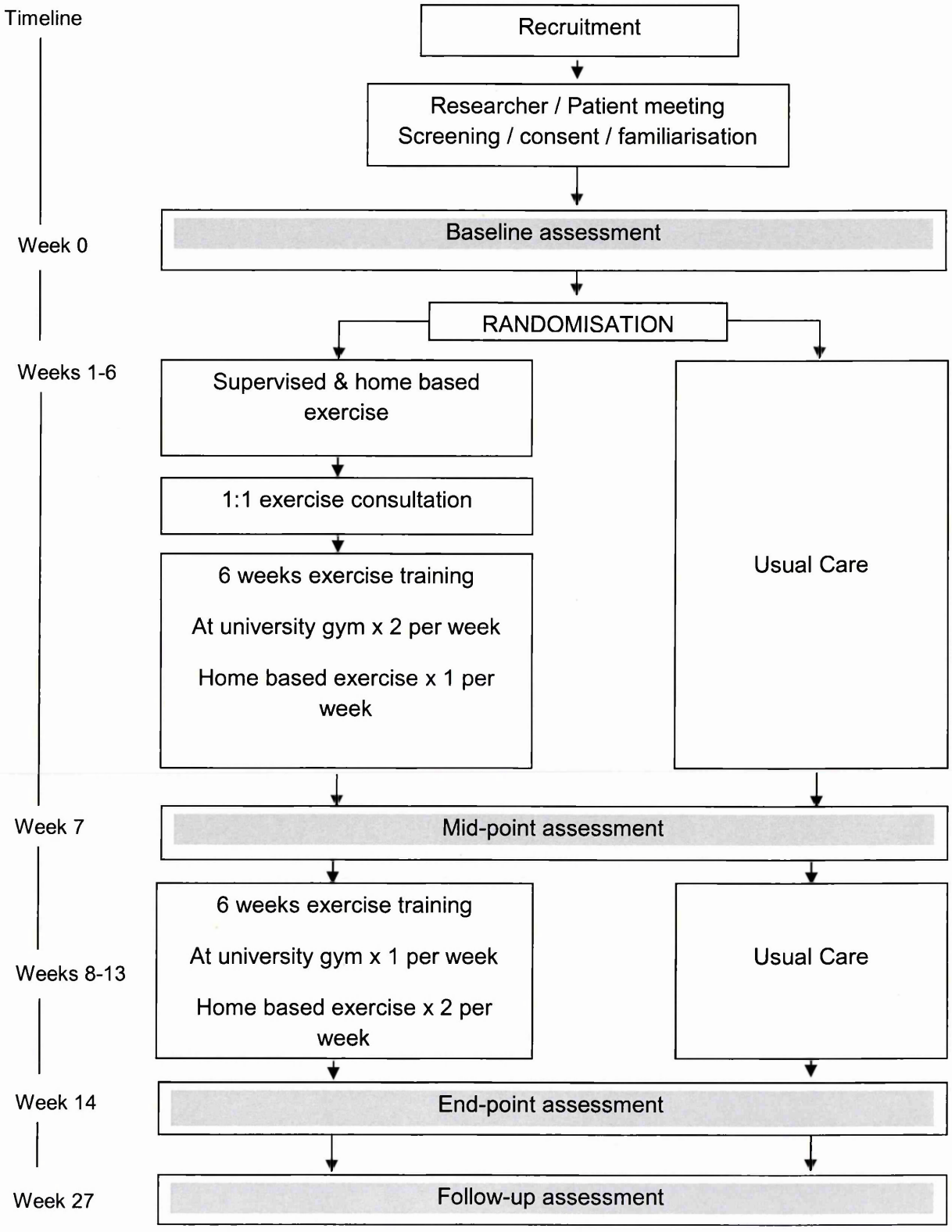


Figure 7.1. Patient pathway through exercise intervention study.

7.2 Ethics

Ethics approval was granted by the Yorkshire and Humber Research Ethics Committee for all procedures being carried out with men with prostate cancer recruited from within Sheffield Teaching Hospitals (appendix 2). To ensure compliance with regional policy the study was also registered with the Sheffield Teaching Hospitals Research and Development department. Procedures for this study all conformed with the Declaration of Helsinki.

7.3 Sample size calculation

Fifty men were recruited for this study and randomly allocated using the nQuery statistical software (nQuery Advisor 6.01, nQuery Statistical Solution, USA) into 2 groups of 25 men. Recruitment of this number of participants was calculated as being sufficient to detect an absolute difference in relative FMD between groups after training of 2.6 ± 3.0%, which is of similar magnitude to that previously reported in exercise studies in elderly patients at increased cardiovascular risk (Gokce *et al.*, 2002; Edwards *et al.*, 2004). This sample size estimate also took account of a drop-out rate of 10% which has been seen in gym-based exercise studies with men on ADT (Segal *et al.*, 2003; Galvão *et al.*, 2006; Galvão *et al.*, 2010; Bourke *et al.*, 2011). Sample size was determined using the nQuery statistical software using 80% power at an alpha level of 0.05.

7.4 Participant recruitment

Men with prostate cancer being treated with ADT were identified from outpatient clinics at the Royal Hallamshire Hospital or Weston Park Hospital, Sheffield, UK. Online clinic letters and blood tests results were used for initial screening of patients for inclusion and exclusion criteria. In men considered suitable, further screening was subsequently performed using patient medical notes which were either seen when patients visited clinic or were requested for viewing through the medical records department. Patients still considered

eligible to participate were then approached in clinic or sent a letter inviting them to participate in the study (copy of letter in appendix 8). Men seen in clinic who showed interest in participating were provided with a participant information sheet and given a minimum of 5 days to consider whether they chose to take part prior to being contacted by a study researcher (copy of participant information sheet in appendix 9). Men contacted through the post were sent copies of the participant information sheet and asked to contact the research team if they were interested in participating. Data for the recruitment of men with prostate cancer is displayed in the consort diagram (Figure 7.2).

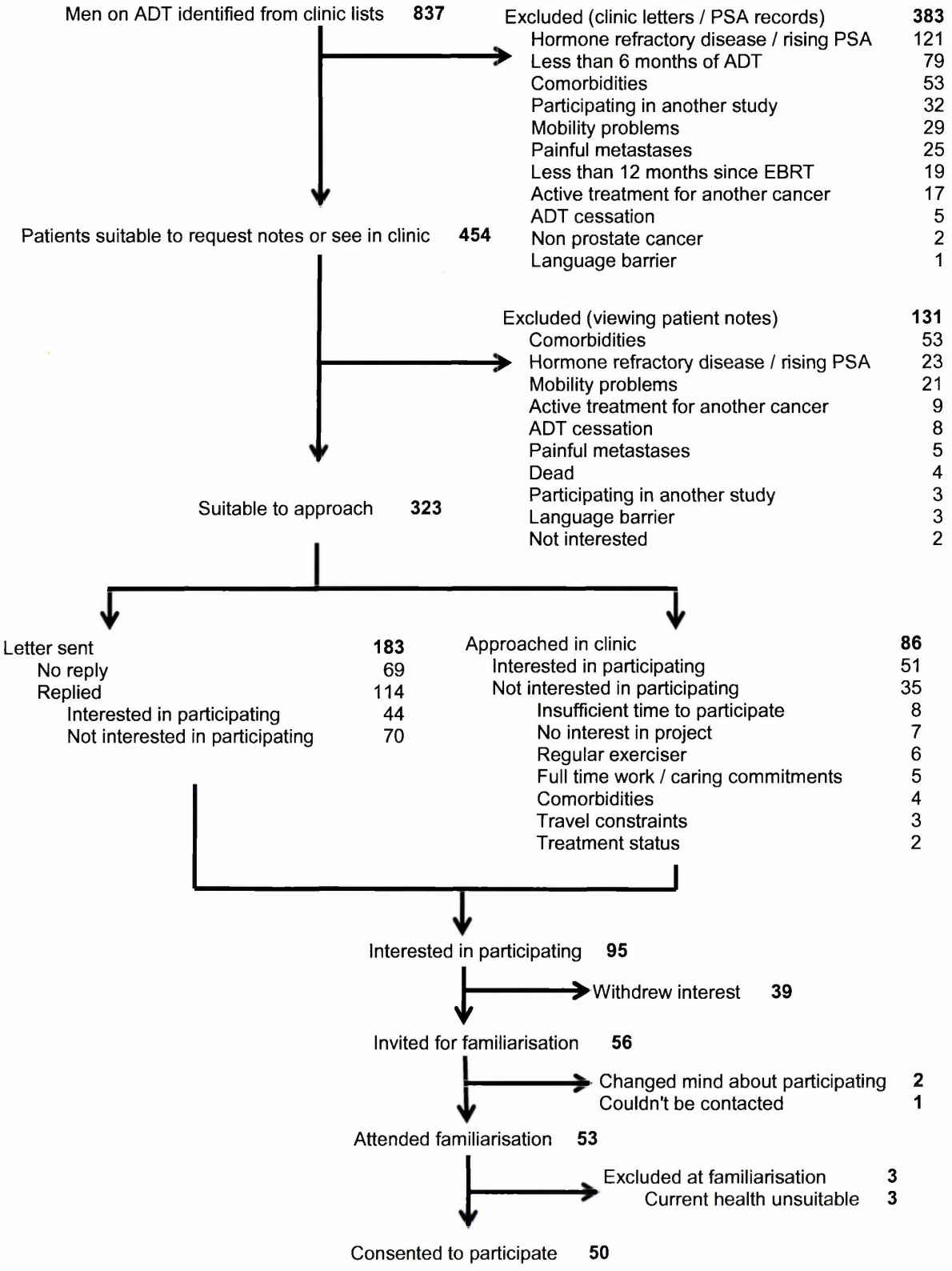


Figure 7.2. Consort diagram for the recruitment of men with prostate cancer treated with ADT.

After screening for inclusion and exclusion criteria only 38% of men identified on ADT were suitable to approach. The recruitment rate of all men approached (n = 269) was 18.6%. Although a greater number of men approached in clinic showed interest in taking part (60% of men approached requested further information compared to 24% of men sent letters), the percentage of men consenting to participate was the same for both techniques (18.6% of men approached by post or in person consented, n = 34 and n = 16, respectively).

Men showing interest in participating in the study were invited into the university to meet a member of the research team to gain more details about the project, complete a medical questionnaire and provide informed consent (appendix 5 and 10, respectively). This initial visit also provided an opportunity to familiarise participants with the research facility and introduce them to all techniques to be used throughout the study.

7.5 Inclusion and exclusion criteria

Criteria for patients being included in the study:

- Histologically confirmed advanced prostate cancer, at least stage T3 N0 M0
- Been in receipt of ADT for a minimum of 6 months and due to receive for at least the next 6 months
- Current stable disease; defined as PSA <5 $ng.ml^{-1}$ or three consecutive decreasing PSA readings
- Able to provide signed informed consent

Criteria for patients being excluded from the study:

- Current participation in regular physical activity meeting the minimum guidelines for older adults described by the American College of Sports Medicine (2009), defined as moderate intensity activity for 30

minutes at least 3 times per week, or vigorous activity for 20 minutes at least 3 times per week for the last 6 months

- Painful bony metastases
- Less than 12 months since completion of radiotherapy
- Having ever received chemotherapy
- Less than 2 months post-surgical treatment
- Unstable angina, uncontrolled hypertension, recent myocardial infarction or pacemaker
- History of sudden onset shortness of breath, blurred vision or fainting spells
- Any physical, neurological or psychiatric impairment or disease such as dementia, multiple sclerosis, severe arthritis or other condition that would limit the ability to understand and complete the study exercises, complete the required questionnaires or recall and record dietary information

7.6 Intervention

The intervention was designed to be the same as that used in previous research with men on ADT (Bourke *et al.*, 2011). That study demonstrated the efficacy of this intervention with improvements in patient wellbeing and physical function detected over a 12 week period. Using this intervention in the current study therefore allowed investigation of whether changes in cardiovascular health were also present in an intervention proven to be well tolerated by this patient group. The aim of the intervention was to encourage participants to make healthy lifestyle changes, focussing primarily on increasing their physical activity and improving their diet.

The exercise training element of the intervention involved participants being asked to take part in supervised gym-based exercise sessions, in addition to being encouraged to increase the amount of physical activity they performed at home. All gym sessions took place in the purpose-built exercise facility in the Centre for Sport and Exercise Science, Sheffield Hallam University, UK, where sessions were conducted in small groups of 1-4 men supervised by an exercise instructor. Gym sessions were tailored to each participant's ability and were designed to be progressive in nature with the volume and intensity of exercise gradually increased over the 12-week course as the patient became able to perform greater workloads in accordance with the guidelines for exercise prescription for cancer survivors published by the American College of Sports Medicine (Schmitz *et al.*, 2010). Each session lasted approximately 1 hour and consisted of a mixture of aerobic, resistance and balance exercises. Sessions commenced with a 10 minute warm-up, including gentle treadmill walking and mobility exercises, prior to participants completing up to 30 minutes of aerobic exercises. Aerobic activities included treadmill walking, upright or recumbent cycling, rowing and arm-cranking. All activities were performed on Life Fitness equipment (Life Fitness UK, Ely, UK), with the exception of rowing (Concept 2 rowing ergometer, Concept 2, Nottingham, UK) and arm-cranking (Pro 2 Total Body Exerciser, SciFit, Binfield, UK). Exercise intensity was prescribed to elicit a heart rate of 55-85% of age-predicted maximum, and/or an RPE (6-20 scale Borg scale; Borg, 1970) of 12-16. Age-predicted maximum heart rate was calculated using the equation:

$$\text{Heart rate maximum} = 220 - \text{age}$$

Participants subsequently completed up to 15 minutes of resistance and balance exercises. Resistance training focused on exercising all major muscle groups using body weight or thera-band for resistance. Participants completed 2 sets of 8-12 repetitions for each exercise. Sessions were concluded with a 5 minute cool-down including static-stretching to improve muscular flexibility. Participant heart rate (Polar F4, Polar Electro, Kempele, Finland) and RPE, were recorded every 5 minutes during aerobic activities.

Prior to commencing exercise training participants attended a 1:1 induction with the gym instructor for guidance on use of exercise equipment and to allow calculation of initial exercise training intensities. Participants were subsequently asked to perform 3 exercise sessions per week for the duration of the 12 week intervention. Through weeks 1-6 participants undertook 2 supervised gym-based sessions per week in addition to performing 1 session per week at home, while for weeks 7-12 participants performed only 1 supervised session in the gym each week, but increased the exercise at home to twice per week. Asking patients to maintain 3 sessions per week, while decreasing the time spent in instructor led sessions, was designed to encourage greater independence in their exercise habits. Participants were given advice on exercising at home including how to use RPE to monitor their exercise intensity. Participants were encouraged to perform at least 30 minutes of exercise each week at an intensity between 11 ('Fairly light') and 15 ('Hard') on the 6-20 Borg scale. A log sheet was provided to each participant for them to record home-based exercise (appendix 11).

In addition to engaging with exercise training, participants were encouraged to improve their diet over the course of the intervention. Participants were given advice on healthy eating when they attended exercise sessions with the main aims being; reduce dietary fat intake to ~25% of total calories, consume at least 5 portions of fruit and vegetables each day, increase fibre consumption, decrease intake of refined carbohydrates, and limit alcohol intake to moderate amounts (defined as 1-2 units per day by British Heart Foundation, 2013). Participants were helped to think of areas of their diet they would like to improve and encouraged to set themselves weekly goals towards achieving these targets. Participants completed 3-day diet diaries at baseline assessment which allowed additional feedback to be given which was tailored to their current diet (copy of diet diary provided in appendix 12).

7.7 Outcome measures

Assessments were completed over two sessions held in the exercise physiology laboratories of the Centre for Sport and Exercise Science, Sheffield Hallam University. The first assessment session included body composition measures, vascular function assessments and blood samples, while at the second session participants completed questionnaires and performed physical function and exercise tolerance tests. Participants were asked to attend the first session in the fasted state having refrained from the consumption of food or beverages (except water) for at least 8 hours, and having avoided tobacco products for at least 12 hours. These sessions were undertaken in the morning in order to minimise the impact of fasting on participants' daily routine. The second assessment session was completed at any time of day most convenient for the participant. Where possible, participants were encouraged to attend assessments at the same time of day for each time point during the study to minimise circadian variations in outcome measures. Participants were asked to refrain from taking part in any strenuous physical activity for at least 12 hours prior to both assessment sessions. Where possible, participants were also asked to refrain from consumption of any vasoactive medications for the 12 hours prior to attending the vascular function assessment.

7.7.1 *Assessments of vascular function*

Vascular function assessments were conducted in a similar manner as previously described in section 1 of this thesis (3.6.1 Assessment of vascular function), with the addition of proximal cuff FMD assessments after the distal cuff FMD test and prior to the GTN scan.

7.7.1.1 Distal cuff FMD assessment

FMD using a distal cuff placement was performed using the same methods as described in section 1 (3.6.1.1 Endothelial-dependent dilatation). Use of a distal cuff placement provided a measure of NO-dependent arterial dilatation.

7.7.1.2 Proximal cuff FMD assessment

Endothelium-dependent dilatation was also assessed using proximal cuff placement. This method of FMD assessment has previously been used in other populations for the assessment of cardiovascular health (Shimbo *et al.*, 2007; Shechter *et al.*, 2009), however, controversy still remains over the validity of this technique (Charakida *et al.*, 2010). Comparison of traditional distal-cuff placement or proximal cuff placement techniques has not previously been performed in men treated with ADT for prostate cancer.

Placement of the occluding cuff proximal to the site of arterial imaging provides an alternative measure of endothelium-dependent dilatation not principally mediated by NO. Participants were given 15 minutes to rest quietly following completion of the distal cuff FMD assessment prior to commencing image acquisition for the proximal cuff test. Resting for this duration between scans was deemed sufficient for arterial tone to return to basal levels and equalled or exceeded the time given in other studies (Guazzi *et al.*, 2004; Tinken *et al.*, 2008). During this period between assessments the cuff was repositioned in the middle of the upper arm with ultrasound imaging subsequently performed distal to the site of cuff placement. Arterial occlusion was performed inflating the cuff to 50 mm Hg above systolic blood pressure with occlusion maintained for 5 minutes. Arterial dilatation was measured as the difference between arterial diameter during the minute of baseline imaging prior to cuff inflation and the peak arterial diameter achieved during the 3 minutes of imaging post cuff release.

7.7.1.3 Endothelial-independent dilatation

Endothelial-independent assessments were performed in all patients in whom GTN administration was not contraindicated. Contraindications were defined in accordance with the guidelines of the British National Formulary (2006), and included: hypersensitivity to nitrates, hypotensive, hypovolaemia, mitral stenosis, marked anaemia, history of migraines, hypothyroidism, recent history of myocardial infarction, severe hepatic or renal impairment, or current use of specific medications for erectile dysfunction (Cialis, Viagra, Levitra), pulmonary hypertension (Adcirca), angina (Isosorbide mononitrate) or hypertension (Candersartan, Losartan, Valsartan, Irbesartan, Telmisartan, Eprosartan, Olmesartan, Enalapril, Lisinopril, Benazepril). Participants were given 15 minutes to rest quietly following completion of endothelial-dependent assessments to ensure recovery of baseline arterial diameter prior to commencing image acquisition. The method for GTN assessments were the same as previously described (3.6.1.2 Endothelial-independent dilatation).

7.7.1.4 Ultrasound analysis

Methods for data capture and analysis of ultrasound assessments were the same as previously described for section 1 in this thesis (3.6.1.3 Ultrasound analysis). Differences between studies were evident in blinding of assessments however. Baseline assessments were analysed as part of the cross-sectional analysis of endothelial function (study 1 in this thesis) with all analyses performed by the principal researcher after the video files had been re-coded by a researcher external to the research team to ensure blinding of participant identity. All subsequent scans were analysed in full by a researcher external to the research team who was blinded to participant group allocation.

7.7.2 *Anthropometry*

Participant stature and body mass were measured using the same techniques as previously described in section 1 (3.6.2 Anthropometry). Similarly, body composition was also assessed using the same technique as previously described (Inbody 720) which has been shown to be an acceptable method for tracking changes in body composition over time (Völgyi *et al.*, 2008; Miyatake *et al.*, 2009).

7.7.3 *Questionnaires*

Disease-specific quality of life (Functional assessment of cancer therapy-prostate, Fact-P; Esper *et al.*, 1995), fatigue (Functional assessment of cancer therapy- fatigue, Fact-F; Yellen *et al.*, 1997) and leisure time physical activity (Godin LSI; Godin and Shephard, 1985) were all assessed through completion of questionnaires. Participants were given time to complete the questionnaires without interference from the study researcher. Responses were subsequently checked for completeness by the researcher in the presence of the participant.

Fact-P is a valid tool for assessment of quality of life in men undergoing therapy for prostate cancer (Esper *et al.*, 1997). This tool uses a 39 item questionnaire with 27 questions on general wellbeing and 12 questions on additional concerns specific to prostate cancer and its treatment (appendix 13). Scores can range from 0-156, with higher scores equating to a better quality of life. Fact-P has previously been used to assess changes in disease-specific quality of life over the course of exercise interventions in men treated with ADT (Segal *et al.*, 2003; Bourke *et al.*, 2011). A 6-point change in Fact-P has been considered the MCID (Cella *et al.*, 2009).

Fatigue was assessed using the 13 item Fact-F questionnaire (appendix 14). Scores ranged from 0-52, with higher scores indicating less fatigue. Fact-F has been shown to have good test-retest reliability (r = 0.90) and internal consistency (alphas 0.93 and 0.95; Yellen *et al.*, 1997). Cella *et al.* (2002)

calculated the MCID for Fact-F as a change of 3 points. Fact-F was previously used to assess changes in fatigue over the duration of exercise interventions in men with prostate cancer treated with ADT (Segal *et al.*, 2003; Bourke *et al.*, 2011).

The volume of physical activity participants completed in their leisure time was quantified using the Godin LSI. Participants were asked to report the number of times they performed more than 15 minutes of strenuous, moderate and mild exercise in an average week. The total leisure score index was subsequently calculated using the equation previously described (3.4 Participant recruitment).

The Godin LSI has previously been assessed for reliability and validity through analysis of repeated measures and comparisons against established physiological techniques. In studies using adult participants, reliability over 2 weeks or 1 month varied across the different activity intensity levels of the Godin LSI. Correlation coefficients of 0.84-0.94 were reported for strenuous exercise, 0.36-0.46 for moderate exercise and 0.24-0.48 for mild exercise. Subsequently, total LSI showed a correlation coefficient of 0.62-0.74 (Godin and Shephard, 1985; Jacobs *et al.*, 1993). Assessments of validity have shown similar variation, with the Godin LSI demonstrating concurrent validity coefficients of 0.32 with accelerometry, 0.56 with maximal oxygen consumption measured using expired gases, and -0.43 with percent body fat measured by hydrostatic weighing (Jacobs *et al.*, 1993).

The use of Godin LSI in previous studies investigating physical activity in men treated with ADT demonstrates that this tool can be successfully applied to men in this population (Culos-Reed *et al.*, 2007; Culos-Reed *et al.*, 2010, Bourke *et al.*, 2011). Moreover, use of this tool in the current study allows comparison of results between studies.

7.7.4 *Exercise tolerance and functional capacity*

Exercise tolerance was assessed with a sub-maximal walking test performed on a treadmill (H/P/ Cosmos Pulsar Treadmill, Traunstein, Germany) using the BSU/Bruce protocol (Kaminskey and Whaley, 1998). This protocol was used in the study by Bourke *et al.* (2011) with no adverse events reported, and thus its use in the current study allowed comparison between studies. The BSU/Bruce protocol achieves identical intensities at 3 minute intervals as the traditional Bruce protocol but uses smaller and more frequent increments in speed and gradient making a smoother ramping of intensity. Participants were given time walking on a treadmill prior to undertaking the test to allow them to become comfortable with treadmill use. Additionally, prior to commencing testing a chest-strap heart rate monitor was fitted and participants were familiarised with the 6-20 Borg scale. During testing heart rate and RPE were recorded at the end of every minute of exercise with the test terminated when participants achieved an RPE of 15 ('Hard') or earlier if the participant requested to stop. All tests were supervised by exercise physiologists external to the research team ensuring participant performance was not influenced by researcher bias.

The 30-second sit-to-stand test was used for assessment of functional capacity. The test was conducted in accordance with the guidelines described by Rikli and Jones (1999). Participants commenced the test with their feet flat on the floor in front of the chair and arms across their chest. The same chair was used for all tests with the back positioned against the wall to minimise the risk of the chair falling during the assessment. Participants were encouraged to have three practice stands prior to commencing the test to ensure correct technique was used.

7.7.5 *Dietary analysis*

Participants completed 3-day diet diaries at baseline, end-point and at the follow-up assessment. Where possible, participants were asked to use the same three days of the week for each assessment. Nutritional intake was

analysed using the NetWisp diet analysis software (version 3.0, Tinuviel Software, Anglesey, UK) with differences in energy intake and macronutrient content examined between time-points. Inputting diet diaries into NetWisp was completed by 2 pairs of researchers external to the research team who were blinded to the participant's group allocation to avoid potential bias in analysis. Disagreement between groups was resolved by consensus opinion.

7.7.6 *Blood markers*

Capillary and venous bloods were sampled from all participants at baseline and end-point. Capillary blood was collected from a finger-prick performed on the middle finger of the left hand for immediate assessment of haemoglobin concentrations. Blood samples (10 µL) were collected on microcuvettes (B-Hemoglobin microcuvettes, HemoCue, Ängelholm, Sweden) prior to analysis using a Haemoglobin Photometer (HemoCue, Ängelholm, Sweden).

Venous blood (20 ml) was drawn from the antecubital vein using standard phlebotomy techniques. Whole blood samples were centrifuged at 3000 rpm for 8 minutes (Heraeus Labofuge 400R, DJB Labcare Ltd, Buckinghamshire, UK) for separation of plasma and serum, which was collected into 3 ml Eppindorf tubes and subsequently frozen at - 80°C (Sanyo VIP-series Ultra Low Temperature Freezer, Sanyo Biomedical, Wood Dale, IL, USA). Batch analyses of samples were carried out in the Department of Clinical Chemistry at the Royal Hallamshire Hospital, Sheffield, UK, using the Cobas 8000 Modular Analyser (Roche Diagnostics, Basel, Switzerland). Samples were analysed for PSA, male sex hormones (testosterone, SHBG) and blood lipid profile (total cholesterol, HDL-C, LDL-C and triglycerides). In addition, free androgen index was calculated using the equation:

$$\text{Free androgen index} = 100 * (\text{testosterone} / \text{SHBG})$$

Free testosterone and bioavailable testosterone were calculated in accordance with the equations proposed by Vermeulen *et al.* (1999) using

the online calculator provided by the International Society for the Aging Male (2013).

7.8 Statistical analyses

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) for Windows (v 19.0.0, IBM inc, NY, USA). Variation between groups for frequency data were examined using Pearson's Chi squared test. Differences in group means at baseline were examined using an independent groups t-test or the Mann Witney-U test after assessments of the distribution of data were completed using the Shapiro-Wilk test. Subsequently, tests of normality of distribution were also performed for complete data sets to be analysed for group and time interactions. Variables found to not be normally distributed were log transformed prior to analysis. Missing data were imputed using an intention-to-treat approach (Gravel *et al.*, 2007). In accordance with the suggestions of Engels and Diehr, (2003) data for participants dropping out of the study was dealt with using the 'last observation carried forward' method where the change over time was assumed to be zero.

Time by group interactions and main effects of time were assessed using mixed-model factorial analysis of variance (ANOVA) or, if there was a statistically significant difference between groups at baseline, mixed-model factorial analysis of covariance (ANCOVA) with baseline included as a covariate. Differences between groups over the 12 weeks of the intervention were assessed using a group by time design with baseline, mid-point and end-point data included as time points. Additionally, differences between groups from baseline to follow-up were assessed with follow-up data also included as a time point in the analysis. Where statistically significant main effects of time were present post-hoc analysis was performed using one-way ANOVA to examine the differences between time points within group. Effect sizes were calculated for variation between groups for the difference from baseline measures using the equations shown in section 1 (3.7 Statistical

analyses). Thresholds were set at 0.2 for a small effect, 0.5 for a medium effect and 0.8 for a large effect (Cohen, 1992). Mean difference between groups in the change (Δ) observed between time-points were also reported. Difference in Δ was calculated as:

Mean difference in Δ = Δ from baseline in the intervention group - Δ from baseline in control group.

A positive score indicated a greater change from baseline in the intervention group and a negative score indicated in greater change from baseline in the controls. In addition 95% confidence intervals (95% CI) were also reported for the difference in Δ.

Relationships between the change in outcome measures from baseline to end-point and the change in exercise tolerance, quality of life and FMD over the same duration, were examined using correlation analysis. In cases where both variables were normally distributed, Pearsons bivariate correlation coefficient was used; however if one or more variables did not achieve normal distribution, Spearmans rank correlation was employed. Correlation coefficients <0.35 were considered weak, 0.36-0.67 moderate, 0.68-0.89 high and ≥0.9 very high (Taylor, 1990). In addition, linear regression was performed to investigate if the change in key outcome measures (arterial dilatation, quality of life and fatigue) from baseline to end-point could be predicted by the change in selected independent variables over the same duration, or the baseline values of the same independent variables. To examine predictors of the change in arterial dilatation ($\log_n$ peak - $\log_n$ baseline), body fat mass, mean arterial pressure, triglyceride concentrations and exercise tolerance were included as independent variables. Predictors of the change in quality of life and fatigue were also examined, with exercise tolerance, body fat mass, mean arterial pressure and haemoglobin concentrations included as independent variables for both.

Data are presented as mean ± SD unless stated. P-values are displayed for time x group interactions unless otherwise stated. Statistical significance was set as $P < 0.05$.

7.9 Reliability of measures

Outcome measures not assessed for reliability during study 1 (treadmill test duration, 30-second sit to stand test) were examined in a group of 7 men (69 ± 4 years of age) who were asked to attend a second assessment session within 7 days of their baseline assessment. Testing procedures were standardized between the two trials, and where possible, participants were asked to attend the second session at the same time of day as they had attended the first.

Reliability data for exercise capacity and functional capacity assessments is presented in Table 7.1. ICC for these measures shows excellent reliability over a 7 day period (Cicchetti, 2000). This level of reliability matches or exceeds that previously reported for assessment of physical capacity in different patient groups (Minor and Johnson, 1996; Labs *et al.*, 1999; Dobrovolny *et al.*, 2003).

Table 7.1. Reliability statistics for exercise capacity and functional capacity assessments.

Outcome measure	Trial 1	Trial 2	SEM	rTEM (%)	CV (%)	ICC
Treadmill test duration (s)	445 (61)	446 (62)	6.01	0.65	0.95	0.99
Treadmill test final heart rate (beats·min^{-1})	132 (24)	135 (20)	3.15	4.33	2.30	0.98
30 second sit to stand test (repetitions)	11 (3)	11 (3)	0.36	7.81	3.19	0.98

Abbreviations. CV: Coefficient of variation, ICC: Intraclass correlation coefficient, rTEM: Relative technical error of measurement, SEM: Standard error of measurement. Data for trials stated as mean (SD).

8.0 RESULTS: Study 2

8.1 Participant demographic details

Demographic details are displayed in Table 8.1. There were no differences between groups for current or previous treatments received for prostate cancer (P >0.05). All participants were actively being treated with LHRH-agonists alone, or in addition to anti-androgen therapy (Bicalutamide). Groups were well matched for age, history of cardiovascular events and current medications (P >0.05). There was little difference between groups for current or previous smoking status (P >0.05). There were no statistically significant differences between groups at baseline for any outcome measures (P >0.05).

Table 8.1. Intervention study demographic details: data displayed as count within group (% of group) unless otherwise stated.

	Intervention (n =25)	Control (n =25)	P
Age: years, Mean (SD)	70 (5)	70 (9)	0.895
Treatment details			
LHRH agonist alone	25 (100)	23 (92)	0.149
LHRH agonist + anti-androgen	0	2 (8)	0.149
Months on ADT: Median (range)	19 (6-138)	18 (6-92)	0.454
Previous EBRT	7 (28)	13 (52)	0.083
Months since EBRT completion: Median (range)	17 (12-95)	20 (12-140)	0.550
Previous radical prostatectomy	1 (4)	3 (12)	0.297
Health history			
Previous myocardial infarction	2 (8)	2 (8)	1.000
Previous stroke	0	3 (12)	0.074
Arterial disease / angina	3 (12)	2 (8)	0.637
Diabetes Mellitus	3 (12)	4 (16)	0.684
Hypertension	16 (64)	11 (44)	0.156
Hypertension diagnosed since ADT commencement	3 (12)	2 (8)	0.637
Medication			
Statin therapy	14 (56)	13 (52)	0.777
Beta blockers	8 (32)	6 (24)	0.529
Aspirin	8 (32)	8 (32)	1.000
Calcium channel blockers	12 (48)	4 (16)	0.015
ACE inhibitors	9 (36)	8 (32)	0.765
Diuretics	4 (16)	6 (24)	0.480
Angiotensin-II inhibitors	3 (12)	3 (12)	1.000
Prostaglandin analogues	7 (28)	6 (24)	0.747
Anti-coagulant therapy	2 (8)	1 (4)	0.552
Anti-diabetic medication	3 (12)	3 (12)	1.000
Lifestyle			
Current smoker	1 (4)	0	0.312
Previous smoker	12 (48)	11 (44)	0.777
Full time / part time employment	4 (16)	5 (20)	0.713
Ethnicity			
White British	25 (100)	22 (88)	0.074
Asian Indian	0	2 (8)	0.149
Black African	0	1 (4)	0.312

Abbreviations: ADT: Androgen deprivation therapy, EBRT: External beam radiotherapy, LHRH: Luteinizing hormone-releasing hormone

8.2 Compliance and attrition

Fifty men completed baseline assessments and were randomised to the intervention or control group. At end-point assessment 16% of the sample (8 men) had withdrawn from the study. An additional 2 men (4% of the initial sample) were lost to follow-up. Four men in the control group missed the mid-point assessment but returned to complete subsequent assessments. A flow diagram detailing patient attrition rates is shown in Figure 8.1.

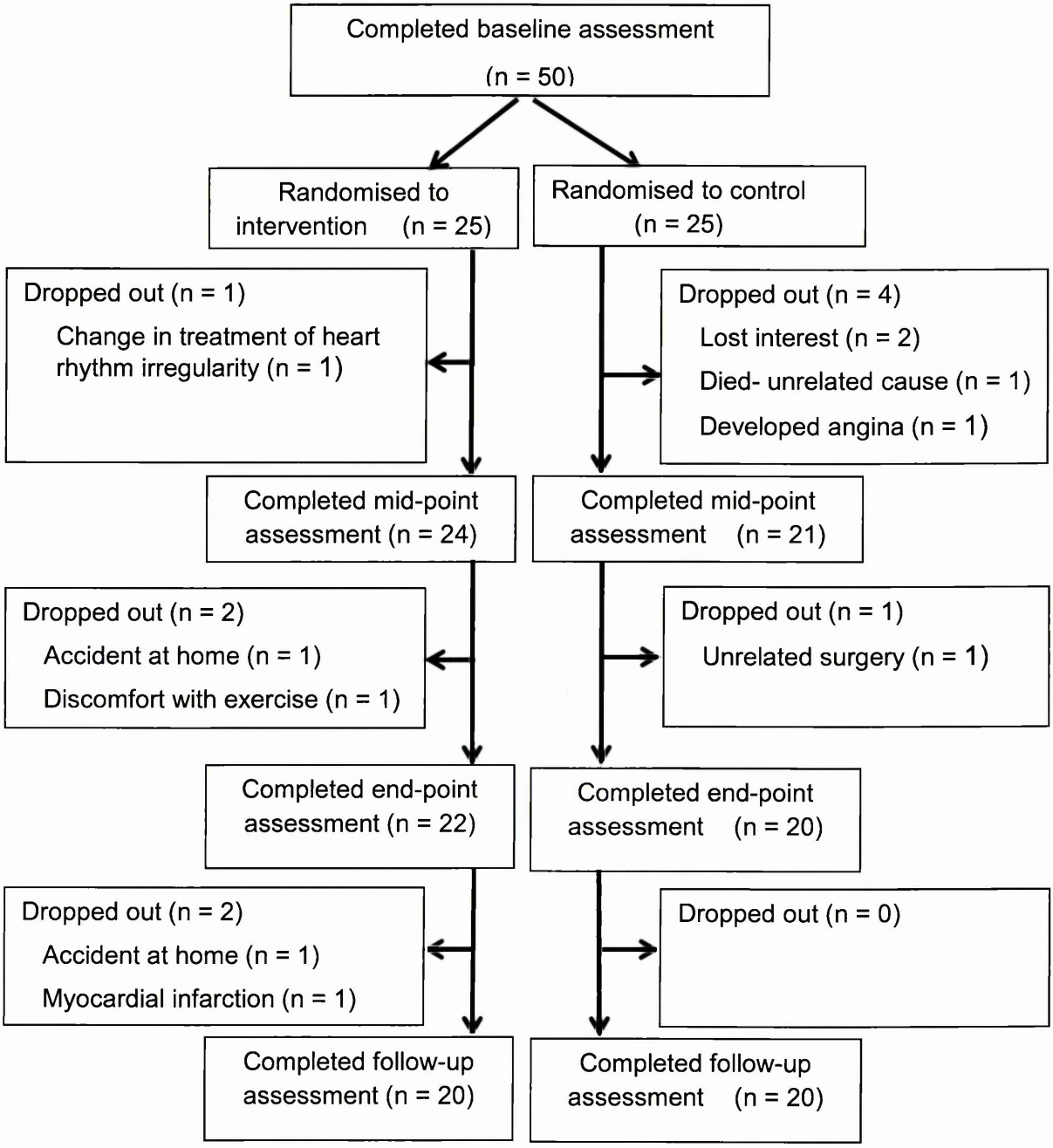


Figure 8.1. Attrition rates for men randomised to the intervention or control groups.

Compliance with exercise sessions for patients completing the intervention was good with 368 of 396 sessions completed (93% of sessions attended). Through weeks 1 to 6, 94% of sessions were completed (249 of 264 sessions) and for weeks 7-12, 90% of sessions were completed (119 of 132 sessions) (P >0.05). Home-based exercise was less well-adhered to with

participants reporting completion of 76% of sessions (301 of 396 sessions completed). Participants reported completion of 83% (110 of 132 sessions) and 72% (191 of 264 sessions) of sessions in the first and second six weeks, respectively (P >0.05).

8.3 Vascular function

Data for assessment of FMD using a distal cuff are displayed in Table 8.2. There was no change in baseline arterial diameter in either group over the duration of the study (P = 0.828). There was a small effect of the intervention on peak arterial diameter (d = 0.47), although the difference between groups at end-point did not achieve statistical significance (P = 0.272, mean difference in Δ = 0.21 mm; 95% CI, -0.04 to 0.46). The magnitude of the difference between groups for peak arterial diameter decreased to follow-up (d = 0.17, P = 0.430). A medium effect was observed for the change from baseline to end-point in absolute and relative FMD (d = 0.55 and d = 0.51, respectively). Mean difference in Δ for absolute FMD at end-point = 0.11 mm (95% CI, 0.01 to 0.21) while for relative FMD mean difference in Δ = 2.2% (95% CI, -0.1 to 4.5). No statistically significant interaction was found for the change to end-point (P >0.05) but there was a main effect of time (P = 0.036). Post-hoc analysis demonstrated a statistically significant increase in relative FMD from baseline to end-point for men in the intervention group (P = 0.045). At follow-up the difference between groups was reduced (mean difference in Δ for absolute FMD = 0.06 mm; 95% CI, -0.05 to 0.18 [d = 0.30], mean difference in Δ for relative FMD = 1.4%; 95% CI, -1.3 to 4.1 [d = 0.29]) with the difference between groups remaining non-significant for the interaction (P >0.05) but a main effect of time remained (P = 0.007).

The change in allometrically scaled FMD between groups is displayed in Figure 8.2, There were no statistically significant interactions at end-point or follow-up after FMD was allometrically scaled for baseline diameter (P >0.05), but there was a main effect of time on the change in scaled FMD (P = 0.007), with post-hoc analysis revealing a statistically significant increase in the

intervention group from baseline to end-point (P = 0.038). There was a medium effect of the intervention on change in scaled FMD at end-point (d = 0.53).

There was no difference between groups for changes in time to peak arterial diameter (P >0.05 at end-point and follow-up). Similarly, no differences were observed at any time point for resting blood flow, peak blood flow or SR AUC (P >0.05).

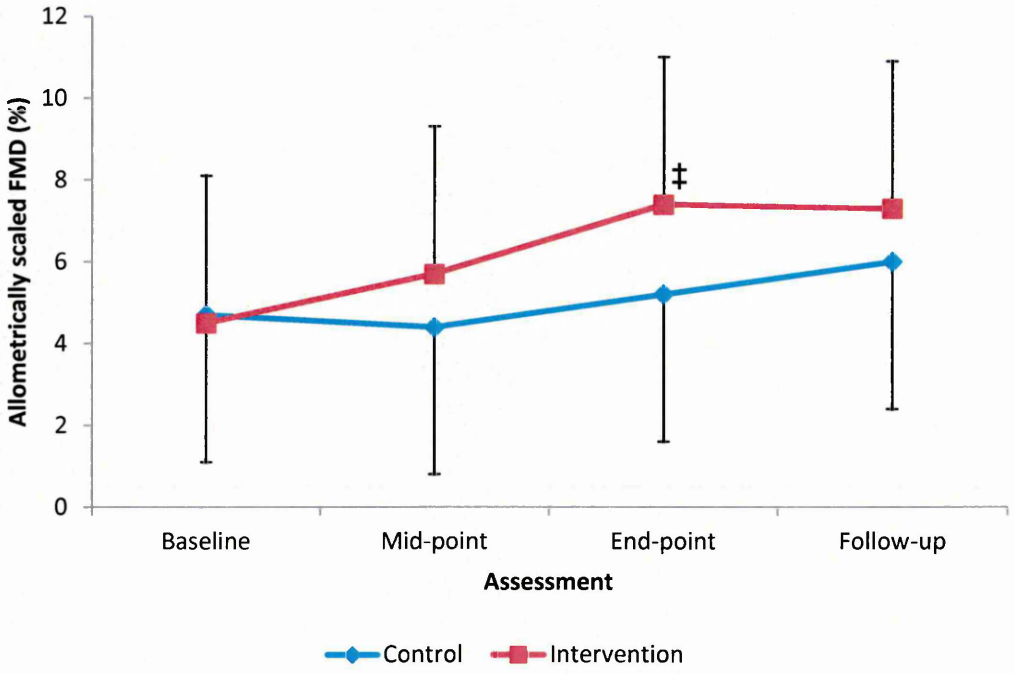


Figure 8.2. Allometrically scaled FMD for the intervention and control groups. Data displayed as mean for group, error bars denote 1 standard deviation. (‡) denotes difference from baseline within the intervention group (P <0.05)

Table 8.2. Assessment of flow-mediated dilatation using a distal cuff placement. Data presented as mean (SD)

	Baseline		Mid-point		End-point		Follow-up		*d*		P	
	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Δ EP - BL	Δ FU - BL	End-point	Follow-up
Baseline arterial diameter (mm)	4.75 (0.55)	4.88 (0.58)	4.78 (0.58)	4.99 (0.76)	4.71 (0.51)	4.93 (0.50)	4.73 (0.62)	4.88 (0.64)	0.24	0.04	0.686	0.828
Peak arterial diameter (mm)	4.97 (0.57)	5.11 (0.67)	4.99 (0.65)	5.29 (0.88)	4.95 (0.50)	5.29 (0.53)	5.01 (0.62)	5.22 (0.65)	0.47	0.17	0.272	0.430
FMD (mm)	0.22 (0.11)	0.23 (0.18)	0.22 (0.18)	0.29 (0.22)	0.24 (0.15)	0.36 (0.19)	0.28 (0.16)	0.35 (0.18)	0.55	0.30	0.183	0.323†
FMD (%)	4.7 (2.4)	4.6 (3.6)	4.5 (3.5)	5.8 (3.9)	5.2 (3.4)	7.3* (4.1)	6.0 (3.7)	7.3 (3.9)	0.51	0.29	0.210†	0.379†
Allometric scaled FMD (%)	4.7 (3.6)	4.5 (3.6)	4.4 (3.6)	5.7 (3.6)	5.2 (3.6)	7.4* (3.6)	6.0 (3.6)	7.3 (3.6)	0.53	0.31	0.174†	0.320†
Time to peak (seconds) §	62.2 (30.9)	59.9 (25.4)	58.4 (33.7)	55.4 (25.3)	64.9 (40.3)	72.7 (41.4)	67.1 (28.1)	71.7 (38.3)	0.25	0.18	0.773	0.891
Resting flow ($ml \cdot min^{-1}$)	108 (56)	128 (59)	118 (77)	136 (62)	104 (44)	127 (61)	96 (43)	118 (60)	0.07	0.03	0.938	0.983
Peak flow ($ml \cdot min^{-1}$)	1367 (442)	1600 (645)	1363 (556)	1542 (643)	1365 (508)	1513 (598)	1289 (464)	1378 (547)	0.14	0.24	0.856	0.796
SR AUC	41331 (18205)	38911 (14737)	35992 (20056)	33224 (14530)	41625 (18372)	41685 (20018)	42739 (17857)	39997 (22534)	0.12	0.02	0.876	0.964

Abbreviations. FMD: Flow mediated dilation, SR AUC: Shear rate area under the curve, BL: Baseline, EP: End-point, FU: Follow-up. (†) denotes main effect of time (P <0.05). (*) denotes significantly different from baseline (P <0.05). (§) denotes data $\log_n$ transformed prior to analysis

The effects of group allocation on changes in proximal cuff FMD and GTN-mediated dilation are presented in Table 8.3. Data for proximal cuff FMD assessments are presented for 48 men because ultrasound scans were of insufficient quality for 1 man in each group. GTN-mediated dilation was assessed in 38 men (intervention = 17, control = 21). Reasons for not administering GTN included use of medications contraindicating GTN use (n = 8), previous adverse reaction to GTN (n = 1), cardiac arrhythmia (n = 1), history of migraines (n = 1) or refusal to undertake assessment (n = 1). Over the 12 weeks of the intervention no interaction effects were observed in any measures for proximal cuff FMD assessments (P >0.05), however, main effects of time were present for the change in baseline arterial diameter (P = 0.036) and peak arterial diameter (P = 0.005). A medium effect size was observed for the difference in peak arterial diameter between baseline and follow-up (d = 0.52) although this difference was not found to be statistically significant (P = 0.289). Differences between groups were evident for GTN-mediated dilation, with an increase in the response to GTN observed at mid-point in men in the control group (P = 0.042 for absolute change in GTN-mediated dilation, P = 0.057 for relative change in GTN-mediated dilation). No differences were observed between groups in response to GTN at end-point or follow-up assessments (P >0.05).

Table 8.3. Assessment of proximal cuff flow-mediated dilatation and GTN-mediated dilatation. Data presented as mean (SD)

	Baseline		Mid-point		End-point		Follow-up		*d*		P	
	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Δ EP - BL	Δ FU - BL	End-point	Follow-up
Prox baseline diameter (mm)	4.96 (0.77)	5.05 (0.55)	4.81 (0.71)	4.96 (0.61)	4.80 (0.62)	4.92 (0.62)	4.67 (0.61)	4.96 (0.61)	0.11	0.48	0.890	0.492†
Prox peak diameter (mm)	5.38 (0.71)	5.42 (0.58)	5.25 (0.65)	5.26 (0.64)	5.18 (0.60)	5.25 (0.64)	5.03 (0.56)	5.29 (0.65)	0.14	0.52	0.914†	0.289†
Prox dilation (mm)	0.42 (0.28)	0.37 (0.21)	0.44 (0.20)	0.30 (0.17)	0.38 (0.24)	0.33 (0.13)	0.36 (0.24)	0.33 (0.15)	0.04	0.10	0.476	0.531
Prox dilation (%)	8.9 (6.2)	7.3 (4.1)	9.5 (4.8)	6.2 (3.5)	8.2 (5.5)	6.9 (3.0)	8.1 (5.9)	6.7 (3.2)	0.05	0.05	0.420	0.553
Allometric scaled Prox dilation (%)	9.0 (4.0)	7.8 (4.1)	9.2 (4.0)	6.4 (4.1)	7.8 (4.0)	6.9 (4.1)	7.4 (4.0)	6.8 (4.1)	0.06	0.04	0.421	0.560
GTN baseline diameter (mm)	5.01 (0.64)	4.96 (0.52)	5.05 (0.56)	4.93 (0.55)	5.10 (0.62)	4.84 (0.55)	5.02 (0.56)	4.78 (0.51)	0.43	0.32	0.236	0.309
GTN peak diameter (mm)	5.61 (0.69)	5.58 (0.61)	5.74 (0.64)	5.47 (0.62)	5.67 (0.61)	5.41 (0.57)	5.61 (0.60)	5.46 (0.52)	0.37	0.18	0.197	0.331
GTN-mediated dilation (mm)	0.59 (0.20)	0.62 (0.25)	0.68 (0.30)	0.55 (0.22)	0.56 (0.23)	0.56 (0.26)	0.59 (0.25)	0.68 (0.31)	0.04	0.16	0.154	0.128
GTN-mediated dilation (%)	12.0 (4.2)	12.5 (5.0)	13.6 (6.0)	11.2 (4.5)	11.3 (4.9)	11.9 (5.5)	11.9 (5.1)	14.5 (7.3)	0.04	0.24	0.129	0.097
Allometric scaled GTN dilation (%)	12.0 (4.8)	12.3 (4.5)	13.8 (4.8)	10.8 (4.5)	11.5 (4.8)	11.4 (4.5)	12.0 (4.8)	13.7 (4.5)	0.06	0.21	0.131	0.105

Abbreviations. GTN: Glyceryl trinitrate, Prox: Proximal cuff flow-mediated dilatation, BL: Baseline, EP: End-point, FU: Follow-up. (†) denotes main effect of time (P <0.05)

8.4 Blood pressure

Data for blood pressure measurements are displayed in Table 8.4. No statistically significant interactions were observed (P >0.05), however main effects of time were observed for diastolic blood pressure (P = 0.009), mean arterial pressure (P = 0.008) and heart rate (P = 0.018). Over the first six weeks of the study systolic and diastolic blood pressure decreased by 6.4 ± 10.2 mm Hg and 2.6 ± 6.7 mm Hg, respectively for men in the intervention group, while controls showed reductions of 1.34 ± 12.4 mm Hg and 1.3 ± 3.7 mm Hg over the same time period (mean difference in Δ = -5.1 mm Hg; 95% CI, -12.0 to 1.7 for systolic and -1.3 mm Hg; 95% CI, -4.5 to 1.9 for diastolic blood pressure). Differences between groups were increased at end-point assessment with systolic and diastolic blood pressure reduced by 6.5 ± 11.5 mm Hg and 4.0 ± 6.1 for intervention and 0.4 ± 17.9 and 0.8 ± 5.2 mm Hg for controls (mean difference in Δ = -6.0 mm Hg; 95% CI, -14.7 to 2.6 for systolic and -3.1 mm Hg; 95% CI, -6.4 to 0.2 for diastolic blood pressure). At follow-up systolic blood pressure showed mean difference in Δ = -0.3 mm Hg (95% CI, -7.7 to 7.1) and for diastolic blood pressure mean difference in Δ = -0.9 mm Hg (95% CI, -3.7 to 1.9). At end-point, mean arterial pressure decreased from baseline by 5.6 ± 8.1 mm Hg for the intervention group and 1.8 ± 8.4 mm Hg for the controls (mean difference in Δ = -3.8 mm Hg; 95% CI, -8.7 to 1.9), while at follow-up mean arterial pressure was decreased from baseline by 4.5 ± 11.3 mm Hg in the intervention group and 3.1 ± 8.5 mm Hg in the controls (mean difference in Δ = -1.4 mm Hg; 95% CI, -6.2 to 3.4). Effect sizes of d = 0.46 and d = 0.14 were found for the change to end-point and follow-up respectively.

Two-men in the control group started or increased medication to treat high blood pressure between the mid-point and end-point assessments, and hence lowered group mean blood pressure at end-point and follow-up as a result of pharmacological intervention. If data for these two men is removed from the subsequent analysis greater differences between groups are evident in systolic blood pressure and mean arterial pressure at end-point assessment (mean difference in Δ for systolic blood pressure = -6.2 mm Hg;

95% CI, -14.9 to 2.5, P = 0.195; mean difference in Δ for mean arterial blood pressure = -4.1 mm Hg; 95% CI, -9.3 to 1.1, P = 0.189).

Table 8.4. Blood pressure data for the intervention and control groups. Data presented as mean (SD).

	Baseline		Mid-point		End-point		Follow-up		*d*		P	
	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Δ EP - BL	Δ FU - BL	End-point	Follow-up
Systolic blood pressure (mm Hg)	145 (18)	144 (18)	144 (17)	138 (16)	145 (19)	138 (19)	142 (21)	140 (18)	0.41	0.02	0.202	0.240
Diastolic blood pressure (mm Hg)	76 (8)	80 (8)	74 (7)	77 (9)	75 (7)	76 (10)	74 (7)	77 (10)	0.56	0.15	0.146†	0.319†
Mean arterial pressure (mm Hg)	103 (11)	106 (12)	101 (9)	101 (12)	102 (9)	100 (14)	100 (11)	101 (16)	0.46	0.14	0.213†	0.483†
Pulse pressure (mm Hg)	69 (16)	64 (14)	69 (20)	60 (13)	70 (18)	62 (14)	68 (18)	64 (14)	0.24	0.05	0.386	0.367
Resting heart rate (beats·min^{-1})	66 (14)	67 (14)	65 (14)	65 (13)	63 (12)	62 (12)	62 (10)	64 (12)	0.22	0.03	0.648†	0.645†

Abbreviations. BL: Baseline, EP: End-point, FU: Follow-up. (†) denotes main effect of time (P <0.05)

8.5 Anthropometric measures

Data for anthropometric measures are displayed in Table 8.5. There were no interaction effects for changes in body mass or BMI (P >0.05), however main effects of time were observed for the change in body mass at end-point and follow-up (P = 0.010 and P = 0.013, respectively), and for the change in BMI at end-point (P = 0.021). Body mass was reduced from baseline by 0.9 ± 2.0 kg at end-point and 1.0 ± 2.9 kg at follow-up assessment for men in the intervention group. Men in the control group lost 0.8 ± 2.8 kg and 0.9 ± 4.0 kg from baseline measures at end-point and follow-up, respectively.

At end-point assessment skeletal muscle was increased (mean difference in Δ = 0.5 kg; 95% CI, 0.0 to 1.0) and body fat mass (mean difference in Δ = -0.9 kg; 95% CI, -2.1 to 0.4) and body fat percentage (mean difference in Δ = -1.1 kg; 95% CI, -1.9 to -0.2) were decreased from baseline measures for men in the intervention compared to the controls. The differences between groups for the change in skeletal muscle mass and body fat percentage demonstrated a statistically significant interaction (P <0.05). In addition, the change in body fat percentage demonstrated a main effect of time for the change to end-point (P = 0.001). Changes in skeletal muscle mass occurred within the first 6 weeks of the intervention, with a difference between groups evident at the mid-point assessment (mean difference in Δ = 0.4 kg; 95% CI, 0.0 to 0.8) (P = 0.022). Reduced visceral fat area was also seen at end-point assessment in men in the intervention compared to controls (mean difference in Δ = -3.6 cm^2; 95% CI, -7.8 to 0.6). At follow-up assessment no interaction effects were evident between groups for body composition, but the effect of time was still present for changes in body fat percentage (P = 0.008).

It must be noted that one man in the control group started medication to achieve a reduction in fat mass during the study (prior to end-point assessment). If subsequent data for this participant is removed from the analysis greater changes are observed between groups in body fat percentage (mean difference in Δ at end-point = -1.2%; 95% CI, -2.0 to -0.4, P = 0.017), body fat mass (mean difference in Δ at end-point = -1.2 kg; 95% CI, -2.0 to -0.4, P = 0.144), BMI (mean difference in Δ at end-point = -0.15

$kg \cdot m^{-2}$; 95% CI, -0.54 to 0.24, P = 0.293) and visceral fat area (mean difference in Δ at end-point = -4.1 cm^2; 95% CI, -8.3 to 0.1, P = 0.089).

Table 8.5. Anthropometric data for the intervention and control groups. Data presented as mean (SD)

	Baseline		Mid-point		End-point		Follow-up		*d*		P	
	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Δ EP - BL	Δ FU - BL	End-point	Follo
Body mass (kg) [§]	87.0 (17.2)	92.5 (15.4)	86.6 (16.5)	92.4 (15.4)	86.2 (16)	91.6 (15.3)	86.1 (15.9)	91.5 (14.7)	0.04	0.02	0.661[†]	0.8
BMI ($kg \cdot m^{-2}$) [§]	28.8 (5.2)	30.6 (5.0)	28.7 (4.8)	30.6 (5.1)	28.5 (4.5)	30.4 (5.2)	28.6 (4.6)	30.3 (5.1)	0.03	0.04	0.727[†]	0.7
Skeletal muscle mass (kg)	31.2 (5.7)	31.9 (4.2)	31.2 (5.5)	32.3 (4.4)	31.1 (5.7)	32.3 (4.5)	31.3 (5.9)	32.1 (4.2)	0.70	0.04	0.033	0.1
Body fat mass (kg) [§]	30.4 (11.5)	34.5 (11.6)	29.9 (10.9)	33.8 (11.5)	29.8 (10.2)	33.1 (11.8)	29.3 (10.4)	33.4 (11.4)	0.40	0.02	0.163	0.2
Body fat (%)	34.3 (7)	36.6 (6.9)	34 (6.7)	35.9 (7.1)	34.1 (6.6)	35.3 (7.5)	33.5 (7.5)	35.7 (7.2)	0.71	0.03	0.030[†]	0.1
Visceral fat area (cm^2) [§]	176 (36)	187 (44)	175 (34)	184 (43)	176 (33)	183 (44)	176 (35)	186 (43)	0.51	0.04	0.126	0.3

Abbreviations. BMI: Body mass index, BL: Baseline, EP: End-point, FU: Follow-up. ([†]) denotes main effect of time ($P < 0.05$). ([§]) denotes data $\log_n$ transformed prior to analysis

8.6 Exercise tests and exercise behaviour

Data for exercise tolerance test results are displayed in Figure 8.3. Treadmill time was increased from baseline at mid-point (Δ from baseline 58.7 ± 58.6 s) and end-point assessments (Δ from baseline 80.3 ± 64.7 s) in men in the intervention group, while men in the control group showed little change in walking time over the same periods (reduced from baseline by 2.6 ± 52.0 s at mid-point and by 7.0 ± 57.1 s at end-point). Accordingly, there was a large effect of the intervention on treadmill walking time (d = 1.46 for change from baseline to end-point) with the interaction demonstrating statistical significance at mid-point and end-point (both P <0.001, mean difference in Δ at end-point = 87.2 s; 95% CI, 50.4 to 124.0) and a main effect of time at end-point assessment (P <0.001). A large effect of the intervention on the change in exercise tolerance from baseline was observed at follow-up (d = 1.26) with a mean difference in Δ = 73.2 s (95% CI, 38.6 to 107.9; P <0.001 for interaction and time).

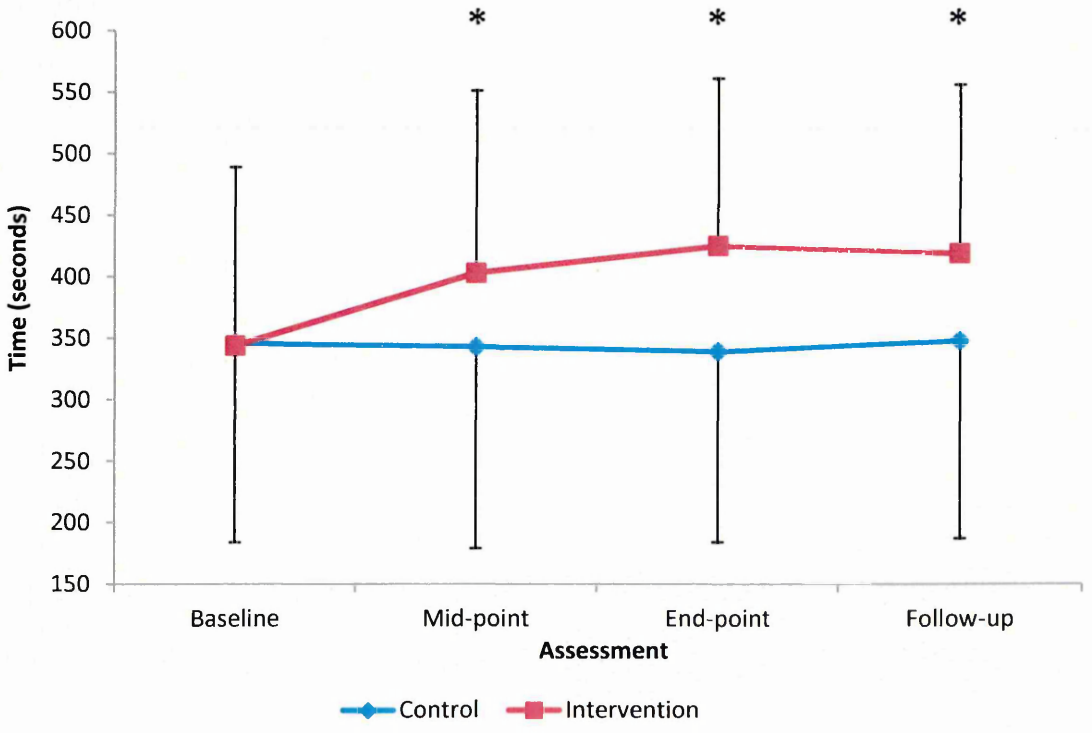


Figure 8.3. Treadmill time for the intervention and control groups. Data displayed as mean for group, error bars denote 1 standard deviation. (*) signifies interaction effect (P <0.05).

Men in the intervention group demonstrated improvements in performance of the 30 second sit-to-stand test exceeding those shown by the controls (Figure 8.4). Statistically significant changes were observed at end-point (P = 0.025) and follow-up (P = 0.048). Performance increased in the intervention group from a mean of 10.6 ± 2.8 repetitions at baseline to 12.7 ± 4.5 repetitions at end-point and 13.0 ± 3.9 repetitions at follow-up. In the control group performance increased from 9.8 ± 3.2 repetitions at baseline to 10.4 ± 3.4 repetitions and 11.2 ± 3.8 repetitions at end-point and follow-up, respectively (mean difference in Δ at end-point = 1.5 reps; 95% CI, 0.1 to 2.9, d = 0.69 for the change from baseline to end-point).

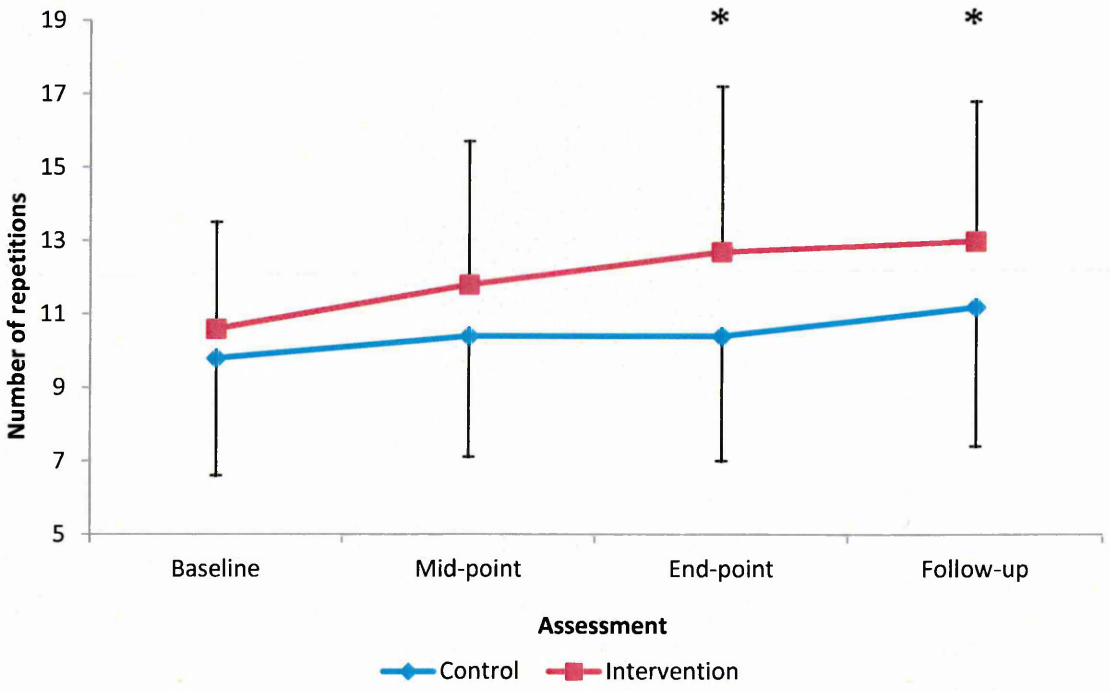


Figure 8.4. Thirty second sit-to-stand test performance for the intervention and control groups. Data displayed as mean for group, error bars denote 1 standard deviation. (*) signifies interaction effect (P <0.05).

Greater increases in leisure time activity were observed in the intervention group compared to the controls (Figure 8.5). Godin LSI score increased from baseline by 9.0 ± 16.1 points in the intervention group at mid-point assessment, while in the controls LSI score reduced by 0.2 ± 8.1 points over the same duration (P = 0.013). At end-point men in the intervention demonstrated a 14.6 ± 24.8 point increase from baseline, in comparison with an increase from baseline of 3.0 ± 11.6 points in the control group (mean difference in Δ = 11.6 points; 95% CI, 0.5 to 22.7, d = 0.61 for the change from baseline to end-point, P = 0.041). At follow-up assessment the mean difference in Δ = 5.8 points (95% CI, -8.1 to 19.8, P = 0.119).

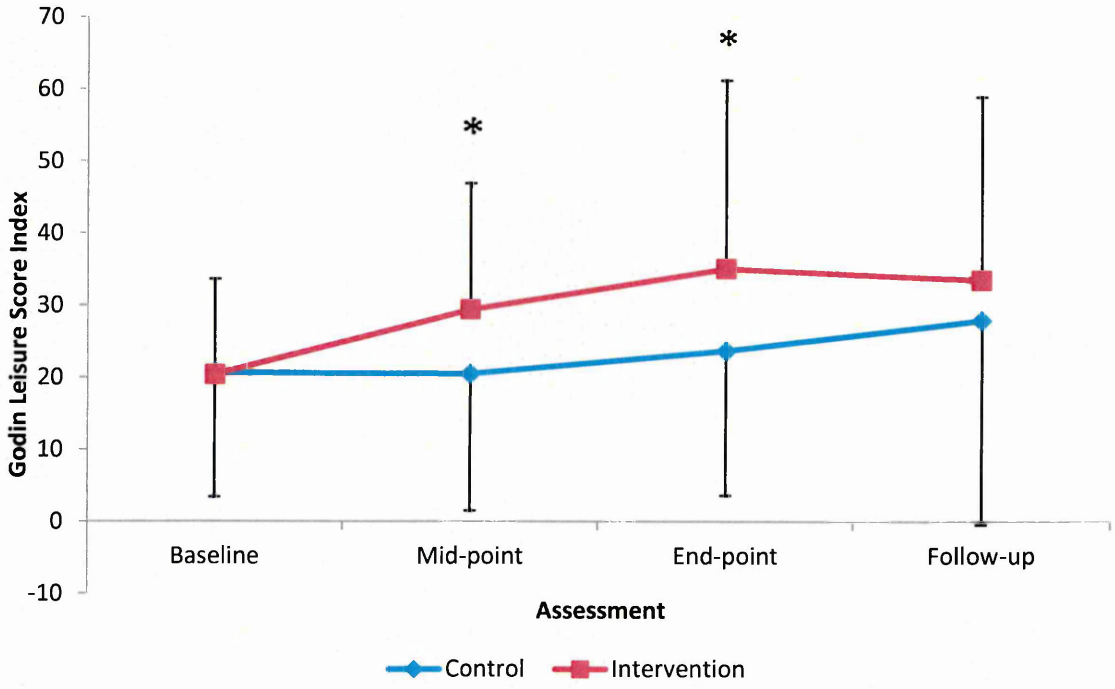


Figure 8.5. Godin LSI results for the intervention and control groups. Data displayed as mean for group, error bars denote 1 standard deviation. (*) signifies difference between intervention and control for change from baseline (P <0.05).

8.7 Fatigue and quality of life

Data for fatigue and quality of life were analysed as the difference between groups for the change from baseline. Results for the difference in fatigue scores from baseline are shown in Figure 8.6. There was a large effect of group on the change in fatigue between baseline and mid-point (d = 0.87), with Fact-F scores increasing by 5.0 ± 6.3 points in the intervention group and by 0.6 ± 3.7 points in the controls (mean difference in Δ = 4.4 points; 95% CI, 1.2 to 7.7, P = 0.006). At end-point assessment the change in Fact-F score from baseline remained greater in men undergoing the intervention (4.8 ± 6.5 points) than in controls (1.0 ± 5.6 points) although there was a slight decrease in the magnitude of the difference between groups from baseline (mean difference in Δ = 3.8 points; 95% CI, -0.1 to 7.7, P = 0.044, d = 0.64). At follow-up assessment there was still a medium effect of group on fatigue (d = 0.54), however the difference in change from baseline between groups decreased (mean difference in Δ = 3.6 points; 95% CI, 0.0 to 7.3) and the effect of group on change from baseline was no longer statistically significant (P = 0.167).

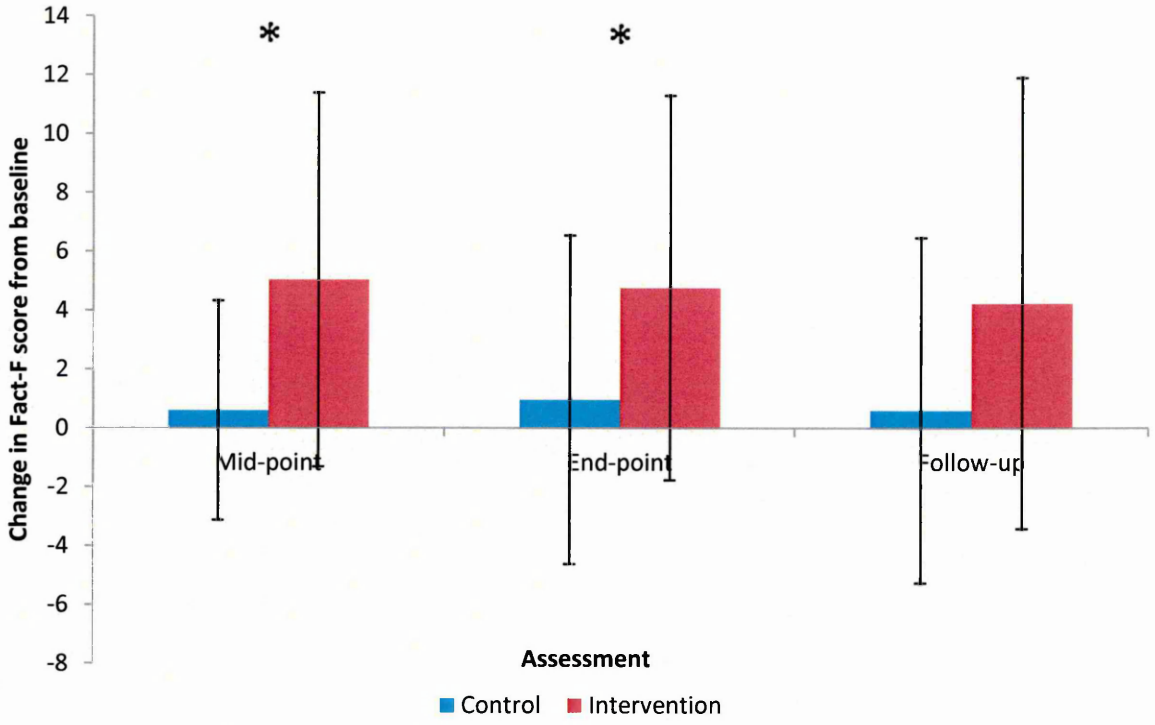


Figure 8.6. Change in fatigue (Fact-F) from baseline for the intervention and control groups. (*) signifies difference between intervention and control for change from baseline (P <0.05). Error bars denote ± 1 standard deviation

Changes in Fact-P scores from baseline are displayed in Figure 8.7. Men in the intervention group demonstrated improved disease-specific quality of life compared to men in the control group (P <0.05 for the difference between groups at mid-point and end-point). There was a medium effect of group (d = 0.71) for the change in fatigue from baseline to mid-point. Fact-P scores increased by 6.7 ± 9.7 points in the intervention group but little change in the controls was observed over this period (0.5 ± 8.0 points, mean difference in Δ = 6.2 points; 95% CI, 1.8 to 10.6, P = 0.033). At end-point Fact-P was increased from baseline by 7.6 ± 9.2 points in the intervention group, while the control group decreased from baseline by 1.8 ± 5.5 points (mean difference in Δ = 9.4 points; 95% CI, 5.4 to 13.4, P <0.001). This represented a large effect of group on the difference from baseline (d = 1.3). Although Fact-P scores remained higher in men in the intervention group at follow-up

(mean difference in Δ = 4.9 points; 95% CI, -0.1 to 9.9), the difference between groups was no longer statistically significant ($P = 0.316$, $d = 0.44$).

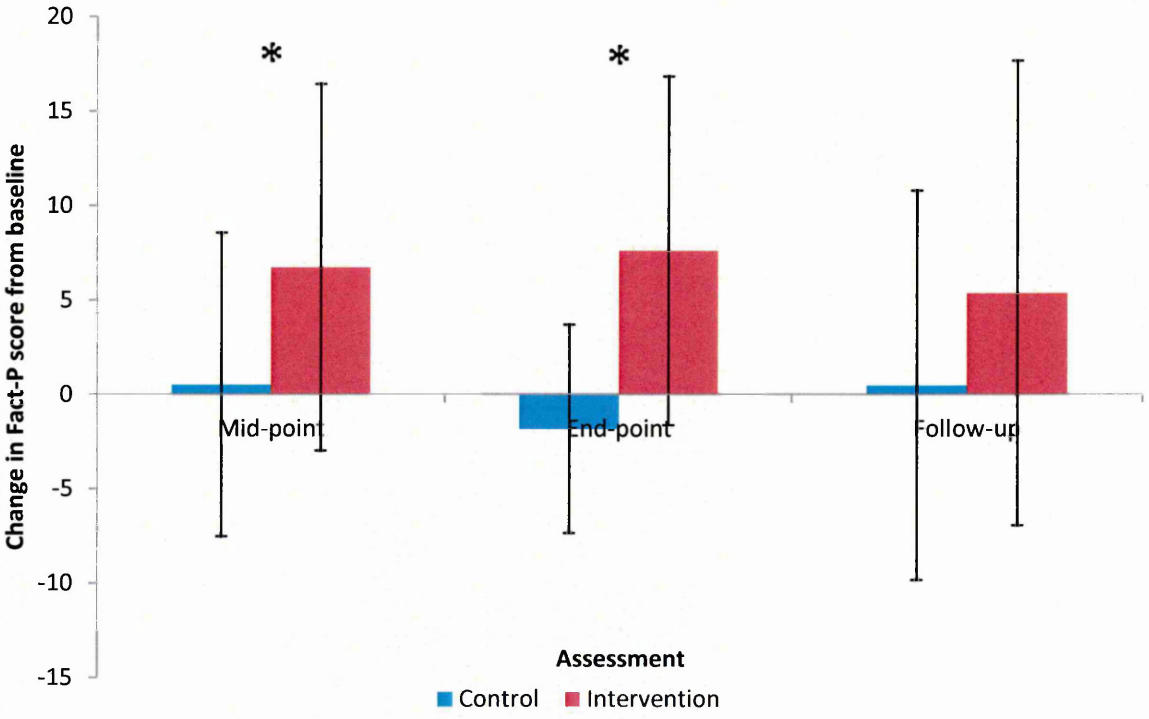


Figure 8.7. Change in disease-specific quality of life (Fact-P) from baseline for the intervention and control groups. (*) signifies difference between intervention and control for change from baseline (P <0.05). Error bars denote ± 1 standard deviation

8.8 Blood markers

Results for blood lipid profile are presented in Table 8.6. Data is shown for 47 men because samples were not obtained or couldn't be analysed in 3 men (n = 1 intervention and n = 2 controls). No differences between groups were observed for changes in total cholesterol, HDL-C, LDL-C or total cholesterol / HDL-C ratio (P >0.05). There was a small effect of group on the change in triglyceride concentrations but the difference was not statistically significant ($P = 0.136$).

Table 8.6.Blood lipid profile at baseline and end-point for the intervention and control groups.

Data presented as mean (SD)

	Baseline		End-point		*d*	P
	Control	Intervention	Control	Intervention	Δ EP - BL	
Total cholesterol ($mmol \cdot L^{-1}$)	4.71 (0.87)	5.00 (1.16)	4.69 (0.85)	4.93 (1.04)	0.13	0.666
HDL-C ($mmol \cdot L^{-1}$)	1.47 (0.49)	1.42 (0.40)	1.45 (0.43)	1.44 (0.38)	0.24	0.416
LDL-C ($mmol \cdot L^{-1}$)	2.45 (0.81)	2.73 (1.14)	2.50 (0.81)	2.74 (1.01)	0.14	0.621
Total cholesterol / HDL-C ratio	3.42 (1.16)	3.74 (1.2)	3.43 (0.95)	3.63 (1.14)	0.24	0.416
Triglycerides ($mmol \cdot L^{-1}$) §	1.72 (0.97)	1.86 (0.72)	1.62 (0.88)	1.65 (0.74)	0.30	0.136

Abbreviations. HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol. (§) denotes data was $\log_n$ transformed prior to analysis

A reduction in haemoglobin concentration of 3 ± 8 $g \cdot l^{-1}$ was observed in men in the intervention group (from 134 ± 13 $g \cdot l^{-1}$ at baseline to 131 ± 13 $g \cdot l^{-1}$ at end-point). This was only marginally less than the reduction in haemoglobin seen in the control group (4 ± 10 $g \cdot l^{-1}$; from 129 ± 16 $g \cdot l^{-1}$ at baseline to 125 ± 18 $g \cdot l^{-1}$ at end-point) with the difference between groups not achieving statistical significance ($P = 0.612$, $d = 0.15$).

Biomarkers of disease progression are reported in Table 8.7. Data for testosterone, SHBG and FAI are missing for n = 4 (n = 1 intervention and n = 3 controls). No differences between groups were observed for changes in serum testosterone or PSA concentrations ($P > 0.05$). There was a medium effect of group on SHBG concentrations ($d = 0.67$) with the difference between groups at end-point assessment achieving statistical significance ($P = 0.033$). Similarly, there was a small effect of group on free androgen index ($d = 0.38$) which demonstrated a statistical trend ($P = 0.072$).

Table 8.7 Biomarkers of disease progression at baseline and end-point for the intervention and control groups. Data presented as mean (SD)

	Baseline		End-point		*d*	P
	Control	Intervention	Control	Intervention	Δ EP - BL	
Serum testosterone ($nmol \cdot L^{-1}$)	0.46 (0.17)	0.48 (0.22)	0.45 (0.18)	0.43 (0.10)	0.32	0.837
Free testosterone ($nmol \cdot l^{-1}$)	0.0066 (0.0036)	0.0071 (0.0034)	0.0068 (0.0042)	0.0064 (0.0030)	0.43	0.137
Bioavailable testosterone ($nmol \cdot l^{-1}$)	0.156 (0.086)	0.166 (0.081)	0.161 (0.099)	0.149 (0.070)	0.43	0.138
SHBG ($nmol \cdot L^{-1}$) [§]	56.90 (31.57)	54.02 (33.00)	53.78 (30.87)	55.85 (34.26)	0.67	0.033
FAI [§]	1.17 (1.00)	1.20 (0.77)	1.22 (1.04)	1.10 (0.76)	0.38	0.072
PSA ($ng \cdot ml$) [§]	1.50 (2.74)	2.15 (4.84)	2.00 (4.05)	3.23 (8.20)	0.21	0.538

Abbreviations. SHBG: Sex-hormone binding globulin, FAI: Free androgen index, PSA: Prostate specific antigen. ([§]) denotes data $\log_n$ transformed prior to analysis

8.9 Diet diaries

In total 70% of diet diaries were returned, with 88%, 66% and 58% returned at baseline, end-point and follow-up, respectively. No differences were observed between groups or over time in total energy intake, or in any of the macro or micronutrients examined ($P > 0.05$; Table 8.8).

Table 8.8. Dietary analysis for the intervention and control groups. Data presented as mean (SD)

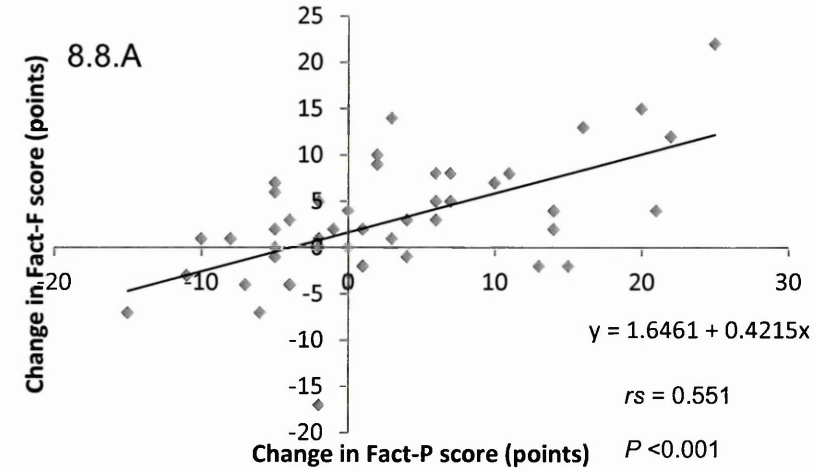
	Baseline		End-point		Follow-up		*d*		P	
	Control	Intervention	Control	Intervention	Control	Intervention	Δ EP - BL	Δ FU - BL	End-point	Follow-up
Total energy intake (kcal)	2085 (528)	1927 (484)	2021 (519)	1886 (477)	1989 (564)	1955 (480)	0.02	0.17	0.894	0.766
Carbohydrates(g) [§]	264.9 (98.8)	225.4 (51.0)	250.0 (69.7)	223.7 (59.4)	235.9 (58.4)	237.0 (92.7)	0.13	0.35	0.792	0.381
Sugars (g) [§]	130 (94)	104 (39)	115 (61)	105 (43)	107 (46)	122 (87)	0.16	0.40	0.589	0.167
Starch (g)	132 (34)	118 (27)	131 (29)	116 (32)	126 (32)	112 (32)	-0.06	-0.02	0.866	0.984
Total fats (g)	77.8 (28.0)	73.7 (31.2)	79.1 (29.3)	69.8 (21.9)	80.7 (36.5)	72.6 (26.2)	-0.16	-0.11	0.591	0.852
Saturated fats (g)	28.0 (10.9)	25.3 (11.8)	29.9 (11.2)	24.3 (8.8)	29.2 (11.7)	25.6 (9.6)	-0.22	-0.07	0.427	0.686
Monounsaturated fats (g)	24.1 (9.9)	21.6 (9.3)	25.1 (10.0)	21.1 (8.2)	25.4 (10.2)	22.8 (10.3)	-0.11	0.02	0.677	0.871
Polyunsaturated fats (g) [§]	10.9 (5.1)	10.1 (4.6)	11.6 (5.8)	10.0 (5.1)	11.7 (5.3)	10.3 (5.7)	-0.11	-0.06	0.630	0.835
Cholesterol (mg)	247 (97)	261 (116)	262 (115)	248 (95)	263 (134)	250 (101)	-0.21	-0.18	0.479	0.727
Protein (g)	81.4 (19.6)	80.3 (28.1)	82.6 (23.4)	81.1 (28.6)	82.6 (21.6)	79.5 (21.2)	-0.01	-0.07	0.955	0.965
Vitamin C (mg)	109 (75)	111 (70)	97 (46)	113 (59)	112 (37)	105 (49)	0.16	-0.12	0.560	0.506
Vitamin E (mg) [§]	6.9 (2.0)	7.1 (3.0)	6.9 (3.6)	6.6 (2.7)	7.3 (3.3)	6.9 (3.0)	-0.14	-0.16	0.953	0.908
Alcohol (g) [§]	10.0 (11.0)	14.5 (14.7)	6.3 (8.8)	14.0 (15.4)	7.3 (10.6)	13.9 (13.5)	0.22	0.14	0.776	0.373

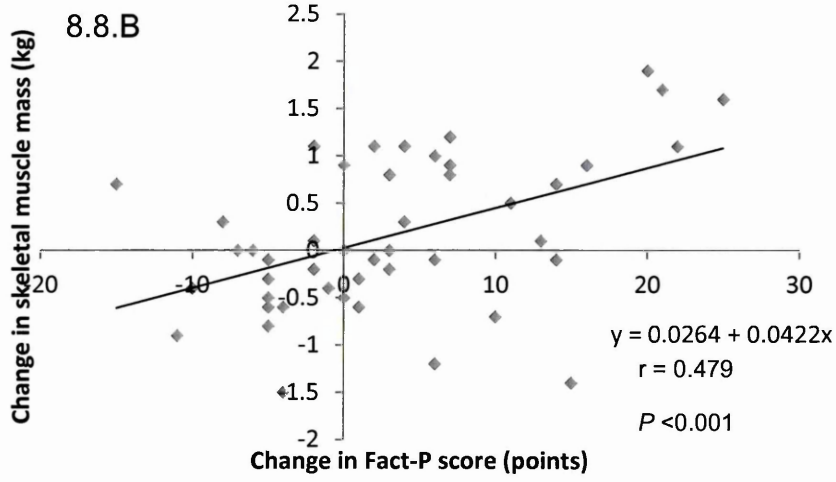
([§]) denotes measures $\log_n$ transformed prior to analysis

8.10 Correlations

Relationships of variables to changes in exercise tolerance from baseline to end-point were examined using non-parametric correlations because data for the change in exercise tolerance was not normally distributed. Positive correlations were observed against changes in Fact-F and Fact-P, with the relationship between the change in exercise tolerance and the change in quality of life considered statistically significant (*rs* = 0.248, *P* = 0.082 and *rs* = 0.361, *P* = 0.010 for correlations with Fact-F and Fact-P, respectively). Furthermore, the change in exercise tolerance demonstrated statistically significant inverse relationships with changes in diastolic blood pressure (*rs* = -0.298, *P* = 0.036), body mass (*rs* = -0.303, *P* = 0.033) and visceral fat area (*rs* = -0.324, *P* = 0.022).

Relationships between changes in quality of life and changes in fatigue, skeletal muscle mass and body fat mass are shown in Figure 8.8. Changes in Fact-P score demonstrated a moderate positive correlation with changes in fatigue (*rs* = 0.551, *P* = <0.001). Moderate correlations were also observed between the change in Fact-P and the changes in skeletal muscle mass (r = 0.479, *P* < 0.001), body fat mass (*rs* = -0.495, *P* < 0.001) and body fat percentage (r = -0.561, *P* <0.001). Weak inverse correlations were found between the change in Fact-P and systolic blood pressure (r = -0.291, *P* = 0.040) and mean arterial pressure (r = -0.298, *P* = 0.036).





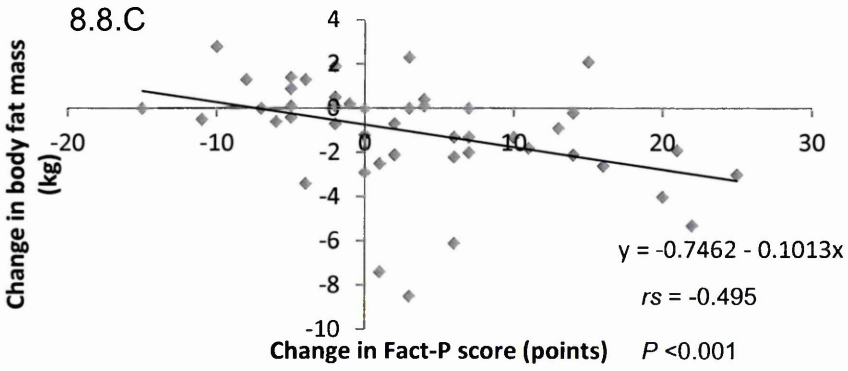


Figure 8.8. Relationships between change in Fact-P score and change in Fact-F (8.8.A), skeletal muscle mass (8.8.B) and body fat mass (8.8.C) from baseline to end-point. Black line denotes line of best fit for each data set.

Changes in relative FMD demonstrated a moderate positive correlation with changes in SHBG (*rs* = 0.423, *P* = 0.002). Changes in relative FMD did not demonstrate correlations with any other variables (*P* >0.05).

No correlation was observed between arterial dilatation measured using a proximal cuff placement and arterial dilatation measured using a distal cuff or GTN-mediated dilatation at any assessment (P >0.05).

8.11 Regression

Linear regression to investigate predictors of the change in arterial dilation for $\log_n$ transformed data ($\log_n$ peak - $\log_n$ baseline) from baseline to end-point showed that the change in exercise capacity had a statistically significant effect (β = 0.318, *P* = 0.028). There was no effect of the change in mean arterial pressure (β = 0.112, *P* = 0.458), body fat mass (β = -0.009, *P* = 0.952) or triglycerides (β = 0.209, *P* = 0.179). This led to an overall fit for this model of R^2 = 0.148. There was no relationship between baseline values of these outcomes and change in arterial dilatation (*P* >0.05 for all independent variables, R^2 = 0.128).

Examining predictors of the change in Fact-P score from baseline to end-point demonstrated that change in exercise tolerance (β = 0.362, *P* = 0.004) and change in body fat mass (β = -0.358, *P* = 0.006) had statistically significant effects, but change in mean arterial pressure (β = -0.175, *P* = 0.157) and change in haemoglobin (β = 0.203, *P* = 0.100) did not (R^2 for model = 0.380). Similarly, change in body fat mass (β = -0.467, *P* = 0.001) was found to be a statistically significant predictor of change in Fact-F score. There was no effect of change in mean arterial pressure (β = -0.163, *P* = 0.203), haemoglobin (β = 0.070, *P* = 0.558) or exercise tolerance (β = 0.194, *P* = 0.125) for change in Fact-F. The overall model fit for change in Fact-F was R^2 = 0.338. Including baseline values of these independent variables into the model for prediction of change in Fact-P or Fact-F demonstrated no

statistically significant relationships (P >0.05 for all independent variables, R^2 = 0.41 and R^2 = 0.16 for change in Fact-P and change in Fact-F, respectively).

8.12 Attrition analysis

Patient characteristics for men dropping out of the study prior to the end-point assessment are displayed in Table 8.9. Baseline exercise tolerance was lower in men dropping out of the study (P = 0.001). There was a trend for increased fatigue in patients who dropped out (P = 0.051).

Table 8.9 Determinants of patient attrition prior to end-point assessment.

	Completers (n = 42)	Non-completers (n = 8)	P
Demographic data, count within group (%) unless stated			
Age, years; Mean (SD)	70 (7)	71 (9)	0.635
Duration of ADT, months; Mean (SD)	27 (28)	36 (40)	0.265
Employed	9 (21)	0 (0)	0.148
Previous cardiovascular events	10 (24)	2 (25)	0.942
Hypertension	28 (67)	4 (50)	0.368
Diabetes Mellitus	6 (14)	1 (12)	0.894
Arthritis	16 (38)	4 (50)	0.529
Baseline data, mean (SD)			
PSA, ng·ml	2.07 (4.20)	0.51 (1.11)	0.065
Mass, kg	90.0 (16.6)	88.3 (16.0)	0.784
BMI, $kg \cdot m^{-2}$	29.6 (5.1)	30.5 (5.7)	0.628
Exercise tolerance, s	375 (137)	191 (139)	0.001
Godin LSI, points	22 (16)	15 (8)	0.260
Fact-F score, points	39 (8)	33 (10)	0.051
Fact-P score, points	118 (19)	107 (21)	0.162

Abbreviations: ADT, Androgen deprivation therapy; BMI, Body mass index; Fact-F, Functional assessment of cancer therapy-Fatigue; Fact-P, Functional assessment of cancer therapy-Prostate; PSA, Prostate-specific antigen.

9.0 DISCUSSION: Study 2

This study demonstrates that, in this sample of men treated with ADT for prostate cancer, a lifestyle intervention including supervised exercise training and dietary advice did have significant effects on exercise tolerance, activity levels, fatigue and general quality of life. In addition, this intervention potentially had beneficial effects on risk factors for cardiovascular disease.

The primary null hypothesis for this study was that no difference would be found in cardiovascular risk between men with prostate cancer treated with ADT taking part in the intervention compared with controls. Although weak evidence was found for a difference between the groups for the primary outcome measure (relative FMD) with a mean difference of 2.2% (95% CI, -0.1 to 4.5) at end-point assessment, this failed to reach the alpha of 0.05 set at the outset in the sample size calculation. However, there is a risk that accepting the null hypothesis constitutes a type II error, in that post-hoc analysis demonstrated differences from baseline in the intervention group of considerable magnitude. Similarly, the effect size for the difference between groups for the change from baseline to end-point is suggestive of a beneficial effect of the intervention on FMD. Hence, the lack of statistical significance for the difference between groups could reflect the relatively small number of completers, as the sample size was calculated assuming an attrition rate of 10% at the end of the intervention, whereas the drop-out observed over this period was found to be 16%. Similarly, increased variance in the results could have had an effect, with a SD of 3.0% used in the sample size calculation and a SD of 5.3% observed for the change in relative FMD over the course of the intervention, thus rendering the study under-powered to detect a change at the 0.05 alpha.

Given the epidemiological data demonstrating a higher risk of cardiovascular disease in men on long-term ADT (Keating *et al.*, 2010; Van Hemelrijck *et al.*, 2010), it remains important to investigate a method of reducing cardiovascular risk in this population. Endothelial function is considered a

surrogate marker of cardiovascular health (Vita and Keaney, 2002), with dysfunction of the endothelium reported to be an important initial event in the development of atherosclerosis (Celermajer, 1997). Hence, longitudinal changes in measures of endothelial function can represent quantifiable evidence of alterations in cardiovascular risk. As such, the findings of the current study provide some evidence for healthy lifestyle changes having a moderate effect on endothelial function, which is suggestive of a reduction in cardiovascular risk in men taking part in the intervention. However, a larger study to confirm this would be required before such a claim can reliably be made.

The changes in body composition observed are congruent with improvements in FMD, as changes in body fat have previously been associated with endothelial function (Parikh *et al.*, 2009) and cardiovascular risk (Taylor *et al.*, 2010). Excess body fat is associated with increased oxidative stress (Perticone *et al.*, 2001). Increased production of reactive oxygen species (including superoxide anion, hydrogen peroxide, hyroxyl radical, hypochlorous acid and peroxynitrite) and a concomitant reduction in antioxidant systems, can lead to a decrease in NO synthesis and an increase in NO degradation (Cai and Harrison, 2000; Higashi *et al.*, 2009). Similarly, evidence of beneficial effects of the intervention on blood pressure could also be influential in changes in endothelial function (Vanhoutte, 1996), with the effects again mediated by changes in oxidative stress (Vaziri, 2008). Although no statistically significant difference was found between groups, the magnitude of the change in diastolic blood pressure (-3.1 mm Hg; 95% CI, -6.4 to 0.2) is suggestive of a moderate effect of the intervention. Confirmation of these findings in a larger study would again be required before such an effect can be described with confidence however.

Changes in body composition and blood pressure might not be expected to account for all of the observed difference in FMD however, as Green *et al.* (2003) previously reported that changes in FMD with exercise training in patients with hypercholesterolemia, diabetes, coronary artery disease and chronic heart failure were not fully explained by changes in traditional

cardiovascular risk factors (plasma lipids, blood pressure, blood glucose, waist-to-hip ratio, BMI). Thus, these findings suggest that additional mechanisms, independent of these cardiovascular risk factors, may account for the improvements in FMD seen with exercise. This could be of importance in the current study where regression analysis suggests a role for exercise to influence endothelial function independent of changes in traditional cardiovascular risk factors. Although no relationship was observed between the change in arterial dilatation and the change in established markers of cardiovascular health (blood pressure, body composition, blood lipids), there was a statistically significant effect of the change in exercise tolerance. Our study was not designed to explain the nature of such a relationship, however previous literature has described several mechanisms that could be involved.

Exercise induced up-regulation of NO synthase and a reduction in oxidative stress as an outcome of increased shear stress could provide one possible mechanism. The review by Higashi and Yoshizumi (2004) describes how chronic increases in arterial flow with exercise training can lead to up-regulation of signalling proteins, heat shock protein and hypoxia-inducible factor-1, resulting in an increase in endothelial NO synthase and consequently an increase in bioavailable NO. Furthermore, they report that prolonged shear stress increases production of antioxidants such as superoxide dismutase, leading to greater scavenging of reactive oxygen species and inhibition of NO degradation. These mechanisms could be influential in the current study, as although no changes in measures of blood flow or SR were observed in the intervention group at rest, the cumulative effects of increased arterial shear stress during exercise training could have mediated such an effect and contributed to the change in FMD observed in the intervention group.

The effects of exercise on endothelial progenitor cells could also have an important role in improvements in endothelial function observed in the intervention group. In a review of the role of endothelial progenitor cells on the beneficial effects of exercise, Lenk *et al.* (2011) describe how physical exercise can increase both the number and functional capacity of circulating

endothelial progenitor cells. They suggest that exercise induced increases in NO concentrations activate MMP-9 within the bone marrow, which leads to enhanced mobilization of progenitor cells. This leads to acute increases in progenitor cell concentrations after a single bout of exercise, while after prolonged exercise training concentrations will remain elevated. Increases in circulating progenitor cells can subsequently lead to improvements in endothelial cell integrity and function due to the function of endothelial progenitor cells promoting endothelial cell repair (Shantsila *et al.*, 2007). This is evidenced in studies demonstrating an association between endothelial progenitor cell concentrations and FMD in the brachial artery (Oliveras *et al.*, 2008; Liao *et al.*, 2010).

Increases in dietary antioxidants could have also influenced endothelial function independently of changes in the traditional cardiovascular risk factors (Marin *et al.*, 2011; Franzini *et al.*, 2012). Marin *et al.* (2011) reported that consumption of a Mediterranean style diet for 4 weeks led to a decrease in endothelial micro-particles and an increase in endothelial progenitor cells in a sample of elderly men and women. Similarly, Franzini *et al.* (2012) found that consumption of a diet high in antioxidants for 2 weeks resulted in improved FMD in elderly men and women in comparison with a low antioxidant diet. Although the mechanisms behind such an association are not fully understood, it is believed that a higher consumption of polyphenols, and vitamins C and E, as would be expected in a Mediterranean style diet high in fruit and vegetables, could be important. Flavanols, a sub-group of polyphenols, have been shown to affect vascular function, causing NO-dependent arterial dilation (Fisher *et al.*, 2003). This response could be an effect of flavanols inducing a reduction in vascular inflammation, as Landberg *et al.* (2011) reported biomarkers of vascular inflammation (CRP, IL-18, vascular cell adhesion molecules) were inversely associated with flavanol consumption.

In addition to potentially contributing to changes in FMD, the improvements observed in body composition are also suggestive of a decrease in cardiovascular risk with the intervention. The volume and distribution of body

fat can influence cardiovascular risk, with excess fat mass and central adiposity shown to be associated with cardiovascular events and overall mortality (Taylor *et al.*, 2010). Although the mechanisms underlying this association are yet to be fully described, it has been suggested that the hormonal and metabolic effects of excess body fat, which include the effects on insulin, glucose, FFA, sex steroids and glucocorticoid activity, can be influential in the development of hypertension and diabetes, and these could also increase the risk of associated cardiovascular events (Després *et al.*, 1990; Jensen, 2008). Conversely, the increase in skeletal muscle mass can indirectly benefit cardiovascular risk by increasing resting metabolic rate (Zurio *et al.*, 1990). It has been proposed that the resulting increase in daily energy expenditure will enable greater control of body mass, although evidence from studies testing this theory by examining the benefits of resistance training on body mass and body fat are currently inconsistent (Donnelly *et al.*, 2009). In addition, greater muscle mass will facilitate participation in greater amounts of physical activity, which is of importance in consideration of the inverse relationship between physical activity and cardiovascular risk (Myers *et al.*, 2004).

Although our findings of improvements in muscle mass do reflect the effects of exercise previously reported in men on ADT, we have provided the first evidence of statistically significant changes in fat mass with a lifestyle intervention in such a patient group. Several studies have described no effects or negative changes in anthropometric measures with exercise-based lifestyle interventions (Galvão *et al.*, 2006; Alberga *et al.*, 2012), however benefits to muscle mass were previously reported by Galvão *et al.* (2010). Over the duration of a 12 week gym-based training regime, Galvão *et al.* (2010) described statistically significant improvements in lean body mass in comparison with a non-exercising control group (mean difference in Δ = 0.76 kg; 95% CI, 0.01 to 1.50), but no differences were found between groups for the effects on body fat mass (mean difference in Δ = -0.01 kg; 95% CI, -0.82 to 0.79) or body fat percentage (mean difference in Δ = -0.34 kg; 95% CI, -1.0 to 0.41).

The reasons for greater fat loss in the current study as compared with previous exercise studies in men on ADT can only be speculated on; however, the delivery of dietary advice in addition to the exercise training could be important. Dietary modification has only been part of one previous exercise study in men on ADT (Bourke *et al.*, 2011) which reported no changes in body mass, BMI or waist-to-hip ratio, but did not investigate further measures of body composition. Changes in dietary content can influence energy intake, which accounts for one side of the energy balance equation that describes the process of body mass management, and hence, provides a key modifiable factor to achieve reductions in body fat mass. Furthermore, small changes in dietary content may be influential in changes in body composition even without changes in absolute energy intake. For example, Fernández de la Puebla *et al.* (2003) demonstrated that dietary modification that included reducing saturated fat consumption and increasing monounsaturated fat intake could decrease body fat mass in hypercholesterolemic males even though total calorie intake was not altered. Although no changes in diet were observed in the current study this could be due, at least in part, to a weakness in the use of diet diaries to monitor dietary content. Diet diaries provide a practical gauge of nutritional consumption; however, the current study found the level of detail with which participants reported food intake varied greatly. In-spite of participants being given clear instructions on recording food content and portion size, many diet diaries were completed with limited details, and thus the accuracy with which dietary content was measured must be questioned. This is an issue that has previously been shown with use of diet diaries (Myers *et al.*, 1988), and hence alternative methods of dietary analysis must be considered in any future studies in this area.

As previously described, the evidence of an effect of the intervention on blood pressure could also be considered indicative of a reduction in cardiovascular risk. High blood pressure is a major risk factor for cardiovascular accidents and is considered the most important cause for global mortality, accounting for 13% of deaths worldwide (World Health

Organisation, 2009). Reducing blood pressure has been associated with a decrease in the risk of cardiovascular events and mortality (Antonakoudis *et al.*, 2007). Accordingly, the statement on management of hypertension by the World Health Organisation and the International Society of Hypertension recommends that all individuals should adopt appropriate lifestyle modifications to reduce blood pressure for reductions in cardiovascular risk (World Health Organization, International Society of Hypertension Writing Group. 2003).

In previous exercise studies in men on ADT, the effects on blood pressure has been under-reported as data for pre and post intervention has only been provided by two studies (Culos-Reed *et al.*, 2010; Nobes *et al.*, 2012). Although Culos-Reed *et al.* (2010) described statistically significant improvements in both systolic and diastolic blood pressure over the duration of their 16 week intervention for men in the exercise group (mean reduction 8.9 ± 20.9 mm Hg and 5.6 ± 11.4 mm Hg for systolic and diastolic blood pressure, respectively), blood pressure changes for men in the non-exercising control group were of a similar magnitude (mean reduction 7.3 ± 19.3 mm Hg and 6.2 ± 9.7 mm Hg for systolic and diastolic blood pressure, respectively), and hence no time by group effect was found. Our data clearly supports these findings as, although we also did not find a statistically significant interaction between groups, small or medium effects of the intervention to reduce systolic, diastolic and mean arterial blood pressure were observed. It is noted that the mean difference between groups in the change of blood pressure measures observed in the current study exceeds that reported by Culos-Reed *et al.* (2010) highlighting the greater strength of the current findings. Differences between groups were observed for changes in blood pressure in the study by Nobes *et al.* (2012) who found a 6.0 ± 10.1 mm Hg decrease in systolic blood pressure in men in the intervention group with little change in the controls. However, the inclusion of treatment with Metformin as part of the intervention delivered to participants means that the effects attributed to lifestyle change alone cannot be deduced from these findings.

Although it has already been stated that the reduction in blood pressure may have beneficial effects for the measures of vascular function, the reverse of this could also be true. Changes in endothelial function leading to an increase in bioavailable NO might also contribute to a reduction in blood pressure (Förstermann and Sessa, 2012), as the vaso-relaxing effects of NO decrease vascular tone and consequently reduce systemic pressure. In addition, exercise induced changes in vasoconstrictor concentrations might also be influential in the reductions in blood pressure observed. Exercise training has been shown to decrease expression of endothelin-1 mRNA (Maeda *et al.*, 2002), while there is some speculation that training can reduce sympathetic nervous system activity leading to a reduction in norepinephrine concentrations (Mueller, 2007).

The observed increase in exercise capacity in the current study can also be considered in the context of evidence of a benefit to cardiovascular health from participation in the intervention. This association can be made in consideration of previous evidence of an inverse relationship between the volume of physical activity performed or the level of physical fitness, and the incidence of cardiovascular events or mortality (Lee and Skerrett, 2001; Myers *et al.*, 2004; Ruiz *et al.*, 2008). In a review of studies investigating the effects of fitness on mortality from cardiovascular disease, Nocon *et al.* (2008) reported a 35% risk reduction (95% CI, 30-40%) for those with the highest fitness levels in comparison with those who have the lowest fitness levels.

The mechanisms behind such a reduction in cardiovascular risk with exercise remain incompletely understood. In a prospective study of 27,055 participants, Mora *et al.*, (2007) reported that the effect of exercise on traditional and novel cardiovascular risk factors (body mass, BMI, blood lipids, blood pressure, homocysteine, diabetic status and inflammatory biomarkers) only accounted for 59% of the reduction in risk, and hence 41% of cardiovascular risk reduction is mediated via other routes. Direct effects of exercise on endothelial function, as previously described, provided one potential means of a reduction in cardiovascular risk without a concomitant

reduction in traditional risk factors, however understanding further mechanisms underlying this association clearly requires further investigations.

The findings of increased exercise tolerance and physical function in men randomised to the intervention are consistent with evidence previously presented on the effects of exercise on such outcomes in men on ADT (Galvão *et al.*, 2006; Culos-Reed *et al.*, 2007; Galvão *et al.*, 2010; Bourke *et al.*, 2011). Although comparisons between studies are limited by the use of different tests for both exercise tolerance and physical function, analysis of the magnitude of change in performance reported in different studies demonstrates the strength of the results in the present study. The change in both physical performance measures at the end-point assessment in the current study were not as large as those reported by Bourke *et al.* (improvements of 41% and 44% for exercise tolerance and physical function, respectively, measured using the same tests as in the current study), however the 23% increase in treadmill time and 20% improvement in chair sit-to-stand test performance found in the current study exceeded the changes in physical performance reported in other studies (Galvão *et al.*, 2006; Culos-Reed *et al.*, 2007; Galvão *et al.*, 2010). While Culos-Reed *et al.* (2007) reported an 11% increase in walking distance for the 6 minute walk test, Galvão *et al.* reported improvements of 7% (Galvão *et al.*, 2006) and 4% (Galvão *et al.*, 2010) for 400 m walk time. There could be a number of reasons for these differences in improvements in exercise performance. Firstly, the different tests used for measurement of physical fitness will allow differences in the strategy of pacing and the self-imposed physical effort on behalf of the participant. Use of the graded treadmill test with predefined speed increments in the current study and that by Bourke *et al.* (2011) meant that participants were not able to self-pace their performance in the same manner as they could in an assessment of time to completion such as the 400 m walk test used by the Galvão group or the 6 minute walk test employed by the Culos-Reed group. Hence, exercising participants on a treadmill up to a pre-defined criterion for test termination could have meant they were encouraged to perform up to the same level of physical strain in

repeat exercise tests, while these other forms of exercise tests could have been hindered by participants not feeling the need to push themselves on subsequent test performances. This demonstrates the importance of future research projects employing similar exercise tests to those previously used as this will allow greater comparison between studies. Additionally, the time spent performing aerobic exercise under supervision could also provide a difference between studies that could affect exercise tolerance results. In the current study, and that by Bourke *et al.* (2011), participants completed 30 minutes of aerobic exercise in each of the 18 sessions; thus accumulating 9 hours of supervised aerobic exercise over the duration of the study. Conversely, Galvão *et al.* (2010) asked participants to perform 15 to 20 minutes of exercise for 24 sessions leading to completion of 6-8 hours of aerobic activity over the duration of the study, while in the resistance exercise based study of Galvão *et al.* (2006), and the home-based exercise studies performed by the Culos-Reed group, participants did not undertake supervised aerobic exercise. Consequently, the greater time spent performing aerobic exercise under supervision could be expected to have led to the greater increases in exercise tolerance observed, although studies investigating the volume of supervised activity required to gain maximum benefits are still warranted in this population.

In addition to evidence of increased physical performance, leisure time physical activity was also shown to be increased in men in the intervention group, with the difference between groups showing significance at the end of the intervention. This finding has clinical significance because Godin LSI quantifies the volume of activity participants were performing in addition to that being prescribed under the supervision of the instructor, and thus provides a measure of whether the increased activity they were performing within the supervised setting was resulting in increased activity outside of this environment. Being able to encourage participants to increase home-based activity was deemed important, as this would be the most sustainable form of activity for them once the intervention was completed and because previous evidence has shown that leisure time and household physical activity is

associated with improvements in cardiovascular risk factors including hypertension, HDL-C and plasma fibrinogen concentrations (Fransson *et al.*, 2003). It is noted that the difference between the groups at end-point was removed at follow-up assessment suggesting that although participants would increase home-based activity while they are engaged in supervised sessions, the cessation of the supervision results in a decrease in activity at home. Clearly this provides an issue for further research as strategies must be employed to ensure activity levels are maintained or increased after the completion of supervised exercise training.

The current study also supports previous research that has shown the benefits of healthy lifestyle changes for overall quality of life and fatigue in men on ADT (Segal *et al.*, 2003; Culos-Reed *et al.*, 2007; Galvão *et al.*, 2010; Bourke *et al.*, 2011). Use of different measurement tools again complicates comparisons between studies, however, comparing the results of the current study against previous investigations that have used Fact-P and Fact-F (Segal *et al.*, 2003; Bourke *et al.*, 2011) shows that our findings are similar to, or exceed, the results reported in these studies. The difference between groups for quality of life at end-point assessment was greater than has previously been reported at the end of an exercise intervention. Bourke *et al.* (2011) reported a non-significant improvement in Fact-P of 5.5 points (95% CI, -4.2-15.3), while data from Segal *et al.* (2003) showed a statistically significant difference between group means at end-point assessment of a similar magnitude (around 5 points). Conversely, the change in fatigue at the end of the intervention in the current study was lower than that reported by Bourke and colleagues (5.4 points; 95% CI, 0.8-10.0) but still exceeded that reported by Segal *et al.* (mean difference -1.6 points). It is worthy of note that our findings are the first to demonstrate mean improvements in both Fact-P and Fact-F exceeding the MCID after a lifestyle intervention in men on ADT.

It is of interest that change in body fat mass was found to be a strong predictor of the changes observed in quality of life and fatigue. Increased body fat mass is an established consequence of ADT (Haseen *et al.*, 2010) attributed to the drastic reduction in serum testosterone concentrations with

treatment (De Pergola, 2000), while negative changes in quality of life and fatigue are also accepted effects of treatment (Herr and O'Sullivan, 2000). Previous research however has not shown a link between these effects. Studies investigating predictors of the negative psychological changes with ADT have either not investigated, or shown no effect of body composition (Stone *et al.*, 2000; Dacal *et al.*, 2005). It could be speculated therefore that the difference in findings in the current study could be due to the direction of the association. While these previous studies have investigated whether body composition at a single time point predicts quality of life or fatigue at that time, or if negative changes in quality of life or fatigue are predicted by alterations in body composition, they have not examined whether positive changes in either psychological well-being or body composition are predictive of each other. With the rapid increase in body fat upon commencement of ADT (van Londen *et al.*, 2008) it could be speculated that the psychological strain of starting more radical treatment for prostate cancer could outweigh the impact of increased fat mass in terms of the determinants of quality of life and fatigue. Conversely, it could also be possible that these results are simply explained by men in this population placing a greater importance on positive body composition changes. Further studies investigating positive or negative changes in psychological well-being and body composition in a larger cohort would be required to further understand the association between these effects of treatment.

Investigation of the differences in FMD cuff placement for measurement of changes in endothelial function in this population demonstrated large discrepancies between techniques. While results for the traditional distal cuff FMD are suggestive of reductions in cardiovascular risk across the duration of the study in both groups, conflicting findings were provided using the proximal cuff method. Furthermore, analysis of the relationship between the magnitude of dilatation achieved using the different techniques demonstrated no correlation between measures. It has previously been reported that FMD assessments conducted using a proximal cuff placement can be more challenging as a result of the occluding cuff collapsing or distorting the distal

arterial segment being imaged (Charakida *et al.*, 2010) and this was found to be the case in the current study. It was observed that arterial movement on cuff inflation and subsequent deflation influenced the data obtained. In such men use of distal cuff occlusion methods therefore provides a more reliable estimate of arterial dimensions.

The results from the current study support evidence that lifestyle interventions in men with prostate cancer treated with ADT are feasible, safe and well-tolerated. No changes in markers of disease progression were observed in the current study, which is in agreement with the findings of previous investigations of lifestyle interventions in men treated for prostate cancer (Schmitz *et al.*, 2010). The current study did find a large effect of the intervention on SHBG concentrations, however this should not be deemed to be detrimental to prostate cancer progression. Such a decrease in SHBG would be expected to be responsible for the observed reduction in bioavailable testosterone in men in the intervention group due to the high affinity of SHBG to bind testosterone (Selby, 1990), and thus there should be a reduction in the amount of testosterone that could drive cancer progression. SHBG has previously been shown to increase after lifestyle interventions including exercise and diet in healthy adult males (Tymchuk *et al.*, 1998; Longcope *et al.*, 2000) with these effects possibly mediated by the impact of these interventions on insulin concentrations. Accordingly, it is noted that the changes observed in SHBG in the current study could also be representative of the effects of the intervention on insulin concentrations, and consequently may also be indicative of improvements in cardiovascular health. SHBG concentrations have been inversely associated with insulin resistance (Wallace *et al.*, 2013), and thus the evidence of a difference between groups in SHBG at the end of the intervention could represent differences in insulin clearance rates and consequently variations between the groups in the risk of developing type II diabetes mellitus. The mechanisms that underlie such a relationship between SHBG and insulin levels remain incompletely understood however, as Wallace *et al.* (2013) state that it is unclear whether

altered SHBG concentrations are a cause or a consequence of changes in insulin resistance.

Participant retention in the current study is comparable to that previously reported in exercise studies in men on ADT. Analysis of studies using primarily gym-based, instructor-led exercise sessions shows median retention rates of 89% (range 63-100%) from baseline to the end of the intervention (Segal *et al.*, 2003; Galvão *et al.*, 2006; Hansen *et al.*, 2009; Galvão *et al.*, 2010; Bourke *et al.*, 2011), which is only marginally higher than that achieved in the current study (84% completed end-point assessment). It should also be noted that comparing retention at follow-up from the current study against the only other study in such a population to include a follow-up assessment (Bourke *et al.*, 2011), demonstrates that loss to follow-up in the current study was far less than previously reported (80% completion of follow-up assessment in the current study compared to 56% completion previously reported).

Attendance at instructor-led exercise sessions was also equal to, or in excess of, attendance rates previously reported in exercise studies using instructor-led, gym-based exercise with men on ADT (Segal *et al.*, 2003; Galvão *et al.*, 2010; Bourke *et al.*, 2011), while compliance with home-based exercise was marginally lower than has previously been reported (Bourke *et al.*, 2011). We observed a small, but insignificant, decrease in attendance at instructor led sessions and compliance with home-based exercise over weeks 7 to 12 in comparison with weeks 1-6, which could be associated with a slight decrease in training impulse when participants switch from having contact with the instructor twice a week to only once a week. Regardless of this effect being observed with decreasing contact time, the current study still supports previous evidence suggesting that, in men with prostate cancer, greater benefits are accrued through supervised exercise training in comparison with home-based exercise (Baumann *et al.*, 2012). Studies in men treated with ADT for prostate cancer using supervised exercise training have shown improvements in psychological well-being, physical function and muscle mass (Segal *et al.*, 2003; Galvão *et al.*, 2010; Bourke *et al.*, 2011),

however, only improvements in exercise test performance have been reported in studies using home-based activity (Culos-Reed *et al.*, 2007; Culos-Reed *et al.*, 2010). In addition, the reductions in measures of exercise tolerance, quality of life and fatigue observed between end-point and follow-up in the current study and that by Bourke *et al.* (2011) are suggestive of patients not being able to maintain performance levels, and the subsequent health benefits, once supervision is removed.

In conclusion, this study demonstrates that a lifestyle intervention including supervised exercise training and dietary advice can lead to statistically significant improvements in activity levels, exercise tolerance, body composition, quality of life and fatigue in men with prostate cancer treated with ADT. The current study also provides evidence that such an intervention can have beneficial effects on markers of cardiovascular risk, including endothelial function and diastolic blood pressure, although the change in these measures must be investigated in a larger cohort before this response can be confirmed. Furthermore, our findings support evidence that lifestyle interventions are well tolerated in this patient group and demonstrate that greater benefits are achieved when patients receive supervised exercise training compared to when they are left unsupported.

10.0 GENERAL DISCUSSION

This general discussion is designed as an appraisal of the research studies completed in this thesis. The key findings are reviewed and the limitations of these studies are discussed with specific regards to the implications for future research in this area.

10.1 Main findings

The key findings of these studies are:

1. Endothelial function is reduced in men with prostate cancer treated with ADT in comparison with a group of matched controls. This finding is of scientific interest as these results directly contradict the findings of the only previous study investigating endothelial function in men treated with ADT (Herman *et al.*, 1997), yet they are congruent with the majority of the scientific literature which describes an increase in cardiovascular risk in men treated with ADT. Although these findings must be confirmed by further studies using a larger sample size, evidence of endothelial dysfunction in men on ADT provides a possible physiological link between the evidence of increased prevalence of cardiovascular risk factors (e.g. increased fat mass, insulin resistance, hyperlipidemia) and data suggesting men on ADT are at increased risk of cardiovascular events. Furthermore, this evidence demonstrates that ultrasound assessment of FMD in the brachial artery can provide a suitable method for monitoring cardiovascular risk in this patient group. Further studies monitoring longitudinal changes in FMD in this patient group with baseline assessments performed prior to commencement of ADT would provide even greater insight into the effects of this form of treatment on vascular function.

2. Supervised exercise training and dietary advice could have beneficial effects on cardiovascular risk in men treated with ADT for prostate cancer. In

addition to statistically significant differences being observed between groups in the changes in body composition over the duration of the intervention, the effects of the intervention on FMD and blood pressure are suggestive of a reduction in cardiovascular risk. Although the changes in these latter measures did not achieve the alpha of 0.05 required for statistical significance, the magnitude of the changes observed within the intervention group, and the evidence of meaningful effect sizes for the difference between groups for the change from baseline, support the notion of a benefit of participation in the intervention. In consideration of previous studies describing an increase in cardiovascular risk in men treated with ADT (Levine *et al.*, 2010; Bourke *et al.*, 2012), our data provides encouraging evidence of the benefits of such an intervention. Investigation of the changes in these measures in a larger cohort will be required before such an effect can be described with confidence.

3. Improvements in physical and mental well-being are observed after a lifestyle intervention including supervised exercise training and dietary advice in men with prostate cancer treated with ADT. Our findings support those previously reporting benefits to exercise tolerance, quality of life and perceptions of fatigue in men treated with ADT taking part in a lifestyle intervention (Segal *et al.*, 2003; Galvão *et al.*, 2010; Bourke *et al.*, 2011). These findings are of clinical importance in consideration of the reduction in general well-being reported in men treated in this manner (Casey *et al.*, 2012). Greater promotion of physical activity is warranted in men on ADT to help to reduce the burden of such side effects of treatment.

4. Improvements observed over a period of supervised exercise training and dietary advice are not maintained after cessation of the supervision. This finding is of clinical importance for the development of further studies investigating the benefits of lifestyle interventions in this population and for health-care providers considering implementing lifestyle interventions in men on ADT. Due to the logistical and economical strains of providing on-going support for patients it is imperative that the benefits accrued from participating in interventions such as this can be maintained once the

supervision is removed. Our finding of a reduction in activity levels and negative changes in measures of physical and mental well-being once the supervised sessions were completed could be considered a weakness of the implementation of the intervention in our study. Strategies to ensure that patients can maintain the benefits achieved over a period of supervision must be designed and tested in this population.

10.2 Study limitations and implications for future research

10.2.1 *Study 1: Cross-sectional evaluation of endothelial function in men on ADT*

The case-control design of this study provides one limitation which should be addressed in future research. Although groups were well-matched for many confounding variables (e.g. age, body mass, smoking status and history of cardiovascular disease), comparing the results of men treated with ADT for prostate cancer against a separate group of control men could result in variables not measured in the current study and unrelated to androgen concentrations influencing the findings (e.g diet, personal stress levels and family history of cardiovascular disease). Moreover, variability of FMD is thought to be lower within participants rather than between individuals leading to possible errors in findings between groups due to FMD variation. Further studies should therefore investigate longitudinal changes in FMD in men on ADT with initial assessments undertaken before starting treatment. Although this was beyond the scope of the current study, our results suggest that FMD is a viable measure of cardiovascular risk in this population and thus demonstrate longitudinal assessments of FMD in men on ADT for prostate cancer are warranted.

In addition, the lack of a control group who have prostate cancer but are not treated with ADT means that the effects of the treatment cannot be distinguished from the effects of the disease. Recent evidence has demonstrated that men with prostate cancer not receiving treatment (under active surveillance) were at increased risk of cardiovascular disease

compared with the general male population (Van Hemelrijck *et al.*, 2010), possibly indicating a direct effect of prostate cancer on cardiovascular disease risk. However, risk factors for prostate cancer include factors that also contribute to increased cardiovascular risk, such as increased body mass. Thus, the evidence of increased risk of cardiovascular disease with prostate cancer might be the result of shared risk factors instead of a direct impact of prostate cancer. Controlling for the effects of disease in the current study was considered outside of the aims of the study which sought to investigate the impact of ADT in the treatment of prostate cancer on cardiovascular risk factors. This is considered pertinent as the use of ADT for reasons other than the treatment of prostate cancer would be very rare. It was also considered that recruitment of a suitable control group of men matched for disease stage and health history would provide logistical and ethical problems. Men with prostate cancer not treated with ADT would be expected to have differences in their disease or health contradicting ADT use making them poorly matched with the ADT group. Therefore, recruitment of suitably matched men would require delaying treatment initiation or suspending an active treatment program to allow measures to be taken; both of which would not be considered ethical. These are issues which further research studies in this area must consider in their study design.

The relatively small sample size is a limitation of our study. Only recruiting twenty men per group means the findings must be confirmed in studies investigating the effects of treatment with ADT on endothelial function in larger cohorts. Furthermore, future studies must ensure inclusion and exclusion criteria allow the results to be a generalisable as possible. Our sample is considered more representative of the wider population from which they were recruited than previous investigations of endothelial function in men on ADT (Herman *et al.*, 1997) in consideration of the inclusion of men with cardiovascular comorbidities (American Heart Association, 2013) and the physically inactive nature of our sample (British Heart Foundation Health Promotion Research Group, 2012). However, because men with ADT were sampled from those entering the intervention study meeting the inclusion

criteria for the cross-sectional evaluation, our results can only be generalised to a small proportion of men. Of the 837 men under treatment with ADT who were screened for participation only 323 met the inclusion criteria for the intervention study (39% of those initially screened), and then only 76% of men in the intervention study met the criteria for inclusion in the cross-sectional study. Assuming this percentage of men meeting the criteria for inclusion in the cross-sectional study could be found in those meeting the criteria for the intervention study, it would suggest that only 29% of men on ADT under the local Urology clinic (n = 245) would be suitable for participation (76% of 323, expressed as a percentage of 837). Clearly, further research in this area must aim to include a greater proportion of men treated in this manner.

10.2.2. *Study 2: Lifestyle intervention in men with prostate cancer treated with ADT*

As is discussed briefly in the experimental discussion (9.0 Discussion: Study 2), the sample size and patient attrition rates limit the findings of the study. This study was powered to detect a 2.6 ± 3.0% difference in relative FMD, with the sample size taking account of an expected 10% attrition rate at the end of the intervention. However, the loss of 8 men at this stage (16% of the initial sample), combined with a higher than expected variance means that our study was under powered to detect a difference of that magnitude between groups. Nevertheless, the 95% CI for the difference detected, suggests that an improvement in FMD of up to 4% is feasible, potentially resulting in a clinically meaningful reduction in cardiovascular risk in this high-risk group. Thus, investigation of changes in endothelial function over the duration of a lifestyle intervention must be performed in studies with larger samples. In addition to providing a clearer picture of the effects of a lifestyle intervention on endothelial function, a larger sample size could also provide greater evidence for the changes in blood pressure observed between groups, as here again our study was limited in its findings by lack of statistical power.

The findings of the intervention study are also influenced by participants in the control group increasing their physical activity levels during the study. It can be expected that increased physical activity in the controls will have had knock-on effects for changes in outcomes observed in this group, and thus will also have influenced the differences found between groups and the magnitude of the effect that can be attributed to the intervention. Although little change was observed in exercise tolerance, Godin LSI scores for men in the control group increased from baseline by 3.0 ± 11.6 points and 7.2 ± 24.3 points at end-point and follow-up, respectively. These findings are of little surprise, as previous studies have reported that such a response is often found in exercise intervention studies (Courneya *et al.*, 2004). This stands to reason, because for patient recruitment the potential benefits accrued through healthy lifestyle changes are provided to the participant as incentive to participate, and thus it must be expected that those not in the intervention will still want to achieve such benefits. It is notable however that the increase in activity and small improvements in outcome measures observed in the controls were generally found after the mid-point assessment. This leads to speculation that the feedback given on the change in measures between baseline and mid-point acted as incentive for these individuals to make such changes. Understanding whether such feedback was a causal factor in increased activity in the control group would be of interest as this information could help to guide those looking to increase activity in this population without performing supervised interventions. Clearly greater effort should go in to reducing such an effect in future studies, and thus, methods to achieve this must be considered.

Conversely however, it must also be noted that the current study may be limited by some participants in the exercise group having no response or adverse metabolic responses to the increase in physical activity in agreement with the work of Timmons *et al.* (2010) and Bouchard *et al.* (2012). Although increased physical activity has been widely associated with improvements in fitness and benefits to numerous cardiometabolic risk factors such as blood pressure, blood lipids, insulin and glucose concentrations, these recent

studies have suggested not everyone will have such responses. The work of Timmons *et al.* (2010) demonstrated that some individuals may have a genetic variation limiting gains in aerobic fitness to exercise training, while the more recent work of Bouchard *et al.* (2012) has described that around 10% of people can have negative responses in measures of such cardiometabolic risk factors after exercise training. In the context of the current study these findings could suggest that the lack of greater difference between groups is not in-fact due to an increase in activity in the control group, but the result of no response or negative responses from some members of the intervention group decreasing the magnitude of the difference between groups. Although such limitations are difficult to overcome these issues must be considered in further studies in this area. Genetic testing prior to study enrolment could distinguish those who could be non-responders, while more tailored training could be beneficial for adverse responders.

As is mentioned in the limitations of the first study, the generalisability of results is an additional limitation of the second study. The fact that only 39% of men treated with ADT identified in clinic met the inclusion criteria for participation demonstrates that greater effort must be placed on ensuring future studies are as inclusive as possible. Although excluding men was necessary for patient safety and to increase the scientific integrity of the study, it means that the results are only applicable to men with prostate cancer treated with ADT who have stable disease, are currently inactive and who have no comorbidities that could have limited their participation in the study. To achieve greater inclusion however the methods for participant recruitment must also be reviewed, as it can be speculated that selection bias could be inherent in recruitment from clinics performed by the primary study researcher. It is possible that men seen in clinic could be deemed unsuitable to participate based upon appearance rather than medical information or verbal confirmation of meeting exclusion criteria.

Similarly, ensuring that the assessments and intervention undertaken in the study are as inclusive as possible for those consenting to participate is a further area for consideration for future research. The finding of lower

baseline exercise tolerance and increased fatigue amongst men dropping out of the current study prior to the end-point assessment is in agreement with previous research on determinants of attrition from physical activity programs for older adults (Jancey *et al.*, 2007). As such, this could have a number of implications for further research in these men. Measures of fatigue or exercise tolerance could be used to screen out those who were more likely to be non-compliant with the aim of decreasing attrition rates in such studies. Alternatively, greater efforts could be made to increase retention of patient groups with low baseline fitness and higher fatigue. This would seem the preferable option, as it is the participants with the lowest exercise capacity and greatest fatigue at baseline that could be expected to gain the greatest benefits from participation in such studies.

It is evident that further research is also warranted to investigate the volume of exercise training required to gain health improvements in such a population. Our intervention was designed to be clinically relevant and so the duration and intensity of exercise completed within the exercise sessions was tailored to the ability and tolerance of individual participants to elicit a heart rate within a specified range, and then progressed as the participants changing fitness and strength permitted. However, the weakness inherent in such an approach is that the intensity and duration of exercise required to achieve this response varied greatly between participants meaning the exact volume of activity performed cannot be specifically noted. This is also the case with home-based activity where participants were asked to use RPE to monitor exercise intensity. Although use of RPE provides a guide for monitoring exercise intensity suitable for this population who would be unlikely to have access to more sophisticated equipment for intensity monitoring, and despite participants been given instructions as to how to use RPE to monitor activity, this again means the activity volume cannot be specifically calculated.

Furthermore, while this study and that of Bourke *et al.* (2011) demonstrate benefits from a lifestyle intervention with progressively decreasing contact time, the ideal frequency and duration of supervised sessions cannot be

deduced from these studies. It has been shown that greater benefits are gained by prostate cancer patients participating in supervised exercise training compared with unsupervised home-based activity (Baumann *et al.*, 2012). However, for such exercise interventions to be adopted as part of standard clinical practice, further information on the volume of training needed is required to understand the supervision patients will require to gain health benefits, and to enable health authorities to ascertain whether supplying such additional care would be cost effective.

Lastly, the duration of follow-up can be considered an additional limitation of the current study and one that further research in this area could look to address. Although this is only the second exercise study in this population to include a follow-up assessment (Bourke *et al.*, 2011), it would be of interest for follow-up to be conducted over a longer duration as this could allow investigation of whether or not participation in such an intervention can lead to long-term reductions in the incidence of cardiovascular events and mortality. Furthermore, undertaking long-term follow-up of patients could provide greater evidence on whether increasing activity levels through participation in such an intervention can reduce prostate cancer specific mortality, as retrospective studies have shown that men with higher activity levels have a reduced rate of disease progression or mortality (Kenfield *et al.*, 2011; Richman *et al.*, 2011).

10.3 Summary

These studies provide novel data on markers of cardiovascular health in men treated with ADT for prostate cancer. The findings of our studies and their implication for future research demonstrate that the cardiovascular health of this patient group remains an area of scientific interest. Further research in this area is clearly warranted to build on the data we have presented.

11.0 REFERENCES

Ahn, J., Albanes, D., Peters, U., Schatzkin, A., Lim, U., Freedman, M., Chatterjee, N., Andriole, G.L., Leitzmann, M.F. and Hayes, R.B. (2007). Dairy products, calcium intake, and risk of prostate cancer in the prostate, lung, colorectal, and ovarian cancer screening trial. *Cancer Epidemiology, Biomarkers and Prevention*, **16**, 2623-2630.

Ahn, J., Moslehi, R., Weinstein, S.J., Snyder, K., Virtamo, J. and Albances, D. (2008). Family history of prostate cancer and prostate cancer risk in the Alpha-Tocopherol, Beta-Carotene cancer prevention (ATBC) study. *International Journal of Cancer*, **123**, 1154-1159.

Akishita, M., Hashimoto, M., Ohike, Y., Ogawa, S., Iijima, K., Eto, M. and Ouchi, Y. (2007). Low testosterone level is an independent determinant of endothelial dysfunction in men. *Hypertension Research*, **30**, 1029-1034.

Alberga, A.S., Segal, R.J., Reid, R.D., Scott, C.G., Sigal, R.J., Khandwala, F., Jaffey, J., Wells, G.A. and Kenny, G.P. (2012). Age and androgen-deprivation therapy on exercise outcomes in men with prostate cancer. *Support Cancer Care*, **20**, 971-981.

Albertson, P.C. (2003). The prostate cancer conundrum. *Journal of the National Cancer Institute*, **95**, 930-931.

Albertsen, P.C., Hanley, J.A. and Fine, J. (2005). 20-year outcomes following conservative management of clinically localised prostate cancer. *Journal of the American Medical Association*, **293**, 2095-2101.

Albertsen, P.C. (2010). Efficacy vs effectiveness in prostate-specific antigen screening. *Journal of the National Cancer Institute*, **102**, 288-289.

Alibhai, S.M.H., Duong-Hua, M., Sutradhar, R., Fleshner, N.E., Warde, P., Cheung, A.M. and Paszat, L.F. (2009). Impact of androgen deprivation

therapy on cardiovascular disease and diabetes. *Journal of Clinical Oncology*, **27**, 3452-3458.

Alicikus, Z.A., Yamada, Y., Zhang, Z., Pei, X., Hunt, M., Kollmeier, M., Cox, B. and Zelefsky, M.J. (2010). Ten-year outcomes of high-dose, intensity-modulated radiotherapy for localized prostate cancer. *Cancer*, **117**, 1429-1437.

Al-Qaisi, M., Kharbanda, R.K., Mittal, T.K. and Donald, A.E. (2008). Measurement of endothelial function and its clinical utility for cardiovascular risk. *Vascular Health and Risk Management*, **4**, 647-652.

Al Suwaidi, J., Higano, S.T., Holmes, D.R., Lennon, R. and Lerman, A. (2001). Obesity is independently associated with coronary endothelial dysfunction in patients with normal or mildly diseased coronary arteries. *Journal of the American College of Cardiology*, **37**, 1523-1528.

American College of Sports Medicine (2009). ACSM's Guidelines for exercise testing and prescription. Eighth Edition. Baltimore: Wolters Kluwer. Lippincott, Williams and Wilkins.

American College of Sports Medicine. (2013). Position stands. Aug/13, http://www.acsm.org/access-public-information/position-stands

American Heart Association (2013). Older Americans and cardiovascular diseases. Statistical fact sheet 2013 update. Mar/13, http://www.heart.org/idc/groups/heart-public/@wcm/@sop/@smd/documents/downloadable/ucm_319574.pdf..

Anderson, T.J. (2006). Arterial stiffness or endothelial dysfunction as a surrogate marker of vascular risk. *Canadian Journal of Cardiology*, **22**, 72B-80B.

Andersson, S.O., Wolk, A., Bergström, R., Adami, H.O., Engholm, G., Englund, A. and Nyrén, O. (1997). Body size and prostate cancer: a20-year follow up study among 135,006 Swedish construction workers. *Journal of the National Cancer Institute*, **89**, 385-389.

Andriole, G.L., Crwford, D., Grub, R.L., Buys, S.S., Chia, D., Church, T.R., Fouad, M.N., Gelmann, E.P., Kvale, P.A., Reding, D.J., Weissfeld, J.L., Yokochi, L.A., O'Brien, B., Clapp, J.D., Rathmell, J.M., Riley, T.L., Hayes, R.B., Kramer, B.S., Izmirlian, G., Miller, A.B., Pinsky, P.F., Prorok, P.C., Gohagan, J.K. and Berg, C.D. (2009). Mortality results from a randomized prostate-cancer screening trial. *New England Journal of Medicine*, **360**, 1310-1319.

Antonakoudis, G., Poulimenos, I., Kifnidis, K., Zouras, C. and Antonakoudis, H. (2007). Blood pressure and cardiovascular risk reduction. *Hippokratia*, **11**, 114-119.

Araujo, A.B., O'Donnell, A.B., Brambilla, D.J., Simpson, W.B., Longcope, C., Matsumoto, A.M. and McKinlay, J.B. (2004). Prevalence and incidence of androgen deficiency in middle-aged and older men: Estimates from the Massachusetts Males Aging Study. *Journal of Clinical Endocrinology and Metabolism*, **89**, 5920-5926.

Arkin, JM., Alsdorf, R., Bigornia, S., Palmisano, J., Beal, R., Istfan, N., Hess, D., Apovian, C.M. and Gokce, N. (2008). Relation of cumulative weight burden to vascular endothelial dysfunction in obesity. *American Journal of Cardiology*, **101**, 98-101.

Arnett, D.K., Evans, G.W. and Riley, W.A. (1994). Arterial stiffness: A new cardiovascular risk factor? *American Journal of Epidemiology*, **140**, 669-682.

Atkinson, G. and Nevill, A.M. (1998). Statistical methods for assessing measurement error (reliability) in variables relevant to sports medicine. *Sports Medicine*, **26**, 217-238.

Atkinson, G., Batterham, A.M. (2013). Allometric scaling of diameter change in the original flow-mediated dilation protocol. *Atherosclerosis*, **226**, 425-427.

Atkinson, G., Batterham, A.M., Thijssen, D.H.J. and Green, D.J. (2013). A new approach to improve the specificity of flow-mediated dilation for indicating endothelial function in cardiovascular research. *Journal of Hypertension*, **31**, 289-291.

Baade, P.D., Coory, M.D. and Aitken, J.F. (2004). International trends in prostate-cancer mortality: the decrease is continuing and spreading. *Cancer causes and control*, **15**, 237-241.

Baade, P.D., Fritschi, L. and Eakin, E.G. (2006). Non-cancer mortality among people diagnosed with cancer (Australia). *Cancer Causes and Control*, **17**, 287-297.

Barchielli, A., Crocetti, E. and Zappa, M. (1999). Has the PSA wave already crashed upon us? Changes in the epidemiology of prostate cancer from 1985 to 1994 in central Italy. *Annals of Oncology*, **10**, 361-362.

Barton, M., Baretella, O. and Meyer, M.R. (2012). Obesity and risk of vascular disease: importance of endothelium-dependent vasoconstriction. *British Journal of Pharmacology*, **165**, 591-602.

Basaria, S., Lieb, J., Tang, A.M., DeWeese, T., Carducci, M., Eisenberger, M. and Dobs, A.S. (2002). Long-term effects of androgen deprivation therapy in prostate cancer patients. *Clinical Endocrinology*, **56**, 779-786.

Basaria, S., Muller, D.C., Carducci, M.A., Egan, J. and Dobs, A.S. (2006). Hyperglycaemia and insulin resistance in men with prostate carcinoma who receive androgen-deprivation therapy. *Cancer*, **106**, 581-588.

Baum, N.H. and Torti, D.C. (2007). Managing hot flashes in men being treated for prostate cancer. *Geriatrics*, **62**, 18-21.

Baumann, F.T., Zopf, E.M. and Bloch, W. (2012). Clinical exercise interventions in prostate cancer patients- a systematic review of randomized controlled trials. *Supportive Care in Cancer*, **20**, 221-233.

Bays, H.E., Gonzalez-Campoy, J.M., Bray, G.A., Kitabchi, A.E., Bergman, D.A., Schorr, A.B., Rodbard, H.W. and Henry, R.R. (2008). Pathogenic potential of adipose tissue and metabolic consequences of adipocyte hypertrophy and increased visceral adiposity. *Expert Reviews of Cardiovascular Therapy*, **6**, 343-368.

Bernini, G., Versari, D., Moretti, A., Virdis, A., Ghiadoni, L., Bardini, M., Taurino, C., Canale, D., Taddei, S. and Salvetti, A. (2006). Vascular reactivity in congenital hypogonadal men before and after testosterone replacement therapy. *Journal of Clinical Endocrinology and Metabolism*, **91**, 1691-1697.

Bhasin, S., Storer, T.W., Berman, N., Callegari, C., Clevenger, B., Phillips, J., Bunnell, T.J., Tricker, R., Shirazi, A. and Casaburi, R. (1996). The effects of supraphysiologic doses of testosterone on muscle size and strength in normal men. *New England Journal of Medicine*, **335**, 1-7.

Bhasin, S., Storer, T.W., Berman, N., Yarasheski, K.E., Clevenger, B., Phillips, J., Lee, W.P., Bunnell, T.J. and Casaburi, R. (1997). Testosterone replacement increases fat-free mass and muscle size in hypogonadal men. *Journal of Clinical Endocrinology and Metabolism*, **82**, 407-413.

Bhasin, S., Woodhouse, L. and Storer, T.W. (2001). Proof of the effect of testosterone on skeletal muscle. *Journal of Endocrinology*, **170**, 27-38.

Bhasin, S. (2003). Effects of testosterone administration on fat distribution, insulin sensitivity, and atherosclerosis progression. *Clinical Infectious Diseases*, **37**, S142-S149.

Bhasin, S., Cunningham, G.R., Hayes, F.J., Matsumoto, A.M., Snyder, P.J., Swerdloff, R.S. and Montori, V.M. (2010). Testosterone therapy in adult men with androgen deficiency syndrome. *Journal of Clinical Endocrinology and Metabolism*, **95**, 2536-2559.

Bianchini, F., Kaaks, R. and Vainio, H. (2002). Overweight, obesity and cancer risk. *Lancet Oncology*, **3**, 565-574.

Bill-Axelson, A., Holmberg, L., Ruutu, M., Häggman, M., Andersson, S.O., Bratell, S., Spångberg, A., Busch, C., Nordling, S., Garmo, H., Palmgren, J., Adami, H.O., Norlén, B.J. and Johansson, J.E. (2005). Radical prostatectomy versus watchful waiting in early prostate cancer. *The New England Journal of Medicine*, **352**, 1977-1984.

Blacher, J., Pannier, B., Guerin, A.P., Marchais, S.J., Safar, M.E. and London, G.M. (1998). Carotid arterial stiffness as a predictor of cardiovascular and all-cause mortality in end-stage renal disease. *Hypertension*, **32**, 570-574.

Black, M.A., Cable, N.T., Thijssen, D.H.J. and Green, D.J. (2008). Importance of measuring the time course of flow-mediated dilatation in humans. *Hypertension*, **51**, 203-210.

Black, L.E., Swan, P.D. and Alvar, B.A. (2010). Effects of intensity and volume on insulin sensitivity during acute bouts of resistance training. *Journal of Strength and Conditioning Research*, **24**, 1109-1116.

Blair, S.N., Kohl, H.W., Paffenbarger, R.S., Clark, D.G., Cooper, K.H. and Gibbons, L.W. (1989). Physical fitness and all-cause mortality. A prospective study of healthy men and women. *Journal of the American Medical Association*, **262**, 2395-2401.

Blair, S.N., Kampert, J.B., Kohl, H.W., Barlow, C.E., Macera, C.A., Paffenbarger, R.S. and Gibbons, L.W. (1996). Influences of cardiorespiratory fitness and other precursors on cardiovascular disease and all-cause mortality in men and women. *Journal of the American Medical Association*, **276**, 205-210.

Blair, S.N. and Morris, J.N. (2009). Healthy heart- and the universal benefits of being physically active: Physical activity and health. *Annals of Epidemiology*, **19**, 253-256.

Blankfield, R.P. (2012). Androgen deprivation therapy for prostate cancer and cardiovascular death. *Journal of the American Medical Association*, **307**, 1252.

Block, G. (1982). A review of validations of dietary assessment methods. *American Journal of Epidemiology*, **115**, 492-505.

Bolla, M., Collette, L., Blank, L., Warde, P., Dubois, J.B., Mirimanoff, R.O., Storme, G., Bernier, J., Kuten, A., Sternberg, C., Mattelaer, J., Lopez Torecilla, J., Pfeffer, J.R., Lino Cutajar, C., Zurlo, A. and Pierart, M. (2002).

Long term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer. *Lancet*, **360**, 103-106.

Borg, G. (1970). Perceived exertion as an indicator of somatic stress. *Scandinavian Journal of Rehabilitation Medicine*, **2**, 92-98.

Borley, N. and Feneley, M.R. (2009). Prostate cancer: diagnosis and staging. *Asian Jounral of Andrology*, **11**, 74-80.

Born, G. and Patrono, C. (2006). Antiplatelet drugs. *British Journal of Pharmacology*, **147**, S241-S251.

Bosland, M.C., Kato, I., Zeleniuch-Jacquotte,A., Schmoll, J., Enk Rueter, E., Melamed, J., Kong, M.X., Macias, V., Kajdacsy-Balla, A., Lumey, L.H., Xie, H., Gao, W., Walden, P., Lepor, H., Taneja, S.S., Randolph, C., Schlicht, M.J., Meserve-Watanabe, H., Deaton, R.J. and Davies, J.A. (2013). Effect of soy protein isolate supplementation on biochemical recurrence of prostate cancer after radical prostatectomy: a randomized trial. *Journal of the American Medical Association*, **310**, 170-178.

Bouchard, C., Blair, S.N., Church, T.S., Earnest, C.P., Hagberg, J.M., Häkkinen, K., Jenkins, N.T., Karavirta, L., Kraus, W.E., Leon, A.S., Rao, D.C., Sarzynski, M.A., Skinner, J.S., Slentz, C.A. and Rankinen, T. (2012). Adverse metabolic response to regular exercise: Is it a rare or common occurrence? *PLoS One*, **7**, e37887.

Bourke, L., Doll, H., Crank, H., Daley, A., Rosario, D. and Saxton, J.M. (2011). Lifestyle intervention in men with advanced prostate cancer receiving androgen suppression therapy: A feasibility study. *Cancer, Epidemiology, Biomarkers and Prevention*, **20**, 647-657.

Bourke, L., Chico, T.J.A., Albertsen, P.C., Hamdy, F.C. and Rosario, D.J. (2012). Cardiovascular risk in androgen suppression: underappreciated, under-researched and unresolved. *Heart*, **98**, 345-348.

Bourke, L., Kirkbride, P., Hooper, R., Rosario, A.J., Chico, T.J.A. and Rosario, D.J. (2013). Endocrine therapy in prostate cancer: time for reappraisal of risks, benefits and cost-effectiveness? *British Journal of Cancer*, **108**, 9-13.

Boutouyrie, P., Bussy, C., Lacolley, P., Girerd, X., Laloux, B. and Laurent, S. (1999). Association between local pulse pressure, mean blood pressure, and large-artery remodelling. *Circulation*, **100**, 1387-1393.

Bower, J. E., Ganz, P.A., Tao, M.L., Hu, W., Belin, T.R., Sepah, S., Cole, S. and Aziz, N. (2009). Inflammatory biomarkers and fatigue during radiation therapy for breast and prostate cancer. *Clinical Cancer Research*, **15**, 5534-5540.

Boyanov, M.A., Boneva, Z. and Christov, V.G. (2003). Testosterone supplementation in men with type 2 diabetes, visceral obesity and partial androgen deficiency. *The Aging Male*, **6**, 1-7.

Braga-Basaria, M., Dobs, A.S., Muller, M., Carducci, M.A., John, M., Egan, J. and Basaria, S. (2006a). Metabolic syndrome in men with prostate cancer undergoing long-term androgen deprivation therapy. *Journal of Clinical Oncology*, **24**, 3979-3983.

Braga-Basaria, M., Muller, M., Carducci, M.A., Dobs, A.S. and Basaria, S. (2006b). Lipoprotein profile in men with prostate cancer undergoing androgen deprivation therapy. *International Journal of Impotence Research*, **18**, 494-498.

Brambilla, D.J., Matsumoto, A.M., Araujo, A.B. and McKinlay, J.B. (2009). The effect of diurnal variation on clinical measurement of serum testosterone and other sex hormone levels in men. *Journal of Clinical Endocrinology and Metabolism*, **94**, 907-913.

Brawley, O.W., Ankerst, D.P. and Thompson, I.M. (2009). Screening for prostate cancer. *CA: A Cancer Journal for Clinicians*, **59**, 264-273.

Bray, F., Jemal, A., Grey, N., Ferlay, J. and Forman, D. (2012). Global cancer transitions according to the Human Development Index (2008-2030): a population-based study. *The Lancet Oncology*, **13**, 790-801.

British Association of Sport and Exercise Sciences. (2013). BASES expert statements. Aug/13, http://www.bases.org.uk/BASES-Expert-Statements

British Heart Foundation, (2010). Ethnic differences in cardiovascular disease. 2010 edition. Aug/13. http://www.bhf.org.uk/plugins/PublicationsSearchResults/DownloadFile.aspx?docid=a60f60ea-3c48-4632-868f-1fcfd00e088f&version=-1&title=Ethnic+Differences+in+Cardiovascular+Disease&resource=HS2010ED

British Heart Foundation, (2012). Coronary heart disease statistics. A compendium of health statistics. London: British Heart Foundation

British Heart Foundation Health Promotion Research Group. (2012). *Physical Activity Statistics 2012*. London: British Heart Foundation

British Heart Foundation. (2013). Alcohol and heart disease, May/13. http://www.bhf.org.uk/heart-health/prevention/healthy-eating/alcohol.aspx

British National Formulary (2006). *British National Formulary 52, September 2006*. London: BMJ Publishing Ltd and RPS Publishing

Brown, N.J. and Vaughan, D.E. (1998). Angiotensin-converting enzyme inhibitors. *Circulation*, **97**, 1411-1420.

Brunner, E., Stallone, D., Juneja, M., Bingham, S. and Marmot, M. (2001). Dietary assessment in Whitehall II: comparison of 7 d diet diary and food-frequency questionnaire and validity against biomarkers. *The British Journal of Nutrition*, **86**, 405-414.

Burgess, C., Cornelius, V., Love, S., Graham, J., Richards, M. and Ramirez, A. (2005). Depression and anxiety in women with early breast cancer: five year observational study. *BMJ*, **330**, 702.

Byar, D.P. and Mostofi, F.K. (1972). Carcinoma of the prostate: prognostic evaluation of certain pathologic features in 208 radical prostatectomies. *Cancer*, **30**, 5-13.

Byrne, N.M., Hills, A.P., Hunter, G.R., Weinsier, R.L. and Schutz, Y. (2005). Metabolic equivalent: one size does not fit all. *Journal of Applied Physiology*, **99**, 1112-1119.

Cai, H. and Harrison, D.G. (2000). Endothelial dysfunction in cardiovascular diseases. The role of oxidant stress. *Circulation Research*, **87**, 840-844.

Campbell, W.W., Crim, M.C., Young, V.R. and Evans, W.J. (1994). Increased energy requirements and changes in body composition with resistance training in older adults. *American Journal of Clinical Nutrition*, **60**, 167-175.

Campia, U., Tesauro, M. and Cardillo, C. (2012). Human obesity and endothelium-dependent responsiveness. *British Journal of Pharmacology*, **165**, 561-573.

Cancer Research UK. (2009). *Monitoring prostate cancer*, Mar/09, http://www.cancerhelp.org.uk/type/prostate-cancer/treatment/monitoring-prostate-cancer#difference

Cancer Research UK. (2010a). *Radiotherapy for prostate cancer*, Oct/10, http://www.cancerhelp.org.uk/type/prostate-cancer/treatment/radiotherapy/

Cancer Research UK. (2010b). *Research into treatments for prostate cancer*, Oct/10, http://www.cancerhelp.org.uk/type/prostate-cancer/treatment/research/research-into-treatments-for-prostate-cancer#radiotherapy

Cancer Research UK. (2013). *Prostate cancer statistics*, May/13, http://www.cancerresearchuk.org/cancer-info/cancerstats/types/prostate/?script=true

Canoy, D., Boekholdt, S.M., Wareham, N., Luben, R., Welch, A., Bingham, S., Buchan, I., Day, N. and Khaw, K.T. (2007). Body fat distribution and risk of coronary heart disease in men and women in the European prospective

investigation into cancer and nutrition in Norfolk cohort. *Circulation*, **116**, 2933-2943.

Capell, W.H., DeSouza, C.A., Poirer, P., Bell, M.L., Stauffer, B.L., Weil, K.M., Hernandez, T.L. and Eckel, R.H. (2003). Short-term triglyceride lowering with fenofibrate improves vasodilator function in subjects with hypertriglyceridemia. *Arteriosclerosis, Thrombosis, and Vascular Biology*, **23**, 307-313.

Carsin, A-E., Drummond, F.J., Black, A., van Leeuwen, P.J., Sharp, L., Murray, L.J., Connolly, D., Egevad, L., Boniol, M., Autier, P., Comber, H. and Gavin, A. (2010). Impact of PSA testing and prostatic biopsy on cancer incidence and mortality: comparative study between the Republic of Ireland and Northern Ireland. *Cancer Causes and Control*, **21**, 1523-1531.

Carson, A.P., Howard, D.L., Carpenter, W.R., Taylor, Y.J., Peacock, S., Schenck, A.P. and Godley, P.A. (2010). Trends and racial differences in the use of androgen deprivation therapy for metastatic prostate cancer. *Journal of Pain and Symptom Management*, **39**, 872-881.

Casey, R.G., Corcoran, N.M. and Goldenberg, S.L (2012). Quality of life issues in men undergoing androgen deprivation therapy: a review. *Asian Journal of Andrology*, **14**, 226-231.

Casiglia, E., Zanette, G., Mazza, A., Donadon, V., Donada, C., Pizziol, A., Tikhonoff, V., Palatini, P. and Pessina, A.C. (2000). Cardiovascular mortality in non-insulin dependent diabetes mellitus. A controlled study among 683 diabetics and 683 age-and sex matched normal subjects. *European Journal of Epidemiology*, **16**, 677-684.

Caspersen, C.J., Powell, K.E. and Christenson, G.M. (1985). Physical activity, exercise, and physical fitness: Definitions and distinctions for health-related research. *Public Health Reports*, **100**, 126-131.

Catalona, W.J., Smith, D.S. and Ornstein, D.K. (1997). Prostate cancer detection in men with serum PSA concentrations of 2.6 to 4.0 ng/ml and benign prostate examination. *Journal of the American Medical Association*, **277**, 1452-1455.

Celermajer, D.S., Sorensen, K.E., Gooch, V.M., Spiegelhalter, D.J., Miller, O.I., Sullivan, I.D., Lloyd, J.K. and Deanfield, J.E. (1992). Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. *The Lancet*, **340**, 1111-1115.

Celermajer, D.S. (1997). Endothelial dysfunction: Does it matter? Is it reversible? *Journal of the American College of Cardiology*, **30**, 325-333.

Cella, D., Eton, D.T., Lai, J-S., Peterman, A.H., Merkel, D.E. (2002). Combining anchor and distribution-based methods to derive minimal clinically important differences on the functional assessment of cancer therapy (FACT) anemia and fatigue scales. *Journal of Pain and Symptom Management*, **24**, 547-561.

Cella, D., Nichol, M.B., Eton, D., Nelson, J.B. and Mulani, P. (2009). Estimating clinically meaningful changes for the functional assessment of cancer therapy-prostate: Results from a clinical trial of patients with metastatic hormone-refractory prostate cancer. *Value in Health*, **12**, 124-129.

Charakida, M., Masi, S., Lüscher, T.F., Kastelein, J.J.P. and Deanfield, J.E. (2010). Assessment of atherosclerosis: the role of flow-mediated dilatation. *European Heart Journal*, **31**, 2854-2861.

Chan, J.M., Rimm, E.B., Colditz, G.A., Stampfer, M.J. and Willett, W.C. (1994). Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. *Diabetes Care*, **17**, 961-969.

Chan, J.M., Stampfer, M.J., Ma, J., Gann, P.H., Gaziano, J.M. and Giovannucci, E.L. (2001). Dairy products, calcium, and prostate cancer risk in the Physicians' Health Study. *The American Journal of Clinical Nutrition*, **74**, 549-554.

Chan, J.M., Holick, C.N., Leitzmann, M.F., Rimm, E.B., Willett, W.C., Stampfer, M.J., Giovannucci, E.L. (2006). Diet after diagnosis and the risk of prostate cancer progression, recurrence, and death (United States). *Cancer Causes and Control*, **17**, 199-208.

Chang, S.S. and Amin, M.B. (2008). Utilizing the Tumour-Node-Metastasis staging for prostate cancer: The sixth Edition, 2002. *CA: A Cancer Journal for Clinicians*, **58**, 54-59.

Chatterjee, A. and Catravas, J.D. (2008). Endothelial nitric oxide (NO) and its pathophysiologic regulation. *Vascular Pharmacology*, **49**, 134-140.

Chen, L., Stacewicz-Sapuntzakis, M., Duncan, C., Sharifi, R., Ghosh, L., van Breeman, R., Ashton, D. and Bowen, P.E. (2001). Oxidative DNA damage in prostate cancer patients consuming tomato sauce-based entrees as a whole-food intervention. *Journal of the National Cancer Institute*, **93**, 1872-1879.

Chen, J., Long, J.B., Hurria, A., Owusu, C., Steingart, R.M. and Gross, C.P. (2012). Incidence of heart failure or cardiomyopathy after adjuvant trastuzumab therapy for breast cancer. *Journal of the American College of Cardiology*, **60**, 2504-2512.

Cherrier, M.M., Aubin, S. and Higano, C.S. (2009). Cognitive and mood changes in men undergoing intermittent combined androgen blockade for non-metastatic prostate cancer. *Psychooncology*, **18**, 237-247.

Chiang, I.N., Chang, S.J., Pu, Y.S., Huang, K.H., Yu, H.J. and Huang, C.Y. (2007). Major complications and associated risk factors of transrectal ultrasound guided prostate needle biopsy: a retrospective study of 1875 cases in Taiwan. *Journal of the Formosan Medical Association*, **106**, 929-934.

Chobanian, A.V., Bakris, G.L., Black, H.R., Cushman, W.C., Green, L.A., Izzo, J.L., Jones, D.W., Materson, B.J., Oparil, S., Wright, J.T., Roccella, E.J. and the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. (2003). Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. *Hypertension*, **42**, 1206-1252.

Chock, B., Lin, T.C., Li, C.S. and Swislocki, A. (2012). Plasma testosterone is associated with Framingham risk score. *The Aging Male*, **15**, 134-139.

Choong, K. and Basaria, S. (2010). Emerging cardiometabolic complications of androgen deprivation therapy. *The Aging Male*, **13**, 1-9.

Chou, T.M., Sudhir, K., Hutchinson, S.J., Ko, E., Amidon, T.M., Collins, P. and Chatterjee, K. (1996). Testosterone induces dilation of canine coronary conductance and resistance arteries in vivo. *Circulation*, **94**, 2614-2619.

Chyou, P.H. and Eaker, E.D. (2000). Serum cholesterol concentrations and all-cause mortality in older people. *Age and Ageing*, **29**, 69-74.

Cicchetti, D.V. (2001). The precision of reliability and validity estimates re-visited: Distinguishing between clinical and statistical significance of sample size requirements. *Journal of Clinical and Experimental Neuropsychology*, **23**, 695-700.

Clancy, J. and McVicar, A, (2009). *Physiology and anatomy for nurses and healthcare practitioners. A homeostatic approach. Third Edition*. London: Hodder Arnold.

Cohen, J. (1992). A power primer. *Psychological Bulletin*, **112**, 155-159.

Colberg, S.R., Sigal, R.J., Fernhall, B., Regensteiner, J.G., Blissmer, B.J., Rubin, R.R., Chasan-Taber, L., Albright, A.L. and Braun, B. (2010). Exercise and type 2 diabetes. The American College or Sports Medicine and the American Diabetes Association: joint position statement. *Diabetes Care*, **33**, e147-e167.

Coldman, A.J., Phillips, N. and Pickles, T.A. (2003). Trends in prostate cancer incidence and mortality: an analysis of mortality change by screening intensity. *Canadian Medical Association Journal*, **168**, 31-35.

Concato, J., Wells, C.K., Horwitz, R.I., Penson, D., Fincke, G., Berlowitz, D.R., Froehlich, G., Blake, D., Vickers, M.A., Gehr, G.A., Raheb, N.H., Sullivan, G. and Peduzzi, P. (2006). The effectiveness of screening for prostate cancer. *Archives of Internal Medicine*, **166**, 38-43.

Cooperberg, M.R., Grossfeld, G.D., Lubeck, D.P. and Carroll, P.R. (2003). National practice patterns and time trends in androgen ablation for localized prostate cancer. *Journal of the National Cancer Institute*, **95**, 981-989.

Cooper-Buschemeyer, W. and Freedland, S.J. (2007). Obesity and prostate cancer: Epidemiology and clinical implications. *European Urology*, **52**, 331-343.

Cornelison, D.D.W. and Wold, B.J. (1997). Single-cell analysis of regulatory gene expression in quiescent and activated mouse skeletal muscle satellite cells. *Developmental Biology*, **191**, 270-283.

Cornelisson, V.A. and Fagard, R.H. (2005). Effect of resistance training on resting blood pressure: a meta-analysis of randomized controlled trials. *Journal of Hypertension*, **23**, 251-259.

Corretti, M.C., Anderson, T.J., Benjamin, E.J., Celermajer, D., Charbonneau, F., Creager, M.A., Deanfield, J., Drexler,H., Gerhard-Herman, M., Herrington, D., Vallance, P., Vita, J. and Vogel, R. (2002). Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery. A report of the international brachial artery reactivity task force. *Journal of the American College of Cardiology*, **39**, 257-265.

Courneya, K.S., Friedenreich, C.M., Quinney, H.A., Fields, A.L., Jones, L.W. and Fairey, A.S. (2004). Predictors of adherence and contamination in a randomized trial of exercise in colorectal cancer survivors. *Psychooncology*, **13**, 857-866.

Cramp, F. and Byron-Daniel, J. (2012). Exercise for the management of cancer-related fatigue in adults. *Cochrane Collaboration*; John Wiley & Sons Ltd Publishers.

Crespo, C.J., Garcia-Palmieri, M.R., Smit, E., Lee, I.M., McGee, D., Muti, P., Fiqueroa Valle, N.R., Ramierez-Marrero, F.A., Freudenheim, J.L. and Sorlie, P. (2008). Physical activity and prostate cancer mortality in Puerto Rican men. *Journal of Physical Activity and Health*, **5**, 918-929.

Cuff, D.J., Meneilly, G.S., Martin, A., Ignaszewski, A., Tildesley, H.D. and Frohlich, J.J. (2003). Effective exercise modality to reduce insulin resistance in women with type 2 diabetes. *Diabetes Care*, **26**, 2977-2982.

Culos-Reed, S.N., Robinson, J.L., Lau, H., O'Connor, K. and Keats, M.R. (2007). Benefits of a physical activity intervention for men with prostate cancer. *Journal of Sport and Exercise Psychology*, **29**, 118-127.

Culos-Reed, S.N., Robinson, J.L., Lau, H., Stephenson, L., Keats, M.R., Norris, S., Kline, G. and Faris, P. (2010). Physical activity for men receiving androgen deprivation therapy for prostate cancer: benefits from a 16-week intervention. *Support Care Cancer*, **18**, 591-599.

Dacal, K., Sereika, S.M. and Greenspan, S.L (2005). Quality of life in prostate cancer patients taking androgen deprivation therapy. *Journal of the American Geriatrics Society*, **54**, 85-90.

D'Agostino, R.B., Vasan, R.S., Pencina, M.J., Wolf, P.A., Cobain, M., Massaro, J.M. and Kannel, W.B. (2008). General cardiovascular risk profile for use in primary care. The Framingham heart study. *Circulation*, **117**, 743-753.

Daher, I.N., Daigle, T.R., Bhatia, N. and Durand, J.B. (2012). The prevention of cardiovascular disease in cancer survivors. *Texas Heart Institute Journal*, **39**, 190-198.

Dall'Era, M.A., Konety, B.R., Cowan, J.E., Shinohara, K., Stauf, F., Cooperberg, M.R., Meng, M.V., Kane, C.J., Perez, N., Master, V.A. and Carroll, P.R. (2008). Active surveillance for the management of prostate cancer in a contemporary cohort. *Cancer*, **112**, 2664-2670.

Damber, J.E. (2004). Decreasing mortality rates for prostate cancer: possible role for hormonal therapy? *BJU International*, **93**, 695-701.

Damber, J.E. and Aus, G. (2008). Prostate cancer. *Lancet*, **371**, 1710-1721.

D'Amico, A.V., Cote, K., Loffredo, M., Renshaw, A.A. and Chen, M.H. (2003). Pretreatment predictors of time to cancer specific death after prostate specific antigen failure. *Journal of Urology*, **169**, 1320-1324.

D'Amico, A.V., Denham, J.W., Crook, J., Chen, M.H., Goldhaber, S.Z., Lamb, D.S., Joseph, D., Tai, K.H., Malone, S., Ludgate, C., Steigler, A. and Kantoff, P.W. (2007). Influence of androgen suppression therapy for prostate cancer on the frequency and timing of fatal myocardial infarctions. *Journal of Clinical Oncology*, **25**, 2420-2425.

Dandona, P. and Rosenberg, M.T. (2010). A practical guide to male hypogonadism in the primary care setting. *The International Journal of Clinical Practice*, **64**, 682-696.

Daniels, N.A., Nielson, C.M., Hoffman, A.R. and Bauer, D.C. (2010). Sex hormones and the risk of incident prostate cancer. *Urology*, **76**, 1034-1040.

Davies, N.J., Batehup, L. and Thomas, R. (2011). The role of diet and physical activity in breast, colorectal, and prostate cancer survivorship: a review of the literature. *British Journal of Cancer*, **105**, S52-S73.

Day, C. and Bailey, C.J. (2011). Obesity in the pathogenesis of type 2 diabetes. *The British Journal of Diabetes and Vascular Disease*, **11**, 55-61.

Deanfield, J.E., Halcox, J.P. and Rabelink, T.J. (2007). Endothelial function and dysfunction. Testing and clinical relevance. *Circulation*, **115**, 1285-1295.

de Ferranti, S. and Mozaffarian, D. (2008). The perfect storm: Obesity, adipocyte dysfunction and metabolic consequences. *Clinical Chemistry*, **54**, 945-955.

de Glisezinski, I., Moro, C., Pillard, F., Marion-Latard, F., Harant, I., Meste, M., Berlan, M., Crampes, F. and Rivière. (2003). Aerobic training improves exercise-induced lipolysis in SCAT and lipid utilization in overweight men. *American Journal of Physiology, Endocrinology and Metabolism*, **285**, E984-E990.

de Jesus, C.M.N., Corrêa, L.A. and Padovani, C.R. (2006). Complications and risk factors in transrectal ultrasound-guided prostate biopsies. *Sao Paulo Medical Journal*, **124**, 198-202.

de Lorgeril, M., Salen, P., Martin, J.L., Monjaud, I., Delaye, J. and Mamelle, N. (1999). Mediterranean diet, traditional risk factors and the rate of cardiovascular complications after myocardial infarction: Final report of the Lyon Diet Heart Study. *Circulation*, **16**, 779-785.

Demark-Wahnefried, W., Robertson, C.N., Walther, P.J., Polascik, T.J., Paulson, D.F. and Vollmer, R.T. (2004). Pilot study to explore effects of low-fat, flaxseed-supplemented diet on proliferation of benign prostatic epithelium and prostate-specific antigen. *Urology*, **63**, 900-904.

Demers, R.Y., Tiwari, A., Wei, J., Weiss, L.K., Severson, R.K. and Monite, J. (2001). Trends in the utilization of androgen-deprivation therapy for patients with prostate carcinoma suggest an effect on mortality. *Cancer*, **92**, 2309-2317.

De Nunzio, C., Albisinni, S., Freedland, S.J., Miano, L., Cindolo, L., Agrò, E.F., Autorino, R., De Sio, M., Schips, L. and Tubaro, A. (2011). Abdominal obesity as factor for prostate cancer diagnosis and high grade disease: A prospective multicenter Italian cohort study. *Urologic Oncology: Seminars and Original Investigations*, **Epub ahead of print**

Department of Health. (2013). Living with and beyond cancer: Taking action to improve outcomes. National Cancer Survivorship Initiative. Mar/13. https://www.gov.uk/government/publications/living-with-and-beyond-cancer-taking-action-to-improve-outcomes

De Pergola, G. (2000). The adipose tissue metabolism: role of testosterone and dehydroepiandrosterone. *International Journal of Obesity*, **24**, S59-S63.

Derweesh, I.H., DiBlasio, C.J., Kincade, M.C., Malcolm, J.B., Lamar, K.D., Patterson, A.L., Kitabchi, A.E. and Wake, R.W. (2007). Risk of new-onset diabetes mellitus and worsening glycaemic variables for established diabetes

in men undergoing androgen-deprivation therapy for prostate cancer. *BJU International*, **100**, 1060-1065.

Després, J.P., Moorjani, S., Lupien, P.J., Tremblay, A., Nadeau, A. and Bouchard, C. (1990). Regional distribution of body fat, plasma lipoproteins, and cardiovascular disease. *Arteriosclerosis, Thrombosis and Vascular Biology*, **10**, 497-511.

Diamandis, E.P. (1998). Prostate-specific antigen: Its usefulness in clinical medicine. *Trends in Endocrinology and Metabolism*, **9**, 310-316.

DiBlasio, C.J., Malcolm, J.B., Derweesh, I.H., Womack, J.H., Kincade, M.C., Mancini, J.G., Ogles, M.L., Lamar, K.D., Patterson, A.L. and Wake, R.W. (2008). Patterns of sexual and erectile dysfunction and response to treatment in patients receiving androgen deprivation therapy for prostate cancer. *BJU International*, **102**, 39-43.

DiBlasio, C.J., Malcolm, J.B., Hammett, J., Wan, J.Y., Aleman, M.A., Patterson, A.L., Wake, R.W. and Derweesh, I.H. (2009). Survival outcome in men receiving androgen-deprivation therapy as primary or salvage treatment for localized or advanced prostate cancer: 20-year single-centre experience. *BJU International*, **104**, 1208-1241.

Di Lorenzo, G., Autorino, R., Perdonà, S. and De Placido, S. (2005). Management of gynecomastia in patients with prostate cancer: a systematic review. *Lancet Oncology*, **6**, 972-979.

Dinenno, F.A., Tanaka, H., Monahan, K.D., Clevenger, C.M., Eskurza, I., DeSouza, C.A. and Seals, D.R. (2001). Regular endurance exercise induces expansive arterial remodelling in the trained limbs of healthy men. *Journal of Physiology*, **534**, 287-295.

Ding, E.L., Song, Y., Malik, Y.S. and Liu, S. (2006). Sex differences of endogenous sex hormones and risk of type 2 diabetes. *Journal of the American Medical Association*, **295**, 1288-1299.

Dobrovolny, C.L., Ivey, F.M., Rogers, M.A., Sorkin, J.D. and Macko, R.F. (2003). Reliability of treadmill exercise testing in older patients with chronic hemiparetic stroke. *Archives of Physical Medicine and Rehabilitation*, **84**, 1308-1312.

Dockery, F., Rajkumar, C., Agarwal, S., Waxman, J. and Bulpitt, C.J. (2000). Androgen deprivation in males is associated with decreased central arterial compliance and reduced central systolic blood pressure. *Journal of Human Hypertension*, **14**, 395-397.

Dockery, F., Bulpitt, C.J., Agarwal, S. and Rajkumar, C. (2002). Testosterone suppression in men with prostate cancer is associated with increased arterial stiffness. *The Aging Male*, **5**, 216-222.

Dockery, F., Bulpitt, C.J., Agarwal, S., Donaldson, M. and Rajkumar, C. (2003a). Testosterone suppression in men with prostate cancer leads to an increase in arterial stiffness and hyperinsulinaemia. *Clinical Science*, **104**, 195-201.

Dockery, F., Bulpitt, C.J., Donaldson, M., Fernandez, S. and Rajkumar, C. (2003b). The relationship between androgens and arterial stiffness in older men. *Journal of the American Geriatrics Society*, **51**, 1627-1632.

Dockery, F., Bulpitt, C.J., Agarwal, S., Vernon, C. and Rajkumar, C. (2009). Effect of androgen suppression compared with androgen receptor blockade on arterial stiffness in men with prostate cancer. *Journal of Andrology*, **30**, 410-415.

Dohle, G.R., Arver, S., Bettocchi, C., Kliesch, S., Punab, M. and de Ronde, W. (2012). Guidelines on male hypogonadism. European Association of Urology. Jan/13, http://www.uroweb.org/guidelines/online-guidelines/

Donald, A.E., Halcox, J.P., Charakida, M., Storry, C., Wallace, S.M.L., Cole, T.J., Friberg, P. and Deanfield, J.E. (2008). Methodological approaches to optimize reproducibility and power in clinical studies of flow-mediated dilation. *Journal of the American College of Cardiology*, **51**, 1959-1964.

Donnelly, J.E., Blair, S.N., Jakicic, J.M., Manore, M.M., Rankin, J.W. and Smith, B.K. (2009). Appropriate physical activity intervention strategies for weight loss and prevention of weight regain for adults. *Medicine and Science in Sports and Exercise*, **41**, 459-471.

Dorland's. (2007). *Dorland's illustrated medical dictionary, 31st Edition.* Philadelphia: Saunders, Elsevier

Doshi, S.N., Naka, K.K., Payne, N., Jones, C.J.H., Ashton, M., Lewis, M.J. and Goodfellow, J. (2001). Flow-mediated dilatation following wrist and upper arm occlusion in humans: The contribution of nitric oxide. *Clinical Science*, **101**, 629-635.

Drake, R.L., Vogl, A.W. and Mitchell, A.W.M. (2010). *Gray's anatomy for students. Second Edition*. Philadelphia: Churchill Livingstone Elsevier.

Duncan, G.E., Perri, M.G., Theriaque, D.W., Hutson, A.D., Eckel, R.H. and Stacpoole, P.W. (2003). Exercise training, without weight loss, increases insulin sensitivity and postheparin plasma lipase activity in previously sedentary adults. *Diabetes Care*, **26**, 557-562.

Dunstan, D.W., Daly, R.M., Owen, N., Jolley, D., de Courten, M., Shaw, J. and Zimmet, P. (2002). High-intensity resistance training improves glycemic control in older patients with type 2 diabetes. *Diabetes Care*, **25**, 1729-1736.

Eastham, J.A., Kattan, M.W., Groshen, S., Scardino, P.T., Rogers, E., Carlton, C.E. and Lerner, S.P. (1997). Fifteen-year survival and recurrence rates after radiotherapy for localized prostate cancer. *Journal of Clinical Oncology*, **15**, 3214-3222.

Eastham, J.A. (2007). Bone health in men receiving androgen deprivation therapy for prostate cancer. *The Journal of Urology*, **177**, 17-24.

Edwards, D.G., Schofield, R.S., Lennon, S.L., Pierce, G.L., Nichols, W.W. and Braith, R.W. (2004). Effects of exercise on endothelial function in men with coronary artery disease. *American Journal of Cardiology*, **93**, 617-620.

Efstathiou, J.A., Bae, K., Shipley, W.U., Hanks, G.E., Pilepich, M.V., Sandler, H.M. and Smith, M.R. (2008). Cardiovascular mortality and androgen deprivation for locally advanced prostate cancer: Analysis of RTOG 92-02. *European Urology*, **54**, 816-824.

Efstathiou, J.A., Bae, K., Shipley, W.U., Hanks, G.E., Pilepich, M.V., Sandler, H.M. and Smith, M.R. (2009). Cardiovascular mortality after androgen deprivation therapy for locally advanced prostate cancer: RTOG 85-31. *Journal of Clinical Oncology*, **27**, 92-99.

Eichler, K., Hempel, S., Wilby, J., Myers, L., Bachmann, L.M. and Kleijnen, J. (2006). Diagnostic value of systematic prostate biopsy methods in the investigation of prostate cancer: a systematic review. *Journal of Urology*, **175**, 1605-1612.

Elliott, J., Fallows, A., Staetsky, L., Smith, P.W.F., Foster, C.L., Maher, E.J. and Corner, J. (2011). The health and well-being of cancer survivors in the UK: findings from a population-based survey. *British Journal of Cancer*, **105**, S11-S20.

Engeland, A., Tretli, S. and Bjørge, T. (2003). Height, body mass index, and prostate cancer: a follow-up of 950,000 Norwegian men. *British Journal of Cancer*, **89**, 1237-1242.

Engels, J.M. and Diehr, P. (2003). Imputation of missing longitudinal data: a comparison of methods. *Journal of Clinical Epidemiology*, **56**, 968-976.

Enger, E.M. and Bernstein, L. (2004). Exercise activity, body size and premenopausal breast cancer survival. *British Journal of Cancer*, **90**, 2138-2141.

Esper, P., Pienta, K. and Cella, D. (1995). FACT-P: a new instrument for quality of life evaluation in prostate cancer (abstract). *Journal of Urology*, **153**.

Esper, P., Mo, F., Chodak, G., Sinner, M., Cella, D. and Pienta, K.J. (1997). Measuring quality of life in men with prostate cancer using the functional assessment of cancer therapy-prostate instrument. *Urology*, **50**, 920-928.

Esposito, K., Nappo, F., Giugliano, F., Giugliano, G., Marfella, R. and Giugliano, D. (2003). Effect of dietary antioxidants on postprandial endothelial dysfunction induced by a high-fat meal in healthy subjects. *The American Journal of Clinical Nutrition*, **77**, 139-143.

Esposito, K., Marfella, R., Ciotola, M., Di Palo, C., Giugliano, F., Giugliano, G., D'Armiento, M., D'Andrea, F. and Giugliano, D. (2010). Effect of a Mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome. *Journal of the American Medical Association*, **292**, 1440-1446.

European Heart Network, (2013). European cardiovascular disease statistics. 2012 Edition. Aug/13. http://www.ehnheart.org/cvd-statistics.html

European Society of Hypertension Guideline Committee. (2003). 2003 European Society of Hypertension - European Society of Cardiology guidelines for the management of arterial hypertension. *Journal of Hypertension*, **21**, 1011-1053.

Evans, W.J. and Campbell, W.W. (1993). Sarcopenia and age related changes in body composition and functional capacity. *Journal of Nutrition*, **123**, 465-468.

Exercise and Sports Science Australia. (2013). Position statements. Aug/13, http://www.essa.org.au/about-us/position-statements/

Fairey, A.S., Courneya, K.S., Field, C.J., Bell, G.J., Jones, L.W. and Mackey, J.R. (2005). Randomized controlled trial of exercise and blood immune function in postmenopausal breast cancer survivors. *Journal of Applied Physiology*, **98**, 1534-1540.

Fansson, E.I., Alfredsson, L.S., de Faire, U.H., Knutsson, A. and Westerholm, P.J. (2003). Leisure time, occupational and household physical activity, and risk factors for cardiovascular disease in working men and women: the WOLF study. *Scandinavian Journal of Public Health*, **31**, 324-333.

Farkas, A., Schneider, D., Perrotti, M., Cummings, K.B. and Ward, W.S. (1998). National trends in the epidemiology of prostate cancer, 1973-1994: Evidence for the effectiveness of prostate-specific antigen screening. *Urology*, **52**, 444-449.

Fentem, P.H. (1994). Benefits of exercise in health and disease. *BMJ*, **308**, 1291-1295.

Fernández de la Puebla, R.A., Fuentes, F., Pérez-Martinez, P., Sánchez, E., Paniaqua, J.A., López-Miranda, J. and Pérez-Jiménez, F. (2003). A reduction in dietary daturated fat decreases body fat content in overweight, hypercholesterolemic males. *Nutrition, Metabolism & Cardiovascular Diseases*, **13**, 273-277.

Fisher, N.D., Hughes, M., Gerhard-Herman, M. and Hollenberg, N.K. (2003). Flavanol-rich cocoa induces nitric-oxide-dependent vasodilation in healthy humans. *Journal of Hypertension*, **21**, 2281-2286.

Foresta, C., Caretta, N., Lana, A., De Toni, L., Biagioli, A., Ferlin, A. and Garolla, A. (2006). Reduced number of circulating endothelial progenitor cells in hypogonadal men. *The Journal of Clinical Endocrinology and Metabolism*, **91**, 4599-4602.

Förstermann, U. and Sessa, W.C. (2012). Nitric oxide synthases: regulation and function. *European Heart Journal*, **33**, 829-837.

Fowke, J.H., Motley, S.S., Concepcion, R.S., Penson, D.F. and Barocas, D.A. (2012). Obesity, body composition and prostate cancer. *BMC Cancer*, **12**,

Franklin, S.F. (2005). Arterial stiffness and hypertension. A two-way street? *Hypertension*, **45**, 349-351.

Fransson, E.I., Alfredsson, L.S., de Faire, U.H., Knutsson, A. and Westerholm, P.J. (2003). Leisure time, occupational and household physical activity, and risk factors for cardiovascular disease in working men and women: the WOLF study. *Scandinavian Journal of Public Health*, **31**, 324-333.

Franzini, L., Ardigò, D., Valtueña, S., Pellegrini, N., Del Rio, D., Bianchi, M.A., Scazzina, F., Piatti, P.M., Brighenti, F. and Zavaroni, I. (2012). Food selection based on high total antioxidant capacity improves endothelial function in a low cardiovascular risk population. *Nutrition, Metabolism & Cardiovascular Diseases*, **22**, 50-57.

Freedland, S.J., Humphreys, E.B., Mangold, L.A., Eisenberger, M., Dorey, F.J., Walsh, P.C. and Partin, A.W. (2005). Risk of prostate cancer-specific mortality following biochemical recurrence after radical prostatectomy. *Journal of the American Medical Association*, **294**, 433-439.

Frisk, J. (2010). Managing hot flushes in men after prostate cancer- A systematic review. *Maturitas*, **65**, 15-22.

Froehner, M. and Wirth, M.P. (2012) Re: Association of androgen deprivation therapy with cardiovascular death in patients with prostate cancer: A meta-analysis of randomized trials. *European Urology*, **62**, 350.

Fu, A.Z., Zhao, Z., Gao, S., Barber, B. and Liu, G.G. (2011). Comorbid conditions in patients with metastatic colorectal cancer. *World Journal of Oncology*, **2**, 225-231.

Galvão, D.A., Nosaka, K., Taaffe, D.R., Spry, N., Kristjanson, L.J., McGuigan, M.R., Suzuki, K., Yamaya, K. and Newton, R.U. (2006). Resistance training and reduction of treatment side effects in prostate cancer patients. *Medicine and Science in Sports and Exercise*, **38**, 2045-2052.

Galvão, D.A., Taaffe, D.R., Spry, N., Joseph, D. and Newton, R.U. (2009). Cardiovascular and metabolic complication during androgen deprivation: exercise as a potential countermeasure. *Prostate Cancer and Prostatic Diseases*, **12**, 233-240.

Galvão, D.A., Taaffe, D.R., Spry, N., Joseph, D. and Newton, R.U. (2010). Combined resistance and aerobic exercise program reverses muscle loss in men undergoing androgen suppression therapy for prostate cancer without bone metastases: A randomized controlled trial. *Journal of Clinical Oncology*, **28**, 340-347.

Ganong, W.F. (2005). *Review of Medical Physiology. Twenty-second edition.* New York: Lange Medical Publications.

Garcia, M., Jemal, A., Ward, E.M., Center, M.M., Hao, Y., Siegel, R.L. and Thun, M.J. (2007). Global Cancer Facts and Figures 2007. Atlanta, GA: American Cancer Society.

Gatzka, C.D., Cameron, J.D., Kingwell, B.A. and Dart, A.M. (1998). Relation between coronary artery disease, aortic stiffness, and left ventricular structure in a population sample. *Hypertension*, **32**, 575-578.

Gibbons, R.J., Balady, G.J., Beasley, J.W., Bricker, J.T., Duvernoy, W.F.C., Froelicher, V.F., Mark, D.B., Marwick, T.H., McCallister, B.D., Thompson, P.D., Winters, W.L. and Yanowitz, F.G. (1997). ACC/AHA Guideline for exercise testing. *Journal of the American College of Cardiology*, **30**, 260-315.

Gillitzer, R. and Thüroff, J.W. (2002). Relative advantages and disadvantages of radical perineal prostatectomy versus radical retropubic prostatectomy. *Critical reviews in Oncology/Hematology*, **43**, 167-190.

Ginsberg, H.N. (2000). Insulin resistance and cardiovascular disease. *The Journal of Clinical Investigation*, **106**, 453-458.

Giovannucci, E., Rimm, E.B., Colditz, G.A., Stampfer, M.J., Ascherio, A., Chute, C.C. and Willett, W.C. (1993). A prospective study of dietary fat and risk of prostate cancer. *Journal of the National Cancer Institute*, **85**, 1571-1579.

Giovannucci, E., Liu, Y., Leitzmann, M.F., Platz, E.A., Stampfer, M.J. and Willett, W.C. (2005). A prospective study of physical activity and incident and fatal prostate cancer. *Archives of Internal Medicine*, **165**, 1005-1010.

Giovannucci, E., Liu, Y., Platz, E.A., Stampfer, M.J. and Willett, W.C. (2007). Risk factors for prostate cancer incidence and progression in the health professionals follow-up study. *International Journal of Cancer*, **121**, 1571-1578.

Go, A.S., Mozaffarian, D., Roger, V.L., Benjamin, E.J., Berry, J.D., Borden, W.B., Bravata, D.M., Dai, S., Ford, E.S., Fox, C.S., Franco, S., Fullerton, H.J., Gillespie, C., Hailpern, S.M., Heit, J.A., Howard, V.J., Huffman, M.D., Kissela, B.M., Kittner, S.J., Lackland, D.T., Lichtman, J.H., Lisabeth, L.D., Magid, D., Marcus, G.M., Marelli, A., Matchar, D.B., McGuire, D.K., Mohler, E.R., Moy, C.S., Mussolino, M.E., Nichol, G., Paynter, N.P., Schreiner, P.J., Sorlie, P.D., Stein, J., Turan, T.N., Virani, S.S., Wong, N.D., Woo, D. and Turner, M.B. (2013). Heart disease and stroke statistics- 2013 update. A report from the American Heart Association. *Circulation*, **127**, e6-e245.

Godin, G. and Shephard, R.J. (1985). A simple method to assess exercise behaviour in the community. *Canadian Journal of Applied Sports Science*, **10**, 141-146.

Gokce, N., Vita, J.A., Bader, D.S., Sherman, D.L., Hunter, L.M., Holbrook, M., O'Malley, C., Keaney, J.F. and Balady, G.J. (2002). Effects of exercise on upper and lower extremity endothelial function in patients with coronary artery disease. *American Journal of Cardiology*, **90**, 124-127.

Gooderham, N.J., Zhu, H., Lauber, S., Boyce, A. and Creton, S. (2002). Molecular and genetic toxicology of 2-amino-1-methyl-6-phenylimidazo [4,5-*b*]pyridine (PhIP). *Mutation Research*, **506**, 91-99.

Gordon, D.J., Probstfield, J.L., Garrison, R.J., Neaton, J.D., Castelli, W.P., Knoke, J.D., Jacobs, D.R., Bangdiwala, S. and Tyroler, H.A. (1989). High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. *Circulation*, **79**, 8-15.

Gosselaar, C., Kranse, R., Roobol, M.J., Roemeling, S. and Schröder, F.H. (2008). The interobserver variability of digital rectal examination in a large randomized trial for the screening of prostate cancer. *The Prostate*, **68**, 985-993.

Gravel, J., Opatrny, L. and Shapiro, S. (2007). The intention-to-treat approach in randomized controlled trials: Are authors saying what they do and doing what they say? *Clinical trials*, **4**, 350-356.

Green, D.J., Walsh, J.H., Maiorana, A., Best, M.J., Taylor, R.R. and O'Driscoll, J.G. (2003). Exercise-induced improvements in endothelial dysfunction is not mediated by changes in CV risk factors: pooled analysis of diverse patient populations. *American Journal of Physiology. Heart and Circulatory Physiology*, **285**, H2679-2687.

Green, D.J., Maiorana, A., O'Driscoll, J.G. and Taylor, R.R. (2004). Effect of exercise training on endothelium-derived nitric oxide function in humans. *Journal of Physiology*, **561**, 1-25.

Green, D.J., O'Driscoll, G., Joyner, M.J. and Cable, N.T. (2008). Exercise and cardiovascular risk reduction: Time to update the rationale for exercise? *Journal of Applied Physiology*, **105**, 766-768.

Green, D.J., Jones, H., Thijssen, D., Cable, N.T. and Atkinson, G. (2011). Flow-mediated dilation and cardiovascular event prediction. Does nitric oxide matter? *Hypertension*, **57**, 363-369.

Greenspan, S.L., Coates, P., Sereika, S.M., Nelson, J.B., Trump, D.L. and Resnick, N.M. (2005). Bone loss after initiation of androgen deprivation therapy in patients with prostate cancer. *The Journal of Clinical Endocrinology and Metabolism*, **90**, 6410-6417.

Griffin, B.P. and Topol, E.J. (2009). *Manual of cardiovascular medicine. Third Edition.* Philadelphia: Lippincott Williams & Wilkins.

Grover-Páez, F. and Zavalza-Gómez, A.B. (2009). Endothelial dysfunction and cardiovascular risk factors. *Diabetes Research and Clinical Practice*, **84**, 1-10.

Guazzi, M., Reina, G., Tumminello, G. and Guazzi, M.D. (2004). Improvement in alveolar-capillary membrane diffusing capacity with exercise training in chronic heart failure. *Journal of Applied Physiology*, **97**, 1866-1873.

Guo, Y., Franks, P.W., Brookshire, T. and Tataranni, P.A. (2004). The intra- and inter-instrument reliability of DXA based on ex vivo soft tissue measurements. *Obesity Research*, **12**, 1925-1929.

Haffner, S.M., Mykkänen, L., Valdez, R.A. and Katz, M.S. (1993). Relationship of sex hormones to lipids and lipoproteins in nondiabetic men. *Journal of Clinical Endocrinology and Metabolism*, **77**, 1610-1615.

Hak, A.S., Witteman, J.C.M., De Jong, F.H., Geerlings, M.I., Hofman, A. and Pols, H.A.P. (2002). Low levels of endogenous androgens increase the risk of atherosclerosis in elderly men: The Rotterdam study. *The Journal of Clinical Endocrinology and Metabolism*, **87**, 3632-3639.

Halbert, J.A., Silagy, C.A., Finucane, P., Withers, R.T., Hamdorf, P.A. and Andrews, G.A. (1997). The effectiveness of exercise training in lowering blood pressure: a meta-analysis of randomised controlled trials of 4 weeks or longer. *Journal of Human Hypertension*, **11**, 641-649.

Haluska, B.A., Jeffries, L., Carlier, S. and Marwick, T.H. (2010). Measurement of arterial distensibility and compliance to assess prognosis. *Atherosclerosis*, **209**, 474-480.

Hamer, M., Chida, Y., Stamatakis, E. (2009). The role of conventional and novel mechanisms in explaining increased risk of cardiovascular events in offspring with positive parental history. *Journal of Hypertension*, **27**, 1966-1971.

Hamer, M., Ingle, L., Carroll, S. and Stamatakis, E. (2012). Physical activity and cardiovascular mortality risk: Possible protective mechanisms? *Medicine and Science in Sports and Exercise*, **44**, 84-88.

Hankey, B.F., Feuer, E.J., Clegg, L.X., Hayes, R.B., Legler, J.M., Prorok, P.M., Ries, L.A., Merrill, R.M. and Kaplan, R.S. (1999). Cancer surveillance series: Interpreting trends in prostate cancer -- Part 1: Evidence of the effects of screening in recent prostate cancer incidence, mortality and survival rates. *Journal of the National Cancer Institute*, **91**, 1017-1024.

Hanks, G.E., Hanlon, A.L., Schultheiss, T.E., Freedman, G.M., Hunt, M., Pinover, W.H. and Movsas, B. (1997). Conformal external beam treatment of prostate cancer. *Urology*, **50**, 87-92.

Hansen, P.A., Dechet, C.B., Porucznik, C.A. and LaStayo, P.C. (2009). Comparing eccentric resistance exercise in prostate cancer survivors on and off hormone therapy: a pilot study. *PM & R, The Journal of Injury, Function and Rehabilitation*, **1**, 1019-1024.

Hara, M., Koyanagi, T., Inoue, T. and Fukuyama, T. (1966). Some physico-chemical characteristics of "seminoprotein". an antigenic component specific for human seminal plasma. Forensic immunological study of body fluids and secretion. VII. *Nihon Hoigaku Zasshi*, **25**, 322-324.

Harman, S.M., Metter, E.J., Tobin, J.B., Pearson, J. and Blackman, M.R. (2001). Longitudinal effects of aging on serum total and free testosterone levels in healthy men. *Journal of Clinical Endocrinology and Metabolism*, **86**, 724-731.

Harris, W.P., Mostaghel, E.A., Nelson, P.S. and Montgomery, B. (2009). Androgen deprivation therapy: Progress in understanding mechanisms of resistance and optimizing androgen depletion. *Nature Clinical Practice*, **6**, 76-85.

Harris, R.A., Nishiyama, S.K., Wray, D.W. and Richardson, R.S. (2010). Ultrasound assessment of flow-mediated dilation. *Hypertension*, **55**, 1075-1085.

Haseen, F., Murray, L.J., Cardwell, C.R., O'Sullivan J.M. and Cantwell, M.M. (2010). The effect of androgen deprivation therapy on body composition in men with prostate cancer: Systematic review and meta-analysis. *Journal of Cancer Survivorship*, **4**, 128-139.

Hawley, J.A. and Lessard, S.J. (2008). Exercise training-induced improvements in insulin action. *Acta Physiologica*, **192**, 127-135.

Heidenreich, A., Aus, G., Bolla, M., Joniau, S., Matveev, V.B., Schmid, H.P. and Zattoni, F. (2008). EAU Guidelines on prostate cancer. *European Urology*, **53**, 68-80.

Heidenreich, A., Bellmunt, J., Bolla, M., Joniau, S., Mason, M., Matveev, V.B., Mottet, N., Schmid, H.P., van der Kwast, T., Wiegel, T. and Zattoni, F. (2011). EAU guidelines on prostate cancer. Part 1: screening, diagnosis, and treatment of clinically localised disease. *European Urology*, **59**, 61-71.

Herman, S.M., Robinson, J.T.C., McCredie, R.J., Adams, M.R., Boyer, M.J. and Celermajer, D.S. (1997). Androgen deprivation therapy is associated with enhanced endothelium-dependent dilation in adult men. *Arteriosclerosis, Thrombosis and Vascular Biology*, **17**, 2004-2009.

Herman, L., Foster, C., Maher, M.A., Mikat, R.P. and Porcari, J.P. (2006). Validity and reliability of the session RPE method for monitoring exercise training intensity. *South African Journal of Sports Medicine*, **18**, 14-17.

Herman, M., Donovan, J., Tran, M., McKenna, B., Gore, J.M., Goldberg, R.J. and Tighe, D.A. (2009). Use of beta-blockers and effects on heart rate and blood pressure post-acute coronary syndromes: are we on target? *American Heart Journal*, **158**, 378-385.

Herr, H.W. and O'Sullivan, M. (2000). Quality of life of asymptomatic men with nonmetastatic prostate cancer on androgen deprivation therapy. *Journal of Urology*, **163**, 1743-1746.

Higashi, Y. and Yoshizumi, M. (2004). Exercise and endothelial function: Role of endothelium-derived nitric oxide and oxidative stress in healthy subjects and hypertensive patients. *Pharmacology and Therapeutics*, **102**, 87-96.

Higashi, Y., Noma, K., Yoshizumi, M. and Kihara, Y. (2009). Endothelial function and oxidative stress in cardiovascular disease. *Circulation Journal*, **73**, 411-418.

Hilaris, B.S., Bodner, W.R. and Mastoras, C.A. (2000). Brachytherapy: A Historical perspective. In *Radiotherapy of Prostate Cancer* (edited by C. Greco and M.J. Zelefsky). pp.255-260. Amsterdam: Harwood Academic Publishers.

Hirai, T., Sasayama, S., Kawasaki, T. and Yagi, S. (1989). Stiffness of systemic arteries in patients with myocardial infarction. *Circulation*, **80**, 78-86.

Hirata, Y., Nagata, D., Suzuki, E., Nishimatsu, H., Suxuki, J-I. and Nagai, R. (2010). Diagnosis and treatment of endothelial dysfunction in cardiovascular disease. *International Heart Journal*, **51**, 1-6.

Holick, C.N., Newcomb, P.A., Trentham-Dietz, A., Titus-Ernstoff, L., Bersch, A.J., Stampfer, M.J., Baron, J.A., Egan, K.M. and Willett, W.C. (2008). Physical activity and survival after diagnosis of invasive breast cancer. *Cancer Epidemiology, Biomarkers and Prevention*, **17**, 379-386.

Holmberg, L., Bill-Axelson, A., Helgesen, F., Salo, J.O., Folmerz, P., Häggman, M., Andersson, S.O., Spångberg, A., Busch, C., Nordling, S., Palmgren, J., Adami, H.O., Johansson, J.E. and Norlén, B.J. (2002). A randomized trial comparing radical prostatectomy with watchful waiting in early prostate cancer. *The New England Journal of Medicine*, **347**, 781-789.

Holmes, M.D., Chen, W.Y., Feskanich, D., Kroenke, C.H. and Colditz, G.A. (2005). Physical activity and survival after breast cancer diagnosis. *Journal of the American Medical Association*, **293**, 2479-2486.

Holzbeierlain, J.M., Castle, E.P. and Brantley Thrasher, J. (2003). Complications of androgen-deprivation therapy for prostate cancer. *Clinical Prostate Cancer*, **2**, 147-152.

Hooning, M.J., Botma, A., Aleman, B.M.P., Baaijens, M.H.A., Bartelink, H., Klijn, J.G.M., Taylor, C.W. and van Leeuwen, F.E. (2007). Long-term risk of cardiovascular disease in 10-year survivors of breast cancer. *Journal of the National Cancer Institute*, **99**, 365-375.

Hopkins, W.G., Marshall, S.W., Batterham, A.M. and Hanin, J. (2009). Progressive statistics for studies in sports medicine and exercise science. *Medicine and Science in Sports and Exercise*, **41**, 3-12.

Horowitz, J.F. (2001). Regulation of lipid mobilization and oxidation during exercise in obesity. *Exercise and Sports Science Reviews*, **29**, 42-46.

Hougaku, H., Fleg, J.L., Najjar, S.S., Lakatta, E.G., Harman, S.M., Blackman, M.R. and Metter, E.J. (2006). Relationship between androgenic hormones and arterial stiffness, based on longitudinal hormone measurements. *American Journal of Physiology- Endocrinology and Metabolism*, **290**, E234-E242.

Howard, G., O'Leary, D.H., Zaccaro, D., Haffner, S., Rewers, M., Hamman, R., Selby, J.V., Saad, M.F., Savage, P. and Bergman, R. (1996). Insulin sensitivity and atherosclerosis. *Circulation*, **93**, 1809-1817.

Hsing, A.W., Tsao, L. and Devesa, S.S. (2000). International trends and patterns of prostate cancer incidence and mortality. *International Journal of Cancer*, **85**, 60-67.

Huggins, C. and Hodges, C.V. (1941). Studies on prostate cancer I. The effect of castration, of estrogen and of androgen injection on serum phosphatases on metastatic carcinoma of the prostate. *Cancer Research*, **1**, 293-297.

Humphrey, P.A. (2004). Gleason grading and prognostic factors in carcinoma of the prostate. *Modern Pathology*, **17**, 292-306.

Hussain, M., Banerjee, M., Sarkar, F.H., Djuric, Z., Pollak, M.N., Doerge, D., Fontana, J., Chinni, S., Davis, J., Forman, J., Wood, D.P. and Kucuk, O. (2003). Soy isoflavones in the treatment of prostate cancer. *Nutrition and Cancer*, **47**, 111-117.

Hussain, S., Gunnell, D., Donovan, J., McPhail, S., Hamdy, F., Neal, D., Albertsen, P., Verne, J., Stephens, P., Trotter, C. and Martin, R.M. (2008). Secular trends in prostate cancer mortality, incidence and treatment: England and Wales, 1975–2004. *BJU International*, **101**, 547-555.

Inaba, Y., Chen, J.A. and Bergmann, S.R. (2010). Prediction of future cardiovascular outcomes by flow-mediated vasodilatation of brachial artery: a meta-analysis. *International Journal of Cardiovascular Imaging*, **26**, 631-640.

International Agency for Research on Cancer. (2009a). GLOBOCAN 2008, All cancers (excluding non-melanoma skin cancer) incidence and mortality worldwide in 2008, Jun/10, http://globocan.iarc.fr/

International Agency for Research on Cancer. (2009b). GLOBOCAN 2008, Prostate cancer incidence and mortality worldwide in 2008, Jun/10, *http://globocan.iarc.fr/*

International Society for the Study of the Aging Male. (2013). Free and bioavailable testosterone calculator, Aug/13, http://www.issam.ch/freetesto.htm

Irwin, M.L., Smith, A.W., McTiernan, A., Ballard-Barbash, R., Cronin, K., Gilliland, F.D., Baumgartner, R.N., Baumgartner, K.B. and Bernstein, L. (2008). Influence of pre- and postdiagnosis physical activity on mortality in breast cancer survivors: The health, eating, activity, and lifestyle study. *Journal of Clinical Oncology*, **26**, 3958-3964.

Iversen, P., Tyrrell, C.J., Kaisary, A.V., Anderson, J.B., Baert, L., Tammela, T., Chamberlain, M., Carroll, K., Gotting-Smith, K. and Blackledge, G.R. (1998). Casodex (Bicalutamide) 150-mg monotherapy compared with castration in patients with previously untreated nonmetastatic prostate cancer: results from two multicenter randomized trials at a median follow-up of 4 years. *Urology*, **51**, 389-396.

Jacobs, D.R., Ainsworth, B.E., Hartman, T.J. and Leon, A.S. (1993). A simultaneous evaluation of 10 commonly used physical activity questionnaires. *Medicine and Science in Sports and Exercise*, **25**, 81-91.

Jancey, J., Lee, A., Howat, P., Clarke, A., Wang, K. and Shilton, T. (2007). Reducing attrition in physical activity programs for older adults. *Journal of Aging and Physical Activity*, **15**, 152-165.

Jensen, M.D. (2008). Role of body fat distribution and the metabolic complications of obesity. *Journal of Clinical Endocrinology and Metabolism*, **93**, S57-S63.

Joannides, R., Haefeli,W.E., Linder, L., Richard, V., Bakkali, E.H. and Lüscher, T.F. (1995). Nitric oxide is responsible for flow-dependent dilatation of human peripheral conduit arteries in vivo. *Circulation*, **91**, 1314-1319.

Jones, R.F. (1936). Surgical treatment of the hypertrophied prostate: Perineal and suprapubic prostatectomy. *Journal of the National Medical Association*, **28**, 145-154.

Jones, R.D., Pugh, P.J., Jones, T.H. and Channer, K.S. (2003). The vasodilatory action of testosterone: a potassium-channel opening or a calcium antagonistic action? *British Journal of Pharmacology*, **138**, 733-744.

Jones, T.H. and Saad, F. (2009). The effects of testosterone on risk factors for, and the mediators of, the atherosclerotic process. *Atherosclerosis*, **207**, 318-327.

Jones, R.E., Brashers, V.L. and Huether, S.E. (2010). Alterations of hormonal regulation. In *Pathophysiology. The biologic basis for disease in adults and children. Sixth edition* (edited by K.L. McCance, S.E. Huether, V.L. Brashers and N.S. Rote), pp. 727-780. Missouri: Mosby Elsevier.

Jones, T.H. (2013). Clinical physiology of testosterone. In *Testosterone Deficiency in Men, Second Edition* (edited by T.H. Jones), pp. 9-20. Oxford: Oxford University Press.

Joyner, M.J. and Green, D.J. (2009). Exercise protects the cardiovascular system: effects beyond traditional risk factors. *Journal of Physiology*, **587**, 5551-5558.

Kadi, F. (2008). Cellular and molecular mechanisms responsible for the action of testosterone on human skeletal muscle. A basis for illegal performance enhancement. *British Journal of Pharmacology*, **154**, 522-528.

Kaminsky, L.A. and Whaley, M.H. (1998). Evaluation of a New Standardized Ramp Protocol: The BSU/Bruce Ramp Protocol. *Journal of Cardiopulmonary Rehabilitation*, **18**, 438-444.

Karling, P., Hammar, M. and Varenhorst, E. (1994). Prevalence and duration of hot flushes after surgical or medical castration in men with prostatic carcinoma. *Journal of Urology*, **152**, 1170-1173.

Katznelson, L., Rosenthal, D.I., Rosol, M.S., Anderson, E.J., Hayden, D.L., Schoenfeld, D.A. and Klibanski, A. (1998). Using quantitative CT to assess adipose distribution in adult men with acquired hypogonadism. *American Journal of Roentgenology*, **170**, 423-427.

Keating, N.L., O'Malley, A.J. and Smith, M.R. (2006). Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. *Journal of Clinical Oncology*, **24**, 4448-4456.

Keating, N.L., O'Malley, A.J., McNaughton-Collins, M., Oh, W.K. and Smith, M.R. (2008). Use of androgen deprivation therapy for metastatic prostate cancer in older men. *BJU International*, **101**, 1077-1083.

Keating, N.L., O'Malley, J.O., Freedland, S.J. and Smith, M.R. (2010). Diabetes and cardiovascular disease during androgen deprivation therapy: Observational study of veterans with prostate cancer. *Journal of the National Cancer Institute*, **102**, 39-46.

Keating, N.L., O'Malley, J.O., Freedland, S.J. and Smith, M.R. (2012). Dose comorbidity influence the risk of myocardial infarction or diabetes during androgen-deprivation therapy for prostate cancer? *European Urology*, **Epub ahead of print.**

Kenfield, S.A., Stampfer, M.J., Giovannucci, E. and Chan, J.M. (2011). Physical activity and survival after prostate cancer diagnosis in the health professionals follow-up study. *Journal of Clinical Oncology*, **29**, 726-732.

Kennedy, J.W., Hirshman, M.F., Gervino, E.V., Ocel, J.V., Forse, R.A., Hoenig, S.J., Aronson, D., Goodyear, L.J., Horton, E.S. (1999). Acute exercise induces GLUT4 translocation in skeletal muscle of normal human subjects and subjects with type 2 diabetes. *Diabetes*, **48**, 1192-1197.

Kesse-Guyot, E., Vergnaud, A.C., Fezeu, L., Zureik, M., Blacher, J., Péneau, S., Hercberg, S., Galan, P. and Czernichow, S. (2010). Associations between dietary patterns and arterial stiffness, carotid artery intima-media thickness and atherosclerosis. *European Journal of Cardiovascular Prevention and Rehabilitation*, **17**, 718-724.

Ketchandji, M., Kuo, Y.F., Shahinian, V.B. and Goodwin, J.S. (2009). Cause of death in older men after the diagnosis of prostate cancer. *Journal of the American Geriatric Society*, **57**, 24-30.

Khan, N.F., Mant, D., Carpenter, L., Forman, D. and Rose, P.W. (2011). Long-term health outcomes in a British cohort of breast, colorectal and prostate cancer survivors: a database study. *British Journal of Cancer*, **105**, S29-S37.

Khaw, K.T. and Barrett-Connor, E. (1988). Blood pressure and endogenous testosterone in men: an inverse relationship. *Journal of Hypertension*, **6**, 329-332.

Khaw, K., Dowsett, M., Folkerd, E., Bingham, S., Wareham, N., Lubens, R., Welch, A. and Day, N. (2007). Endogenous testosterone and mortality due to all causes, cardiovascular disease, and cancer in men. European prospective investigations into cancer in Norfolk (EPIC-Norfolk) prospective population study. *Circulation*, **116**, 2694-2701.

Khder, Y., Bray-Desboscs, L., Aliot, E. and Zannad, F. (1997). Effects of blood pressure control on radial artery diameter and compliance in hypertensive patients. *American Journal of Hypertension*, **10**, 269-274.

Khoshdel, A.R., Carney, S.L., Nair, B.R. and Gillies, A. (2007). Better management of cardiovascular disease by pulse wave velocity: Combing clinical practice with clinical research using evidence-based medicine. *Clinical Medicine and Research*, **5**, 45-52.

Kiechl, S., Willeit, J., Egger, G., Poewe, W. and Oberhollenzer, F. (1997). Body iron stores and the risk of carotid atherosclerosis. *Circulation*, **96**, 3300-3307.

Kim, J.W., Park, C.G., Hong, S.J., Park, S.M., Rha, S.W., Seo, H.S., Oh, D.J. and Rho, Y.M. (2005). Acute and chronic effects of cigarrete smoking on arterial stiffness. *Blood Pressure*, **14**, 80-85.

Kim, J-A., Montagnani, M., Koh, K.K. and Quon, M.J. (2006). Reciprocal relationships between insulin resistance and endothelial dysfunction. Molecular and pathophysiological mechanisms. *Circulation*, **113**, 1888-1904.

Kinlay, M., Creager, M.A., Fukumoto, M., Hikita, H., Fang, J.C., Selwyn, A.P. and Ganz, P. (2001). Endothelium-derived nitric oxide regulates arterial elasticity in human arteries in vivo. *Hypertension*, **38**, 1049-1053.

Kiratli, B.J., Srinivas, S., Perkash, I. and Terris, M.K. (2001). Progressive decrease in bone density over 10 years of androgen deprivation therapy in patients with prostate cancer. *Urology*, **57**, 127-132.

Kirwan, J.P., Del Aguila, L.F., Hernandez, J.M., Williamson, D.L., O'Gorman, D.J., Lewis, R. and Krishnan, R.K. (2000). Regular exercise enhances insulin activation of IRS-1-associated PI3-kinase in human skeletal muscle. *Journal of Applied Physiology*, **88**, 797-803.

Klein, B.E., Klein, R., Moss, S.E. and Cruickshank, K.J. (1996). Parental history of diabetes in a population-based study. *Diabetes Care*, **19**, 827-830.

Klotz, L. (2005). Active surveillance for prostate cancer: for whom? *Journal of Clinical Oncology*, **23**, 8165-8169.

Knobf, M.T. and Coviello, J. (2012). Lifestyle interventions for cardiovascular disease risk reduction in women with breast cancer. *Current Cardiology Reviews*, **7**, 250-257.

Koh, K.A., Sesso, H.D., Paffenbarger, R.S. and lee, I-M. (2006). Dairy products, calcium and prostate cancer risk. *British Journal of Cancer*, **95**, 1582-1585.

Kokkinos, P. and Myers, J. (2010). Exercise and physical activity. Clinical outcomes and applications. *Circulation*, **122**, 1637-1648.

Kraniou, G.N., Cameron-Smith, D. and Hargreaves, M. (2006). Acute exercise and GLUT4 expression in human skeletal muscle: influence of exercise intensity. *Journal of Applied Physiology*, **101**, 934-937.

Krone, R.J. (2010). Managing coronary artery disease in the cancer patient. *Progress in Cardiovascular Disease*, **53**, 149-156.

Kucuk, O., Sarkar, F.H., Djuric, Z., Sakr, W., Pollak, M.N., Khachik, F., Banerjee, M., Bertram, J.S. and Wood, D.P. (2002). Effects of lycopene supplementation in patients with localized prostate cancer. *Experimental Biology and Medicine*, **227**, 881-885.

Kumanov, P., Tomova, A., Kirilov, G., Dakovska, L. and Schinkov, A. (2002). Increased plasma endothelin levels in patients with male hypogonadism. *Andrologia*, **34**, 29-33.

Kumanov, P., Tomova, A. and Kirilov, G. (2007). Testosterone replacement therapy in male hypogonadism is not associated with increase of endothelin-1 levels. *International Journal of Andrology*, **30**, 41-47.

Kumar, S., Shelley, M., Harrison, C., Coles, B., Wilt, T.J. and Mason, M. (2009). *Neo-adjuvant and adjuvant hormone therapy for localised and locally advanced prostate cancer*. Cochrane Database of Systematic Reviews: John Wiley & Sons Ltd Publishers.

Kunath, F., Keck, B., Rücker, G., Motschall, E., Wullich, B., Antes, G. and Meerpohl, J.J. (2013). Early versus deferred androgen suppression therapy for patients with lymph node-positive prostate cancer after local therapy with curative intent: a systematic review. *BMC Cancer*, **13**, 1-13.

Kvåle, R., Auvinen, A., Adami, H.O., Klint, A., Hernes, E., Møller, B., Pukkala, E., Storm, H.H., Tryggvadottir, L., Tretli, S., Wahlqvist, R., Weiderpass, E. and Bray, F. (2007). Interpreting trends in prostate cancer incidence and mortality in the five nordic countries. *Journal of the National Cancer Institute*, **99**, 1881-1887.

Labrie, F., Dupont, A., Belanger, A., Cusan, L, Lacourciere, Y., Monfette, G., Laberge, J.G., Emond, J.P., Fazekas, A.T., Raynaud, J.P. and Husson, J.M. (1982). New hormonal therapy in prostatic carcinoma: combined treatment with an LHRH agonist and an antiandrogen. *Clinical and Investigative Medicine*, **5**, 267-275.

Labs, K.H., Nehler, M.R., Roessner, M., Jaeger, K.A. abd Hiatt, W.R. (1999). Reliability of treadmill testing in peripheral arterial disease: a comparison of a constant load with a graded load treadmill protocol. *Vascular Medicine*, **4**, 239-246.

Lage, M.J., Barber, B.L. and Markus, R.A. (2007). Association between androgen-deprivation therapy and incidence of diabetes among males with prostate cancer. *Urology*, **70**, 1104-1108.

Lakka, T.A., Venäläinen, J.H., Rauramaa, R., Salonen, R., Tuomilehto, J. and Salonen, J.T. (1994). Relation of leisure-time physical activity and cardiorespiratory fitness to the risk of acute myocardial infarction in men. *The New England Journal of Medicine*, **330**, 1549-1554.

Lamy, P.P., (1988). Potential adverse effects of antihypertensive drugs in the elderly. *Journal of Hypertension*, **6**, S81-S85.

Landberg, R., Sun, Q., Rimm, E.B., Cassidy, A., Scalbert, A., Mantzoros, C.S., Hu, F.B. and van Dam, R.M (2011). Selected dietary flavonoids are associated with markers of inflammation and endothelial dysfunction in U.S. women. *Journal of Nutrition*, **141**, 618-625.

LaPorte, R.E., Montoye, H.J. and Caspersen, C.J. (1985). Assessment of physical activity in epidemiologic research: Problems and prospects. *Public Health Reports*, **100**, 131-146.

Larrañaga, N., Galceran, J., Ardanaz, E., Franch, P., Navarro, C., Sánchez, M.J. and Pastor-Barriuso, R. (2010). Prostate cancer incidence trends in Spain before and during the prostate-specific antigen era: impact on mortality. *Annals of Oncology*, **21**, 83-89.

Laurent, S., Boutouyrie, P., Asmar, R., Gautier, I., Laloux, B., Guize, L., Ducimetiere, P. and Benetos, A. (2001). Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension*, **37**, 1236-1241.

Laurent, S., Boutouyrie, P. and Lacolley, P. (2005). Structural and genetic bases of arterial stiffness. *Hypertension*, **45**, 1050-1055.

LeBlanc, E.S., Wang, P.Y., Lee, C.G., Barrett-Connor, E., Cauley, J.A., Hoffman, A.R., Laughlin, G.A., Marshall, L.M. and Orwoll, E.S. (2011). Higher testosterone levels are associated with less loss of lean body mass in older men. *Journal of Clinical Endocrinology and Metabolism*, **96**, 3855-3863.

Lee, H.H.K., Warde, P. and Jewett, M.A.S. (1999a). Neoadjuvant hormonal therapy in carcinoma of the prostate. *BJU International*, **83**, 438-448.

Lee, C.D., Blair, S.N. and Jackson, A.S. (1999b). Cardiorespiratory fitness, body composition, and all-cause cardiovascular disease mortality in men. *The American Journal of Clinical Nutrition*, **69**, 373-380.

Lee, I.M. and Skerrett, P.J. (2001). Physical activity and all-cause mortality: what is the dose-response relation? *Medicine and Science in Sports and Exercise*, **33**, S459-S471.

Leigh, S.A. (1996). Defining our destiny. In *A Cancer Survivor's Almanac: Charting your Journey* (edited by B. Hoffman), pp 261-271. Minneapolis: Chronimed Publishing.

Lenk, K., Uhlemann, M., Schuler, G. and Adams ,V. (2011). Role of endothelial progenitor cells in the beneficial effects of physical exercise on atherosclerosis and coronary artery disease. *Journal of Applied Physiology*, **111**, 321-328.

Levine, G.N., D'Amico, A.V., Berger, P., Clark, P.E., Eckel, R.H., Keating, N.L., Milani, R.V., Sagalowsky, A.I., Smith, M.R. and Zakai, N. (2010). Androgen-deprivation therapy in prostate cancer and cardiovascular risk. *CA: A Cancer Journal for Clinicians*, **60**, 194-201.

Li, J. and Al-Azzawi, F. (2009) Mechanism of androgen receptor action. *Maturitas*, **63**, 142-148.

Liao, Y., Chen, L.L., Zeng, T., Li, Y., Yu, F., Hu, L. and Yue, L. (2010). Number of circulating endothelial progenitor cells as a marker of vascular endothelial function for type 2 diabetes. *Vascular Medicine*, **15**, 279-285.

Lichtenstein, P., Holm, N.V., Verkasalo, P.K., Iliadou, A., Kaprio, J., Koskenvuo, M., Pukkala, E., Skytthe, A. and Hemminki, K. (2000). Environmental and heritable factors in the causation of cancer. Analyses of cohorts of twins from Sweden, Denmark and Finland. *The New England Journal of Medicine,* **343**, 78-85.

Lichtenstein, A.H., Appel, L.J., Brands, M., Carnethon, M., Daniels, S., Franch, H.A., Franklin, B., Kris-Etherton, P., Harris, W.S., Howard, B., Karanja, N., Lefevre, M., Rudel, L., Sacks, F., Van Horn, L., Winston, M. and Wylie-Rosett, J. (2006). American Heart Association scientific statement. Diet and lifestyle recommendations revision 2006. *Circulation*, **114**, 82-96.

Littrup, P.J., Lee, F. and Mettlin, C. (1992). Prostate cancer screening: Current trends and future implications. *CA: A Cancer Journal for Clinicians*, **42**, 198-211.

Lloyd, J.C., Antonelli, J.A., Phillips, T.E., Masko, E.M., Thomas, J.A., Poulton, S.H., Pollak, M. and freedland, S.J. (2010). Effect of isocaloric low fat diet on prostate cancer xenograft progression in a hormone deprivation model. *Journal of Urology*, **183**, 1619-1624.

Loeb, S. and Catalona, W.J. (2007). Prostate-specific antigen in clinical practice. *Cancer Letters*, **249**, 30-39.

Longcope, C., Feldman, H.A., McKinlay, J.B. and Araujo, A.B. (2000). Diet and sex hormone-binding globulin. *The Journal of Clinical Endocrinology & Metabolism*, **85**, 293-296.

Lowitz, B.B and Casciato, D.A. (2012) Principles and definitions of cancer. In *Manual of Clinical Oncology. Seventh Edition* (edited by D.A. Casciato and M.C. Territo), pp, 2-18. Philadelphia: Lippincott Williams & Wilkins.

Lu, Y.L., Kuang, L., Zhu, H., Wu, H., Wang, X.F., Pang, Y.P., Wang, N.J. and Yu, D.L. (2007). Changes in the aortic endothelium ultrastructure in male rats following castration, replacement with testosterone and administration of 5α-reductase inhibitor. *Asian Journal of Andrology*, **9**, 843-847.

Lund Nilsen, T.I. and Vatten, L.J. (1999). Anthropometry and prostate cancer risk: a prospective study of 22,248 Norwegian men. *Cancer Causes and Control*, **10**, 269-275.

Lu-Yao, G., Albertson, P.C., Stanford, J.L., Stukel, T.A., Walker-Corkery, E. and Barry, M.J. (2002). Natural experiment examining the impact of aggressive screening and treatment on prostate cancer mortality in two fixed cohorts from Seattle area and Connecticut. *BMJ-Clinical Research*, **325**: 740.

Lu-Yao, G., Albertson, P.C., Stanford, J.L., Stukel, T.A., Walker-Corkery, E. and Barry, M.J. (2008). Screening, treatment, and prostate cancer mortality in the Seattle area and Connecticut: Fifteen-year follow-up. *Journal of General Internal Medicine*, **23**, 1809-1814.

Macmillan Cancer Support. (2008). Two million reasons: The cancer survivorship agenda. London: Macmillan Cancer Support

Macmillan Cancer Support. (2010). *Radiotherapy for early prostate cancer*, Feb/10, http://www.macmillan.org.uk/Cancerinformation/Cancertypes/Prostate/Treatmentforearlyprostatecancer/Radiotherapy.aspx

Maddams, J., Brewster, D., Gavin, A., Steward, J., Elliott, J., Utley, M. and Møller, H. (2009). Cancer prevalence in the United Kingdom: estimates for 2008. *British Journal of Cancer*, **101**, 541-547.

Maeda, S., Miyauchi, T., Kakiyama, T., Sugawara, J., Iemitsu, M., Irukayama-Tomobe, Y., Murakami, H., Kumagai, Y., Kuno, S. and Matsuda,

M. (2001). Effects of exercise training of 8-weeks and detraining on plasma levels of endothelium-derived factors, endothelin-1 and nitric oxide, in healthy young humans. *Life Sciences*, **69**, 1005-1016.

Maeda, S., Miyauchi, T., Iemitsu, M., Tanabe, T., Yokota, T., Goto, K., Yamaguchi, I. and Matsuda, M. (2002). Effects of exercise training on expression of endothelin-1 mRNA in the aorta of aged rats. *Clinical Science*, **103**, 1185-1235.

Mahler, R.J. and Adler, M.L. (1999). Type 2 diabetes mellitus: Update on diagnosis, pathophysiology, and treatment. *The Journal of Clinical Endocrinology and Metabolism*, **84**, 1165-1171.

Mammi, C., Calanchini, M., Antelmi, A., Cinti, F., Rosano, G.M.C., Lenzi, A., Caprio, M. and Fabbri, A. (2012). Androgens and adipose tissue in males: A complex and reciprocal interplay. *International Journal of Endocrinology*, **2012**, 1-8.

Mannion, T.C., Vita, J.A., Keaney, J.F., Benjamin, E.J., Hunter, L. and Polak, J.F. (1998). Non-invasive assessment of brachial artery endothelial vasomotor function: the effect of cuff position on level of discomfort and vasomotor responses. *Vascular Medicine*, **3**, 263-267.

Manson, J.E., Nathan, D.M., Krolewski, A.S., Stampfer, M.J., Willett, W.C. and Hennekens, C.H. (1992). A prospective study of exercise and incidence of diabetes among US male physicians. *The Journal of the American Medical Association*, **268**, 63-67.

Marcella, S.W., Rhoads, G.G., Carson, J.L., Merlino, F. and Wilcox, H. (2008). Prostate-specific antigen screening and mortality from prostate cancer. *Journal of General Internal Medicine*, **23**, 248-253.

Marieb, E.N. and Hoehn, K. (2010). *Human anatomy and physiology. Eigth edition*. San Francisco: Pearson Education Publishing.

Marin, C., Ramirez, R., Delgado-Lista, J., Yubero-Serrano, E.M., Perez-Martinez, P., Carracedo, J., Garcia-Rios, A., Rodriguez, F., Guiterrez-

Mariscal, F.M., Gomez, P., Perez-Jimenez, F. and Lopez-Miranda, J. (2011). Mediterranean diet reduces endothelial damage and improves the regenerative capacity of endothelium. *American Journal of Clinical Nutrition*, **93**, 267-274.

Mariotto, A.B., Yabroff, R., Shao, Y., Feuer, E.J. and Brown, M.L. (2011). Projections of the cost of cancer care in the United States: 2010-2020. *Journal of the National Cancer Institute*, **103**, 117-128.

Martin, N.R.W. and Lewis, M.P. (2012). Satellite cell activation and number following acute and chronic exercise: A mini review. *Cellular and Molecular Exercise Physiology*, **1**, e3.

Massie, M.J. (2004). Prevalence of depression in patients with cancer. *Journal of the National Cancer Institute Monographs*, **2004**, 57-71

Matsumoto, A.M. (2005). Fundamental aspects of hypogonadism in the aging male. *The Aging Male*, **5**, S3-S10.

Mattace-Raso, F.U.S., van der Cammen, T.J.M., Hofman, A., van Popele, N.M., Bos, M.L., Schalekamp, M.A.D.H., Asmar, R., Reneman, R.S., Hoeks, A.P.G., Breteler, M.M.B. and Witteman, J.C.M. (2006). Arterial stiffness and risk of coronary heart disease and stroke. The Rotterdam Study. *Circulation*, **113**, 657-663.

McDonald, C., Bauer, J.D. and Capra, S. (2011). Body composition and breast cancer- the role of lean body mass. *Cancer Forum*, **35**, 2.

McEniery, C.M., Hall, I.R., Qasem, A., Wilkinson, I.B. and Cockcroft, J.R. (2005). Normal vascular aging: Differential effects on wave reflection and aortic pulse wave velocity. The Anglo-Cardiff collaborative trial (ACCT). *Journal of the American College of Cardiology*, **46**, 1753-1760.

McLaren, D., Kelly, D., Akhtar, S., Channer, K. and Jones, T. (2012). Low testosterone is associated with decreased expression of glut-4 and hexokinase 2 in muscle of the testicular feminised mouse. *Endocrine Abstracts*, **29**, P559.

McLeod, D.G. and Iverson, P. (2000). Gynecomastia in patients with prostate cancer: a review of treatment options. *Urology*, **56**, 713-720.

McLoed, D.G., Iverson, P., See, W.A., Morris, T., Armstrong, J. and Wirth, M.P. (2005). Bicalutamide 150 mg plus standard care vs standard care alone for early prostate cancer. *BJU International*, **97**, 247-254.

McMillan, E.M. and Newhouse, I.J. (2011). Exercise is an effective treatment modality for reducing cancer-related fatigue and improving physical capacity in cancer patients and survivors: a meta-analysis. *Applied Physiology, Nutrition and Metabolism*, **36**, 892-903.

McNeal, J.E. (1968). Regional morphology and pathology of the prostate. *American Journal of Clinical Pathology*, **49**, 347-357.

Mead, A., Atkinson, G., Albin, D., Alphey, D., Baic, S., Boyd, O., Cadigan, L., Clutton, L., Craig, L., Flanagan, C., Greene, P., Griffiths, E., Lee, N.J., Li, M., McKechnie, L., Ottaway, J., Paterson, K., Perrin, L., Rigby, P., Stone, D., Vine, R., Whitehead, J., Wray, L. and Hooper, L. (2006). Dietetics guidelines on food and nutrition in the secondary prevention of cardiovascular disease-evidence from systematic reviews of randomized controlled trials. *Journal of Human Nutrition and Dietetics*, **19**, 401-419.

Mehta, S., Dallas, F., Rosario, D. and Ong, A. (2007). Diseases of the kidney and urinary system. In *Medicine and Surgery. An Integrated Textbook* (edited by E. Lim, Y.K. Loke and A. Thompson), pp 681-771. Philadelphia: Elsevier.

Meng, M.V., Grossfeld, G.D., Sadetsky, N., Mehta, S.S., Lubeck, D.P. and Carroll, P.R. (2002). Contemporary patterns of androgen deprivation therapy use for newly diagnosed prostate cancer.*Urology*, **60**, 7-11.

Messing, E.M., Manola, J., Sarosdy, M., Wilding, G., Crawford, D. and Trump, D. (1999). Immediate hormonal therapy compared with observation after radical prostatectomy and pelvic lymphadenectomy in men with node-positive prostate cancer. *The New England Journal of Medicine*, **341**, 1781-1788.

Meyerhardt, J.A., Giovannucci, E.L., Holmes, M.D., Chan, A.T., Chan, J.A., Colditz, G.A. and Fuchs, C.S. (2006a). Physical activity and survival after colorectal cancer diagnosis. *Journal of Clinical Oncology*, **24**, 3527-3534.

Meyerhardt, J.A., Heseltine, D., Niedzwiecki, D., Hollis, D., Saltz, L.B., Mayer, R.J., Thomas, J., Nelson, H., Whittom, R., Hantel, A., Schilsky, R.L. and Fuchs, C.S. (2006b). Impact of physical activity on cancer recurrence and survival in patients with stage III colon cancer: Findings from CALGB 89803. *Journal of Clinical Oncology*, **24**, 3535-3541.

Michaud, D.S., Augustsson, K., Rimm, E.B., Stampfer, M.J., Willett, W.C. and Giovannucci, E. (2001). A prospective study on intake of animal products and risk of prostate cancer. *Cancer Causes and Control*, **12**, 557-567.

Milardi, D., Grande, G., Giampietro, A., Vendittelli, F., Palumbo, S., Tartaglione, L., Marana, R., Pontecorvi, A., De Marinis, L., Zuppi, C. and Capoluongo, E. (2012). Circulating endothelial cells as marker of endothelial damage in male hypogonadism. *Journal of Andrology*, **33**, 1291-1297.

Miller, D.C., Gruber, S.B., Hollenbeck, B.K., Montie, J.E. Wie, J.T. (2006). Incidence of initial local therapy among men with lower-risk prostate cancer in the United States. *Journal of the National Cancer Institute*, **98**, 1134-1141.

Miner, M.M., Khera, M., Bhattacharya, R.K., Blick, G. and Kushner, H. (2011). Baseline data from the TRiUS registry: symptoms and comorbidities of testosterone deficiency. *Postgraduate Medicine*, **123**, 17-27.

Minor, M.A. and Johnson, J.C. (1996). Reliability and validity of a submaximal treadmill test to estimate aerobic capacity in women with rheumatic disease. *Journal of Rheumatology*, **23**, 1517-1523.

Mistry, K. and Cable, G. (2003). Meta-analysis of prostate-specific antigen and digital rectal examination as screening tests for prostate carcinoma. *The Journal of the American Board of Family Practice*, **16**, 95-101.

Mistry, M., Parkin, D.M., Ahmad, A.S. and Sasieni, P. (2011). Cancer incidence in the United Kingdom: projections to the year 2030. *British Journal of Cancer*, **105**, 1795-1803.

Mitchell, G.F., Hwang, S.J., Vasan, R.S., Larson, M.G., Pencina, M.J., Hamburg, N.M., Vita, J.A., Levy, D. and Benjamin, E.J. (2010). Arterial stiffness and cardiovascular events. The Framingham heart study. *Circulation*, **121**, 505-511.

Miyatake, N., Tanaka, A., Eguchi, M., Miyachi, M., Tabata, I. and Numata, T. (2009). Reference data of multi frequencies bioelectric impedance method in Japanese. *Journal of Anti-Aging Medicine*, **6**, 10-14.

Mohamedali, H.Z., Breunis, H., Timilshina, N. and Alibhai, A.M.H. (2011). Changes in blood glucose and cholesterol levels due to androgen deprivation therapy in men with non-metastatic prostate cancer. *Canadian Urological Association Journal*, **5**, 28-32.

Mohile, S.G., Mustian, K., Bylow, K., Hall, W. and Dale, W. (2009). Management of complication of androgen deprivation therapy in the older man. *Critical Reviews in Oncology/Hematology*, **70**, 235-255.

Molinari, C., Battaglia, A., Grossini, E., Mary, D.A.S.G., Vassanelli, C. and Vacca, G. (2002). The effect of testosterone on regional blood flow in prepubertal anaesthetized pigs. *Journal of Physiology*, **543**, 365-372.

Montgomery, R.B., Mostaghel, E.A., Vessella, R., Hess, D.L., Kalhorn, T.F., Higano, C.S., True, L.D. and Nelson, P.S. (2008). Maintenance of intratumoral androgens in metastatic prostate cancer: A mechanism for castration-resistant tumour growth. *Cancer Research*, **1**, 4447-4454.

Montorsi, P., Ravagnani, P.M., Galli, S., Ali, S.G., Briganti, A., Salonia, A. and Montorsi, F. (2009). The triad of endothelial dysfunction, cardiovascular disease and erectile dysfunction: Clinical implications. *European Urology Supplements*, **8**, 58-66.

Mora, S., Cook, N., Buring, J.E., Ridker, P.M. and Lee, I.M. (2007). Physical activity and reduced risk of cardiovascular events. Potential mediating mechanisms. *Circulation*, **116**, 2110-2118.

Morote, J., Martinez, E., Trilla, E., Esquena, S., Abascal, J.M., Encabo, G. and Reventós, J. (2003). Osteoporosis during continuous androgen deprivation: influence of the modality and length of treatment. *European Urology*, **44**, 611-615.

Moreau, J.P., Delavault, P. and Blumberg, P. (2006). Luteinizing hormone-releasing hormone agonists in the treatment of prostate cancer: A review of their discovery, development and place in therapy. *Clinical Therapeutics*, **28**, 1485-1508.

Mudali, S. and Dobs, A.S. (2004). Effects of testosterone on body composition of the aging male. *Mechanisms of Aging and Development*, **125**, 297-304.

Mueller, P.J. (2007). Exercise training and sympathetic nervous system activity: Evidence for physical activity dependent neural plasticity. *Clinical and Experimental Pharmacology and Physiology*, **34**, 377-384.

Mullen, M.J., Kharbanda, R.K., Cross, J., Donald, A.E., Taylor, M., Vallance, P., Deanfield, J.E. and MacAllister, R.J. (2001). Heterogenous nature of flow-mediated dilatation in human conduit arteries in vivo. Relevance to endothelial dysfunction in hypercholesterolemia. *Circulation*, **88**, 145-151.

Mulligan, T., Frick, M.F., Zuraw, Q.C., Stemhagen, A. and McWhirter, C. (2006). Prevalence of hypogonadism in males aged at least 45 years: the HIM study. *International Journal of Clinical Practice*, **60**, 762-769.

Myers, R.J., Klesges, R.C., Eck, L.H., Hanson, C.L. and Klem, M.L. (1988). Accuracy of self-reports of food intake in obese and normal-weight individuals: effects of obesity on self-reports of dietary intake in adult females. *American Journal of Clinical Nutrition*, **48**, 1248-1251.

Myers, J. (2003). Exercise and cardiovascular health. *Circulation*, **107**, e2-e5.

Myers, J., Kaykha, A., George, S., Abella, J., Zaheer, N., Lear, S., Yamazaki, T. and Froelicher, V. (2004). Fitness versus physical activity patterns in predicting mortality in men. *American Journal of Medicine*, **117**, 912-918.

Na, Y.M., Kim, M.Y., Kim, Y.K., Ha, Y.R. and Yoon, D.S. (2000). Exercise therapy effect on natural killer cell cytotoxic activity in stomach cancer patients after curative surgery. *Archives of Physical Medicine and Rehabilitation*, **81**, 777-779.

Naharci, M.I., Pinar, M., Bolu, E. and Olgun, A. (2007). Effect of testosterone on insulin sensitivity in men with idiopathic hypogonadotropic hypogonadism. *Endocrine Practice*, **13**, 629-635.

Nalesnik, J.G., Mysliwiec, A.G. and Canby-Hagino, E. (2004). Anaemia in men with advanced prostate cancer: Incidence, etiology, and treatment. *Reviews in Urology*, **6**, 1-4.

Naseem, K.M. (2005). The role of nitric oxide in cardiovascular disease. *Molecular Aspects of Medicine*, **26**, 33-65.

Nasseri, K., Mills, P.K. and Allan, M. (2007). Cancer incidence in the Middle Eastern population of California, 1988-2004. *Asian Pacific Journal of Cancer Prevention*, **8**, 405-411.

National Cancer Institute. (2012). What is cancer? Feb/12, http://www.cancer.gov/cancertopics/cancerlibrary/what-is-cancer

National Cancer Survivorship Initiative. (2013). What is the National Cancer Survivorship Initiative? May/13, www.ncsi.org.uk

National Institute for Health and Clinical Excellence. (2008). NICE clinical guideline 58. Prostate cancer. Diagnosis and treatment. Feb/08, www.nice.org.uk

Neal, A.J. and Hoskin, P.J. (2003). *Clinical Oncology. Basic principles and practice. Third edition*. London: Arnold, Hodder Headline Group.

Nelson, W.G., De Marzo, A.M. and Isaacs, W.B. (2003). Prostate cancer. Mechanisms of disease. *The New England Journal of Medicine*, **349**, 366-381.

Nguyen, P.L., Je, Y., Schutz, F.A.B., Hoffman, K.E., Hu, J.C., Parekh, A., Beckman, J.A. and Choueiri, T.K. (2011). Association of androgen deprivation therapy with cardiovascular death in patients with prostate cancer. A meta-analysis of randomized trials. *Journal of the American Medical Association*, **306**, 2359-2366.

Nieman, D.C., Cook, V.D., Henson, V.A., Suttles, J., Rejeski, W.J., Ribisi, P.M., Fagoaga, O.R. and Nehlsen-Cannarella, S.L. (1995). Moderate exercise training and natural killer cell cytotoxic activity in breast cancer patients. *International Journal of Sports Medicine*, **16**, 334-337.

Nigam, A., Mitchell, G.F., Lambert, J. and Tardif, J-C. (2003). Relation between conduit vessel stiffness (assessed by tonometry) and endothelial function (assessed by flow-mediated dilatation) in patients with and without coronary heart disease. *American Journal of Cardiology*, **92**, 395-399.

Nishiyama, T., Ishizaki, F., Anraku, T., Shimura, H. and Takahashi, K. (2005). The influence of androgen deprivation therapy on metabolism in patients with prostate cancer. *The Journal of Clinical Endocrinology and Metabolism*, **90**, 657-660.

Nobes, J.P., Langley, S.E.M., Klopper, T., Russell-Jones, D. and Laing, R.W. (2012). A prospective, randomized pilot study evaluating the effects of metformin and lifestyle intervention on patients with prostate cancer receiving androgen deprivation therapy. *BJU International*, **109**, 1495-1502.

Nocon, M., Hiemann, T., Müller-Riemenschneider, F., Thalau, F., Roll, S. and Willich, S.N. (2008). Association of physical activity with all-cause and cardiovascular mortality: a systematic review and meta-analysis. *European Journal of Cardiovascular Prevention and Rehabilitation*, **15**, 239-246.

Noon, J.P. (2009). The arterial pulse wave and vascular compliance. *Progress in Cardiovascular Nursing*, **24**, 53-58.

Nuttings, A., Horwich, A., Fisher, C., Parsons, C. and Dearnaley, D.P. (1997). Small-cell carcinoma of the prostate. *Journal of the Royal Society of Medicine*, **90**, 340-341.

Oberaigner, W., Horninger, W., Klocker, H., Schönitzer, D., Stühlinger, W. and Bartsch, G. (2006). Reduction of prostate cancer mortality in Tyrol, Austria, after introduction of prostate-specific antigen testing. *American Journal of Epidemiology*, **164**, 376-384.

O'Donovan, G., Blazevich, A.J., Boreham, C., Cooper, A.R., Crank, H., Ekelund, U., Fox, K.R., Gately, P., Giles-Corti, B., Gill, J.M.R., Hamer, M., McDermott, I., Murphy, M., Mutrie, N., Reilly, J.J., Saxton, J.M. and Stamatakis, E. (2010). The ABC of physical activity for health: A consensus statement from the British Association of Sport and Exercise Sciences. *Journal of Sports Sciences*, **28**, 573-591.

O'Dwyer, K.M. and Frattini, M.G. (2010). Principles of neoplasia. In *Synopsis of Clinical Oncology* (edited by M.D. Stubblefield and M.W. O'Dell), pp, 3-13. New York: Demos Medical Publishing.

Office for National Statistics. (2012). Cancer Registration Statistics England, Feb/13, http://www.ons.gov.uk/ons/search/index.html?newquery=cancer+statistics+registrations

Oliver, S.E., May, M.T. and Gunnell, D. (2001). International trends in prostate cancer mortality in the PSA era. *International Journal of Cancer*, **92**, 893-898.

Oliveras, A., de la Sierra, A., Martínez-Estrada, O.M., Larrousse, M., Vázquez, S., Soler, M.J., Zuasti, M., Vila, J.S., Reina, M., Roca-Cusachs, A. and Lloveras, J. (2008). Putative endothelial progenitor cells are associated with flow-mediated dilation in refractory hypertensives. *Blood Pressure*, **17**, 298-305.

Oppenheim, D.S., Greenspan, S.L., Zervas, N.T., Schoenfeld, D.A. and Klibanski, A. (1989). Elevated serum lipids in hypogonadal men with and without hyperprolactinemia. *Annals of Internal Medicine*, **111**, 288-292.

Oxford Press. (2007). *Oxford, Concise Colour Medical Dictionary. Fourth Edition*, Oxford: Oxford University Press

Pace, G., Pomante, R. and Vicentini, C. (2010). Sarcoma of prostate: case report and review of the literature. *Archive of Italian Urology and Andrology*, **82**, 105-108.

Paffenbarger, R.S., Wing, A.L., Hyde, R.T. and Jung, D.L. (1983). Physical activity and incidence of hypertension in college alumni. *American Journal of Epidemiology*, **117**, 245-257.

Page, W.F., Braun, M.M., Partin, A.W., Caporaso, N. and Walsh, P. (1997). Heredity and prostate cancer: A study of World War II veteran twins. *The Prostate*, **33**, 240-245.

Pal, S.K., Kim, H.L. and Figlin, R.A. (2012) Urinary tract cancers. In *Manual of Clinical Oncology. Seventh Edition* (edited by D.A. Casciato and M.C. Territo), pp, 365-394. Philadelphia: Lippincott Williams & Wilkins.

Panju, A.H., Breunis, H., Cheung, A.M., Leach, M., Fleshner, M., Warde, P., Duff-Canning, S., Krahn, M., Naglie, G., Tannock, I., Tomlinson, G. and Alibhai, S.M.H. (2009). Management of decreased bone mineral density in men starting androgen-deprivation therapy for prostate cancer. *BJU International*, **103**, 753-757.

Pannier, B., Guérin, A.P., Marchais, S.J., Métivier, F. and London, G.M. (2007). Arterial structure and function in end-stage renal disease. *Artery Research*, **1**, 79-88.

Papsidero, L.D., Wang, M.C., Valenzuela, L.A., Murphy, G.P. and Chu, T.M. (1980). A prostate antigen in sera of prostatic cancer patients. *Cancer Research*, **40**, 2428-2432.

Parikh, N.I., Keyes, M.J., Larson, M.G., Pou, K.M., Hamburg, N.M., Vita, J.A., O'Donnell, C.J., Vasan, R.S., Mitchell, G.F., Hoffmann, U., Fox, C.S. and Benjamin, E.J. (2009). Visceral and subcutaneous adiposity and brachial artery vasodilator function. *Obesity*, **17**, 2054-2059.

Parker, B.A., Trehearn, T.L. and Meendering, J.R. (2009). Pick your poiseuille: normalizing for shear stimulus in studies of flow-mediated dilation. *Journal of Applied Physiology*, **107**, 1357-1359.

Parkin, D.M., Pisani, P. and Ferlay, J. (1999). Global cancer statistics. *CA: A Cancer Journal for Clinicians*, **49**, 33-64.

Parkin, D.M. (2001). Global cancer statistics. *The Lancet- Oncology*, **2**, 533-543.

Parkin, D.M., Bray, F., Ferlay, J. and Pisani, P. (2005). Global cancer statistics, 2002. *CA- A Cancer Journal for Clinicians*, **55**, 74-108.

Patnaik, J.L., Byers, T., DiGuiseppi, C., Dabelea, D. and Denberg, T.D. (2011). Cardiovascular disease competes with breast cancer as the leading cause of death for older females diagnosed with breast cancer: a retrospective cohort study. *Breast Cancer research*, **13**, R64.

Pelzer, A.E., Bektic, J., Berger, A.P., Halpern, E.J., Koppelstätter, F., Klauser, A., Rehder, P., Horninger, W., Bartsch, G. and Frauscher, F. (2005). Are transition zone biopsies still necessary to improve prostate cancer detection? Results from the Tyrol screening project. *European Urology*, **48**, 916-921.

Perlmutter, M.A. and Lepor, H. (2007). Androgen deprivation therapy in the treatment of advanced prostate cancer. *Reviews in Urology*, **9**, S3-S8.

Perrault, L.P., Mahlberg, F., Breugnot, C., Bidouard, J-P., Villeneuve, N., Vilaine, J-P. and Vanhoutte, P.M. (2000). Hypercholesterolemia increases coronary endothelial dysfunction, lipid content, and accelerated atherosclerosis after heart transplantation. *Arteriosclerosis, Thrombosis and Vascular Biology*, **20**, 728-736.

Perticone, F., Ceravolo, R., Candigliota, M., Ventura, G., Iacopino, S., Sinopoli, F. and Mattioli, P.L. (2001). Obesity and body fat distribution induce endothelial dysfunction by oxidative stress. Protective effect of vitamin C. *Diabetes*, **50**, 159-165.

Pescatello, L.S., Franklin, B.A., Fagard, R., Farquhar, W.B., Kelley, G.A. and Ray, C.A. (2004). American College of Sports Medicine Position Stand: Exercise and Hypertension. *Medicine and Science in Sports and Exercise*, **36**, 533-553.

Petak, S.M., Nankin, H.R., Spark, R.F., Swerdloff, R.S. and Rodriguez-Rigau, L.J. (2002). American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of hypogonadism in adult male patients - 2002 update. *Endocrine Practice*, **8**, 440-456.

Pilepich, M.V., Winter, K., John, M.J., Mesic, J.B., Sause, W., Rubin, P., Lawton, C., Machtay, M. and Grignon, D. (2001). Phase III Radiation Therapy Oncology Group (RTOG) trial 86-10 of androgen deprivation adjuvant to definitive radiotherapy in locally advanced carcinoma of the prostate. *International Journal of Radiation, Oncology, Biology, Physics*, **50**, 1243-1252.

Pilepich, M.V., Winter, K., Lawton, C., Krisch, R.E., Wolkov, H.B., Movsas, B., Hug, E.B., Asbell, S.O. and Grignon, D. (2005). Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma- Long term results of phase III RTOG 85-31. *International Journal of Radiation, Oncology, Biology, Physics*, **61**, 1285-1290.

Platz, E.A., Leitzmann, M.F., Rifai, N., Kantoff, P.W., Chin, Y.C., Stampfer, M.J., Willett, W.C. and Giovannucci, E. (2005). Sex steroid hormones and the androgen receptor gene CAG repeat and the subsequent risk of prostate cancer in the prostate-specific antigen era. *Cancer Epidemiology, Biomarkers and Prevention*, **14**, 1262-1269.

Pollock, M.L., Franklin, B.A., Balady, G.J., Chaitman, B.L., Fleg, J.L., Fletcher, B., Limacher, M., Piña, I.L., Stein, R.A., Williams, M and Bazzarre, T. (2000). Resistance exercise in individuals with and without cardiovascular disease. *Circulation*, **101**, 828-833.

Pommerville, P.J. and de Boer, J.G. (2010). GnRH antagonists in the treatment of advanced prostate cancer. *The Canadian Journal of Urology*, **17**, 5063-5070.

Porter, R. (1997). *The greatest benefit to mankind. A medical history of humanity from antiquity to the present.* London: Fontana Press, Harper Collins Publishers.

Preston, D.M., Torréns, J.I., Harding, P., Howard, R.S., Duncan, W.E. and McLeod, D.G. (2002). Androgen deprivation in men with prostate cancer is associated with an increased rate of bone loss. *Prostate Cancer and Prostatic Disease*, **5**, 304-310.

Priebe, H.J. (2000). The aged cardiovascular risk patient. *British Journal of Anaesthesia*, **85**, 763-778.

Quaglia, A., Parodi, S., Grosclaude, P., Martinez-Garcia, C., Coebergh, J.W. and Vercelli, M. (2003). Differences in the epidemic rise and decrease of prostate cancer among geographical areas in Southern Europe: An analysis of differential trends in incidence and mortality in France, Italy and Spain. *European Journal of Cancer*, **39**, 654-665.

Quinn, M. and Babb, P. (2002). Patterns and trends in prostate cancer incidence, survival, prevalence and mortality. Part 1: International comparisons. *BJU International*, **90**, 162-173.

Raguso, C.A., Kyle, U., Kossovsky, M.P., Roynette, C., Paoloni-Giacobino, A., Hans, D., Genton, L. and Pichard, C. (2006). A 3-year longitudinal study on body composition changes in the elderly: Role of physical exercise. *Clinical Nutrition*, **25**, 573-580.

Rajagopalan, S. and Harrison, D.G. (1996). Reversing endothelial dysfunction with ACE inhibitors. A new trend? *Circulation*, **94**, 240-243.

Regit-Zagrosek, V., Lehmkuhl, E. and Weickert, M.O. (2006). Gender differences in the metabolic syndrome and their role for cardiovascular disease. *Clinical Research in Cardiology*, **95**, 136-147.

Reuss-Borst, M., Hartmann, U., Scheede, C. and Weiß, J. (2012). Prevalence of osteoporosis among cancer patients in Germany: prospective data from an oncological rehabilitation clinic. *Osteoporosis International*, **23**, 1437-1444.

Rewers, M., Zaccaro, D., D'Agostino, R., Haffner, S., Saad, M.F., Selby, J.V., Bergman, R. and Savage, P. (2004). Insulin sensitivity, insulinemia, and coronary artery disease. *Diabetes Care*, **27**, 781-787.

Richards, M., Corner, J. and Maher, J. (2011). The National Cancer Survivorship Initiative: new and emerging evidence on the ongoing needs of cancer survivors. *British Journal of Cancer*, **105**, S1-S4.

Richman, E.L., Stampfer, M.J., Paciorek, R., Broering, J.M., Carroll, P.R. and Chan, J.M. (2010). Intakes of meat, fish, poultry and eggs and risk of prostate cancer progression. *American Journal of Clinical Nutrition*, **91**, 712-721.

Richman, E.L., Kenfield, S.A., Stampfer, M.J., Paciorek, A., Carroll, P.R. and Chan, J.M. (2011). Physical activity after diagnosis and risk of prostate cancer progression: Data from the Cancer of the Prostate Strategic Urologic Research Endeavor. *Cancer Research*, **71**, 1-7.

Ridker, P.M. (2007). C-Reactive protein and the prediction of cardiovascular events among those at intermediate risk. *Journal of the American College of Cardiology*, **49**, 2129-2138.

Rikli, R.E. and Jones, C.J. (1999). Development and validation of a functional fitness test for community residing older adults. *Journal of Aging and Physical Activity*, **7**, 129-161.

Rizzo, M. and Berneis, K. (2006). Low-density lipoprotein size and cardiovascular risk assessment. *The Quarterly Journal of Medicine*, **99**, 1-14.

Roach, M., Bae, K., Speight, J., Wolkov, H.B., Rubin, P., Lee, R.J., Lawton, C., Valicenti, R., Grignon, D. and Pilepich, M.V. (2008). Short-term neoadjuvant androgen deprivation therapy and external-beam radiotherapy for locally advanced prostate cancer: Long-term results of RTOG 8610. *Journal of Clinical Oncology*, **26**, 585-591.

Roberts, S.G., Blute, M.L., Bergstralh, E.J., Slezak, J.M. and Zincke, H. (2001). PSA doubling time as a predictor of clinical progression after biochemical failure following radical prostatectomy for prostate cancer. *Mayo Clinic Proceedings*, **76**, 576-581.

Rock, C.L., Doyle, C., Demark-Wahnefried, W., Meyerhardt, J., Courneya, K.S., Schwartz, A.L., Bandera, E.V., Hamilton, K.K., Grant, B., McCullough, M., Byers, T. and Gansler, T. (2012). Nutrition and physical activity guidelines for cancer survivors. *CA Cancer Journal for Clinicians*, **62**, 242-274.

Roddam, A.W., Allen, N.E., Appleby,P., Key, T.J., Dorgan, J.F., Albanes, D., Taylor, P.R., Ferrucci, L., Carter, H.B., metter, E.J., Chen, C., Weiss, N.S., Goodman, G., Hsing, A.W., Comstock, G., Helzlsouer, K., Travis, R., Riboli, E., Kaaks, R., Knekt, P., Heliövaara, M., Platz, E.A., Willert, W.C., Vatten, L., Ursin, G., Tamakoshi, A., Ozasa, K., Nomura, A.M., Stemmermann, G.N., Schaefer, C., Quesenberry, C.P., Vogelman, J.H., Severi, G., English, D.R., Giiles, G.G., Luostarinen, T., Stenman, U.H., Tenkanen, L., Gislefoss, R., Stattin, P., Hallmans, G., Stocks, T., Chan, J.M., Stampfer, M., Gann, P., Oliver, S.E., Holly, J.M., Donovan, J., Barrett-Connor, E. and Garland, C. (2008). Endogenous sex hormones and prostate cancer: a collaborative analysis of 18 prospective studies. *Journal of the National Cancer Institute*, **100**, 170-183.

Rodriguez, C., McCullough, M.L., Mondul, A.M., Jacobs, E.J., Chao, A., Patel, A.V., Thun, M.J. and Calle, E.E. (2006). Meat consumption among black and white men and risk of prostate cancer in the cancer prevention study II,

Nutrition cohort. *Cancer Epidemiology, Biomarkers and Prevention*, **15**, 211-216.

Rodriguez, C., Freedland, S.J., Deka, A., Jacobs, E.J., McCullough, M.L., Patel, A.V., Thun, M.J. and Calle, E.E. (2007). Body mass index, weight change, and risk of prostate cancer in the cancer prevention study II nutrition cohort. *Cancer Epidemiology, Biomarkers and Prevention*, **16**, 63-69.

Rosano, G.M., Leonardo, F., Pagnotta, P., Pelliccia, F., Cerquetani, E., della Monica, P.L., Bonfiqli, B., Volpe, M and Chierchia, S.L. (1999). Acute anti-ischemic effect of testosterone in men with coronary artery disease. *Circulation*, **99**, 1666-1670.

Sabiston, C.M. and Brunet, J. (2012). Reviewing the benefits of physical activity during cancer survivorship. *American Journal of Lifestyle Medicine*, **6**, 167-177.

Sacco, R.L., Gan, R., Boden-Albala, B., Lin, I.F., Kargman, D.E., Hauser, W.A., Shea, S. and Paik, M.C. (1998). Leisure-time physical activity and ischemic stroke risk. The northern Manhattan stroke study. *Stroke*, **29**, 380-387.

Sader, M.A., Griffiths, K.A., Skilton, M.R., Wishart, S.M., Handelsman, D.J. and Celermajer, D.S. (2003). Physiological testosterone replacement and arterial endothelial function in men. *Clinical Endocrinology*, **59**, 62-67.

Saigal, C.S., Gore, J.L., Krupski, T.L., Hanley, J., Schonlau, M. and Litwin, M.S. (2007). Androgen deprivation therapy increases cardiovascular morbidity in men with prostate cancer. *Cancer*, **110**, 1493-1500.

Salonia, A., Gallina, A., Briganti, A., Suardi, N., Capitanio, U., Abdollah, F., Bertini, R., Freschi, M., Rigatti, P. and Montorsi, F. (2011). Circulating estradiol, but not testosterone, is a significant predictor of high-grade prostate cancer in patients undergoing radical prostatectomy. *Cancer*, **117**, 5029-5038.

Sandgren, T., Sonesson, B., Ahlgren, Å.R. and Länne, T. (1999). The diameter of the common femoral artery in healthy human: Influence of sex, age and body size. *Journal of Vascular Surgery*, **29**, 503-510.

Saylor, P.J. and Smith, M.R. (2009). Metabolic complications of androgen deprivation therapy for prostate cancer. *Journal of Urology*, **181**, 1998-2008.

Schnell, G.B., Robertson, A., Houston, D., Malley, L. and Anderson, T.J. (1999). Impaired brachial artery endothelial function is not predicted by elevated triglycerides. *Journal of the American College of Cardiology*, **33**, 2038-2043.

Shantsila, E., Watson, T. and Lip, G.Y.H. (2007). Endothelial progenitor cells in cardiovascular disorders. *Journal of the American College of Cardiology*, **49**, 741-752.

Shefer, G., Rauner, G., Yablonka-Reuveni, Z. and Benayahu, D. (2010). Reduced satellite cell numbers and myogenic capacity in aging can be alleviated by endurance exercise. *PLoS One*, **5**, e13307.

Schenk, S., Saberi, M. and Olefsky, J.M. (2008). Insulin sensitivity: modulation by nutrients and inflammation. *The Journal of Clinical Investigation*, **118**, 2992-3002.

Schmitz, K.H., Courneya, K.S., Matthews, C., Demark-Wahnefried, W., Galvão, D.A., Pinto, B.M., Irwin, M.L., Wolin, K.Y., Segal, R.J., Lucia, A., Schneider, C.M., von Gruenigen, V.E. and Schwartz, A.L. (2010). American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. *Medicine and Science in Sports and Exercise*, **42**, 1409-1426.

Schoenfeld, B.J. (2010). The mechanisms of muscle hypertrophy and their application to resistance training. *Journal of Strength and Conditioning*, **24**, 2857-2872.

Schow, D.A., Renfer, L.G., Rozanski, T.A. and Thomspon, I.M. (1998). Prevalence of hot flushes during and after neoadjuvant hormonal therapy for localized prostate cancer. *Southern Medical Journal*, **91**, 855-857.

Schram, M.T., Henry, R.M.A., van Dijk, R.A.J.M., Kostense, P.J., Dekker, J.M., Nijpels, G., Heine, R.J., Bouter, L.M., Westerhof, N. and Stehouwer, C.D.A. (2004). Increased central artery stiffness in impaired glucose metabolism and type 2 diabetes. The Hoorn Study. *Hypertension*, **43**, 176-181.

Schröder, F.H., Hugosson, J., Roobol, M.J., Tammela, T.L.J., Ciatto, S., Nelen, V., Kwiatkowski, M., Lujan, M., Lilja, H., Zappa, M., Denis, L.J., Recker, F., Berenguer, A., Määttänen, L., Bagma, C.H., Aus, G., Villers, A., Rebillard, X., van der Kwast, T., Blijenberg, B.G., Moss, S.M., de Koning, H.J. and Auvinenn, A. (2009). Screening and prostate-cancer mortality in a randomized European study. *New England Journal of Medicine*, **360**, 1320-1328.

See, W.A. (2003). Adjuvant hormone therapy after radiation or surgery for localized or locally advanced prostate cancer. *Current Treatment Options in Oncology*, **4**, 351-362.

Segal, K.R., Edano, A., Abalos, A., Albu, J., Blando, L., Thomas, M.B. and Pi-Sunyer, X. (1991). Effects of exercise training on insulin sensitivity and glucose metabolism in lean, obese, and diabetic men. *Journal of Applied Physiology*, **71**, 2402-2411.

Segal, R.J., Reid, R.D., Courneya, K.S., Malone, S.C., Parliament, M.B., Scott, C.G., Venner, P.M., Quinney, H.A., Jones, L.W., Slovenic D'Angelo, M.E. and Wells, G.A. (2003). Resistance exercise in men receiving androgen deprivation therapy for prostate cancer. *Journal of Clinical Oncology*, **21**, 1653-1659.

Segal, R.J., Reid, R.D., Courneya, K.S., Sigal, R.J., Kenny, G.P., Prud'Homme, D.G., Malone, S.C., Wells, G.A ., Scott, C.G. and Slovenic D'Angelo, M.E. (2009). Randomized controlled trial of resistance and aerobic exercise in men receiving radiation therapy for prostate cancer. *Journal of Clinical Oncology,* **27**, 344-351.

Selby, C. (1990). Sex hormone binding globulin: origin, function and clinical significance. *Annals of Clinical Biochemistry*, **27**, 532-541.

Selvin, E., Feinleib, M., Zhang, L., Rohrmann, S., Rifal, N., Nelson, W.G., Dobs, A., Basaria, S., Golden, S.H. and Platz, E.A. (2007). Androgens and diabetes in men. Results from the third national health and nutrition examination survey (NHANES III). *Diabetes Care*, **30**, 234-238.

Senn, S. (1994). Testing for baseline balance in clinical trials. *Statistics in Medicine*, **13**, 1715-1726.

Sesti, G. (2006). Pathophysiology of insulin resistance. *Best Practice and Research. Clinical Endocrinology and Metabolism*, **20**, 665-679.

Severi, G., Morris, H.A., MacInnis, R.J., English, D.R., Tilley, W., Hopper, J.L., Boyle, P. and Giles, G.G. (2006). Circulating steroid hormones and the risk of prostate cancer. *Cancer Epidemiology, Biomarkers and Prevention*, **15**, 86-91.

Shahani, S., Braga-Basaria, M. and Basaria, S. (2008). Androgen deprivation therapy in prostate cancer and metabolic risk for atherosclerosis. *Journal of Clinical Endocrinology and Metabolism*, **93**, 2042-2049.

Shahinian, V.B., Kuo, Y-F., Freeman, J.L., Orihuela, E. and Goodwin, J.S. (2005). Increasing use of gonadotropin-releasing hormone agonists for the treatment of localized prostate carcinoma. *Cancer*, **103**, 1615-1624.

Shahinian, V.B., Kuo, Y-F., Freeman, J.L. and Goodwin, J.S. (2006). Risk of the "Androgen Deprivation Syndrome" in men receiving androgen deprivation for prostate cancer. *Archives of Internal Medicine*, **166**, 465-471.

Shantsila, E., Watson, T. and Lip, G.Y.H (2007). Endothelial progenitor cells in cardiovascular disorders. *Journal of the American College of Cardiology*, **49**, 741-752.

Shariat, S.F., Scardino, P.T. and Lilja, H. (2008). Screening for prostate cancer: An update. *Canadian Journal of Urology*, **15**, 4363-4374.

Shechter, M., Issachar, A., Marai, I., Koren-Morag, N., Freinark, D., Shahar, Y., Shechter, A. and Feinberg, M.S. (2009). Long-term association of brachial artery flow-mediated vasodilation and cardiovascular events in middle-aged subjects with no apparent heart disease. *International Journal of Cardiology*, **134**, 52-58.

Sheean, P.M., Hoskins, K. and Stolley, M. (2012). Body composition changes in females treated for breast cancer: a review of the evidence. *Breast Cancer Research and Treatment*, **135**, 663-680.

Sherwood, L. (2007). *Human physiology, from cells to systems. Sixth edition*. Belmont, CA: Thomson Higher Education.

Shikanov, S., Kocherginsky, M., Shalhav, A.L. and Eggener, S.E. (2012). Cause-specific mortality following radical prostatectomy. *Prostate Cancer and Prostatic Diseases*, **15**, 106-110.

Shimbo, D., Grahame-Clarke, C., Miyake, Y., Rodriguez, C., Sciacca, R., Di Tullio, M., Boden-Albala, B., Sacco, R. and Homma, S. (2007). The association between endothelial dysfunction and cardiovascular outcomes in a population-based multi-ethnic cohort. *Atherosclerosis*, **192**, 197-203.

Shimizu, H., Ross, R.K., Bernstein, L., Yatani, R., Henderson, B.E. and Mack, T.M. (1991). Cancers of the prostate and breast among Japanese and white immigrants in Los Angeles County. *British Journal of Cancer*, **63**, 963-966.

Shinozaki, K., Hirayama, A., Nishio, Y., Yoshida, Y., Ohtani, T., Okamura, T., Masada, M., Kikkawa, R., Kodama, K. and Kashiwagi, A. (2001). Coronary endothelial dysfunction in the insulin-resistant state is linked to abnormal pteridine metabolism and vascular oxidative stress. *Journal of the American College of Cardiology*, **38**, 1821-1828.

Shoji, T., Emoto, M., Shinohara, K., Kakiya, R., Tsujimoto, Y., Kishimoto, H., Ishimura, E., Tabata, T. and Nishizawa, Y. (2001). Diabetes mellitus, aortic stiffness, and cardiovascular mortality in end-stage renal disease. *Journal of the American Society of Nephrology*, **12**, 2117-2124.

Siddiqui, S.A., Boorjian, S.A., Blute, M.L., Rangel, L.J., Bergstralh, E.J., Karnes, R.J. and Frank, I. (2011). Impact of adjuvant androgen deprivation therapy after radical prostatectomy on the survival of patients with pathological T3b prostate cancer. *BJU International*, **107**, 383-388.

Siervogel, R.M. (1983). Genetic and familial factors in essential hypertension and related traits. *American Journal of Physical Anthropology*, **26**, 37-63.

Simon, D., Charles, M.A., Nahoul, K., Orssaud, G., Kremski, J., Hully, V., Joubert, E., Papoz, L. and Eschwege, E. (1997). Association between plasma total testosterone and cardiovascular risk factors in healthy adult men: The Telecom Study. *The Journal of Clinical Endocrinology and Metabolism*, **82**, 682-685.

Sinha, R., Park, Y., Graubard, B.I., Leitzmann, M.F., Hollenbeck, A., Schatzkin, A. and Cross, A.J. (2009). Meat and meat related compounds and risk of prostate cancer in a large prospective cohort study in the United States. *American Journal of Epidemiology*, **170**, 1165-1177.

Sitia, S., Tomasoni, L., Atzeni, F., Ambrosio, G., Cordiano, C., Catapano, A., Tramontana, S., Perticone, F., Naccarato, P., Camici, P., Cortigiani, L., Bevilacqua, M., Milazzo, L., Cusi, D., Barlassina, C., Sarzi-Puttini, P. and Turiel, M. (2010). From endothelial dysfunction to atherosclerosis. *Autoimmunnity Reviews*, **9**, 830-834.

Smith, J.C., Bennett, S., Evans, L.M., Kynaston, H.G., Parmar, M., Mason, M.D., Cockcroft, J.R., Scanlon, M.F. and Davies, J.S. (2001). The effects of induced hypogonadism on arterial stiffness, body composition, and metabolic parameters in males with prostate cancer. *The Journal of Clinical Endocrinology and Metabolism*, **86**, 4261-4267.

Smith, M.R., Finkelstein, J.S., McGovern, F.J., Zeitman, A.L., Fallon, M.A., Schoenfeld, D.A. and Kantoff, P.W. (2002). Changes in body composition during androgen deprivation therapy for prostate cancer. *The Journal of Clinical Endocrinology and Metabolism*, **87**, 599-603.

Smith, M.R., Lee, H. and Nathan, D.M. (2006). Insulin sensitivity during combined androgen blockade for prostate cancer. *The Journal of Clinical Endocrinology and Metabolism*, **91**, 1305-1308.

Smith, M.R., Lee, H., Fallon, M.A. and Nathan, D.M. (2008a). Adipocytokines, obesity, and insulin resistance during combined androgen blockade for prostate cancer. *Urology*, **71**, 318-322.

Smith, M.R., Lee, H., McGovern, F., Fallon, M.A., Goode, M., Zeitman, A. and Finkelstein, J.S. (2008b). Metabolic changes during gonadotropin-releasing hormone agonist therapy for prostate cancer. *Cancer*, **112**, 2188-2194.

Smither, A.R., Guralnick, M.L., Davis, N.B. and See, W.A. (2007). Quantifying the natural history of post-radical prostatectomy incontinence using objective pad test. *BMC Urology*, **7**:2.

Solomon, H., Man, J.W. and Jackson, G. (2003). Erectile dysfunction and the cardiovascular patient: endothelial dysfunction is the common denominator. *Heart*, **89**, 251-254.

Solomon, T.P.J., Sistrum, S.N., Krishnan, R.K., Del Aguila, L.F., Marchetti, C.M., O'Carroll, S.M., O'Leary, V.B. and Kirwan, J.P. (2008). Exercise and diet enhance fat oxidation and reduce insulin resistance in older obese adults. *Journal of Applied Physiology*, **104**,1313-1319.

Soutar, A.K. and Naoumova, R.P. (2007). Mechanisms of disease: genetic causes of familial hypercholesterolemia. *Nature Clinical Practice. Cardiovascular Medicine*, **4**, 214-225.

Sriprasad, S., Feneley, M.R. and Thompson, P.M. (2009). History of prostate cancer treatment. *Surgical Oncology*, **18**, 185-191.

Steinberg, G, D., Carter, B.S., Beaty, T.H., Childs, B. and Walsh, P.C. (1990). Family history and the risk of prostate cancer. *Prostate*, **17**, 337-347.

Stempkowski, L. (2006). Hormonal therapy. In *Contemporary issues in prostate cancer. A nursing perspective. Second Edition* (edited by J.Held-Warmkessel), pp. 248-283. Sudbury, MA: Jones and Bartlett Publishers.

Stěpán, J.J., Lachman, M., Zvěrina, J., Pacovský, V. and Baylink, D.J. (1989). Castrated men exhibit bone loss: effect of calcitonin treatment on biochemical indices of bone remodelling. *The Journal of Clinical Endocrinology and Metabolism*, **69,** 523-527.

Sternfeld, B., Weltzien, E., Quesenberry, C.P., Castillo, A.L., Kwan, M., Slattery, M.L. and Caan, B.J. (2009). Physical activity and risk of recurrence and mortality in breast cancer survivors: findings from the LACE study. *Cancer Epidemiology, Biomarkers and Prevention*, **18**, 87-95.

Stevens, J., Cai, J., Pamuk, E.R., Williamson, D.F., Thun, M.J. and Wood, J.L. (1998). The effect of age on the association between body-mass index and mortality. *The New England Journal of Medicine*, **338**, 1-7.

Stewart, K.J., Bacher, A.C., Turner, K., Lim, J.G., Hees, P.S., Shapiro, E.P., Tayback, M. and Ouyang, P. (2005). Exercise and risk factors associated with metabolic syndrome in older adults. *American Journal of Preventive Medicine*, **28**, 9-18.

Stone, P., Hardy, J., Huddart, R., A'Hern, R. and Richards, M. (2000). Fatigue in patients with prostate cancer receiving hormone therapy. *European Journal of Cancer*, **36**, 1134-1141.

Storey, D.J., McLaren, D.B., Atkinson, M.A., Butcher, I., Frew, L.C., Smyth, J.F. and Sharpe, M. (2012). Clinically relevant fatigue in men with hormone-sensitive prostate cancer on long-term androgen deprivation therapy. *Annals of Oncology*, **23**, 1542-1549.

Strum, S.B., McDermed, J.E., Scholz, M.C., Johnson, H. and Tisman, G. (1997). Anaemia associated with androgen deprivation therapy in men with prostate cancer receiving combined hormone blockade. *British Journal of Urology*, **79**, 933-941.

Stuart, G.R., Holcroft, J., de Boer, J.G. and Glickman, B.W. (2000). Prostate mutations in rats induced by the suspected human carcinogen 2-amino-1-methyl-6-phenylimidazo[4,5-*b*] pyridine. *Cancer Research*, **60**, 266-268.

Studer, U.E., Wheln, P., Albrecht, W., Casselman, J., de Reijke, T., Hauri, D., Loidl, W., Isorna, S., Sundaram, S.K., Debois, M. and Collette, L. (2006). Immediate or deferred androgen deprivation for patients with prostate cancer not suitable for local treatment with curative intent: European Organisation for Research and Treatment of Cancer (EORTC) Trial 30891. *Journal of Clinical Oncology*, **24**, 1868-1876.

Suk, S.H., Sacco, R.L., Boden-Albala, B., Cheun, J.F., Pittman, J.G., Elkind, M.S. and Paik, M.C. (2003). Abdominal obesity and risk of ischemic stroke. The Northern Manhattan stroke study. *Stroke*, **34**, 1586-1592.

Sullivan, R., Peppercorn, J., Sikora, K., Zalcberg, J., Meropol, N.J., Amir, E., Khayat, D., Boyle, P., Autier, P., Tannock, I.F., Fojo, T., Siderov, J., Williamson, S., Camporesi, S., McVie, J.G., Purushotham, A.D., Naredi, P., Eggermont, A., Brennan, M.F., Steinberg, M.L., De Ridder, M., McCloskey, S.A., verellen, D., Roberts, T., Storme, G., Hicks, R.J., Ell, P.J., Hirsch, B.R., Carbone, D.P., Schulman, K.A., Catchpole, P., Taylor, D., Geissler, J., Brinker, N.G., Meltzer, D., Kerr, D. and Aapro, M. (2011). Delivering affordable cancer care in high-income countries. *The Lancet Oncology*, **12**, 933-980.

Suzuki, H., Kamiya, N., Imamoto, T., Kawamura, K., Yano, M., Takano, M., Utsumi, T., Naya, Y. and Ichikawa, T. (2008). Current topics and perspectives relating to hormone therapy for prostate cancer. *International Journal of Clinical Oncology*, **13**, 401-410.

Svartberg, J., von Mühlen, D., Schirmer, H., Barrett-Connor, E., Sundfjord, J and Jorde, R. (2004). Association of endogenous testosterone with blood pressure and left ventricular mass in men. The Tromsø study. *European Journal of Endocrinology*, **150**, 65-71.

Talcott, J.A., Rieker, P., Propert, K.J., Clark, J.A., Wishnow, K.I., Loughlin, K.R., Richie, J.P. and Kantoff, P.W. (1997). Patient-reported impotence and incontinence after nerve-sparing radical prostatectomy. *Journal of the National Cancer Institute*, **89**, 1117-1123.

Tambalis, K., Panagiotakos, D.B., Kavouras, S.A. and Sidossis, L.S. (2009). Responses of blood lipids to aerobic, resistance, and combined aerobic with resistance exercise training: A systematic review of current evidence. *Angiology*, **60**, 614-632.

Tammela, T. (2004). Endocrine treatment of prostate cancer. *Journal of Steroid Biochemistry and Molecular Biology*, **92**, 287-295.

Tanasescu, M., Leitzmann, M.F., Rimm, E.B., Willett, W.C., Stampfer, M.J. and Hu, F.B. (2002). Exercise type and intensity in relation to coronary heart disease in men. *The Journal of the American Medical Association*, **288**, 1994-2000.

Taylor, R. (1990). Interpretation of the correlation coefficient: A basic review. *Journal of Diagnostic Medical Sonography*, **1**, 35-39.

Taylor, A.E., Ebrahim, S., Ben-Shlomo, Y., Martin, R.M., Whincup, P.H., Yarnell, J.W., Wannamethee, S.G. and Lawlor, D.A. (2010). Comparison of the associations of body mass index and measures of central adiposity and fat mass with coronary heart disease, diabetes and all-cause mortality: a study using data from 4 UK cohorts. *American Journal of Clinical Nutrition*, **91**, 547-556.

Thijssen, D.H.J., Maiorana, A.J., O'Driscoll, G., Cable, N.T., Hopman, N.T.E. and Green, D.J. (2010). Impact of inactivity and exercise on the vasculature in humans. *European Journal of Applied Physiology*, **108**, 845-875.

Thijssen, D.H.J., Black, M.A., Pyke., K.E., Padilla., J., Atkinson, G., Harris, R.A., Parker, B., Widlansky, M.E., Tschakovsky, M.E. and Green, D.J. (2011). Assessment of flow-mediated dilation in humans: a methodological and physiological guideline. *American Journal of Physiology - Heart and Circulatory Physiology*, **300**, H2-H12.

Thompson, I.M., Ernst, J.J., Gangai, M.P. and Spence, C.R. (1984). Adenocarcinoma of the prostate: results of routine urological screening. *Journal of Urology*, **132**, 690-692.

Thompson, I.M. (2001). Flare associated with LHRH-agonist therapy. *Reviews in Urology*, **3**, S10-S14.

Thompson, C.A., Shanafelt, T.D. and Loprinzi, C.L (2003). Andropause: Symptom management for prostate cancer patients treated with hormonal ablation. *The Oncologist*, **8**, 474-487.

Thompson, I.M., Pauler, D.K., Goodman, P.J., Tangen, C.M., Lucia, M.S., Parnes, H.L., Minasian, L.M., Ford, L.G., Lippman, S.G., Crawford, E.D., Crowley, J.J. and Coltman, C.A. (2004). Prevalence of prostate cancer among men with a prostate-specific antigen level ≤ 4.0 ng per millilitre. *The New England Journal of Medicine*, **350**, 2239-2246.

Thompson, D., Karpe, F., Lafontan, M. and Frayn, K. (2012). Physical activity and exercise in the regulation of human adipose tissue physiology. *Physiological Reviews*, **92**, 157-191.

Thompson, F.E. and Subar, A.F. (2013). Dietary assessment methodology. In *Nutrition in the prevention and treatment of disease. Third Edition* (edited by A.M. Coulston, C.J. Boushey and M.G. Ferruzzi), pp. 5-46. London: Elsevier.

Timmons, J.A., Knudsen, S., Rankinen, T., Koch, L.G., Sarzynski, M., Jensen, T., Keller, P., Scheele, C., Vollaard, N.B.J., Nielsen, S., Åkerström, T., MacDougald, O.A., Jansson, E., Greenhaff, P.L., Tarnopolsky, M.A., van Loon, L.J.C., Pedersen, B.K., Sundberg, C.J., Wahlestedt, C., Britton, S.L. and Bouchard, C. (2010). Using molecular classification to predict gains in maximal aerobic capacity following endurance exercise training in humans. *Journal of Applied Physiology*, **108**, 1487-1496.

Tinken, T.M., Thijssen, D.H.J., Black, M.A., Cable, N.T. and Green, D.J. (2008). Time course of change in vasodilator function and capacity in

response to exercise training in humans. *Journal of Physiology*, **586**, 5003-5012.

Tolis, G., Ackman, D., Stellos, A., Mehta, A., Labrie, F., Fazekas, A.T.A., Comaru-Schally, A.M. and Schally, A.V. (1982). Tumor growth inhibition in patients with prostatic carcinoma treated with luteinizing hormone-releasing hormone agonists. *Proceedings of the National Academy of Science*, **79**, 1658-1662.

Tomlinson, S.S. and Mangione, K.K. (2005). Potential adverse effects of statins on muscle. *Physical Therapy*, **85**, 459-465.

Törnblom, M., Norming, U., Adolfsson, J., Becker, C., Abrahamsson, P-A., Lilja, H. and Gustafsson, O. (1999). Diagnostic value of percent free prostate-specific antigen: Retrospective analysis of a population-based screening study with emphasis on men with PSA levels less than 3.0 ng/ml. *Urology*, **53**, 945-950.

Tortora, G.J. and Derrickson, B. (2006). *Principles of anatomy and physiology, 11th Edition*. New Jersey, USA: Wiley Publishers.

Traish, A.M., Saad, F. and Guay, A. (2009a). The dark side of testosterone deficiency: II. Type 2 diabetes and insulin resistance. *Journal of Andrology*, **30**, 23-32.

Traish, A.M., Saad, F., Feeley, R.J. and Guay, A. (2009b). The dark side of testosterone deficiency: III. Cardiovascular disease. *Journal of Andrology*, **30**, 477-494.

Trichopoulou, A., Costacou, T., Bamia, C. and Trichopoulou, D. (2003). Adherence to a Mediterranean diet and survival in a Greek population. *The New England Journal of Medicine*, **26**, 2599-2608.

Tsai, E.C., Boyko, E.J., Leonetti, D.L. and Fujimoto, W.Y. (2000). Low serum testosterone level as a predictor of increased visceral fat in Japanese-American men. *International Journal of Obesity*, **24**, 485-491.

Tuttle, J.L., Nachreiner, R.D., Bhuller, A.S., Condict, K.W., Connors, B.A., Herring, B.P., Dalsing, M.C. and Unthank, J.L. (2001). Shear level influences resistance artery remodelling: wall dimensions, cell density, and eNOS expression. *American Journal of Physiology- Heart and Circulatory Physiology*, **281**, H1380-H1389.

Tymchuk, C.N., Tessler, S.B., Aronson, W.J. and Barnard, R.J. (1998). Effects of diet and exercise on insulin, sex-hormone-binding globulin, and prostate-specific antigen. *Nutrition and Cancer*, **31**, 127-131.

Tymchuk, C.N., Hartiala, J., Patel, P.I., Mehrabian, M. and Allayee, H. (2006). Nonconventional genetic risk factors for cardiovascular disease. *Current Atherosclerosis Reports*, **8**, 184-192.

Uehata, A., Lieberman, E.H., Gerhard, M.D., Anderson, T.J., Ganz, P., Polak, J.F., Creager, M.A. and Yeung, A.C. (1997). Noninvasive assessment of endothelium-dependent flow-mediated dilation of the brachial artery. *Vascular Medicine*, **2**, 87-92.

Ukoli, F.A., Taher, K., Egbagbe, E., Lomotey, M., Oguike, T., Akumabor, P., Osime, U. and Beech, D. (2009). Association of self reported consumption of cooked meat, fish, seafood and eggs with prostate cancer risk among Nigerians. *Infectious Agents and Cancer*, **4**, S6.

Ulloa, E.W., Salup, R., Patterson, S.G. and Jacobsen, P.B. (2009). Relationship between hot flashes and distress in men receiving androgen deprivation therapy for prostate cancer. *Psycho-Oncology*, **18**, 598-605.

Underwood, J.C.E. (2007). Disorders of the metabolism and homeostasis. In *General and systematic pathology, Fourth Edition* (edited by J.C.E. Underwood), pp. 125-148. London: Churchill Livingstone.

Vaitkevicius, P.V., Fleg, J.L., Engel, J.H., O'Connor, F.C., Wright, J.G., Lakatta, L.E., Yin, F.C.P. and Lakatta, E.G. (1993). Effects of age and aerobic capacity on arterial stiffness in healthy adults. *Circulation*, **88**, 1456-1462.

van den Bergh, R.C.N., Vasarainen, H., van der Poel, H.G., Vis-Maters, J.J., Rietbergen, J.B., Pickles, T., Cornel, E.B., Valdagni, R., Jaspars, J.J., van der Hoeven, J., Staerman, F., Oomens, E.H., Ranniko, A., Roemeling, S., Steyerberg, E.W., Roobol, M.J., Schröder, F.H. and Bangma, C.H. (2010). Short-term outcomes of the prospective multicentre 'Prostate Cancer International: Active Surveillance' study. *BJU International*, **105**, 956-962.

Vanhees, L., Lefevre, J., Philippaerts, R., Martens, M., Huygens, W., Troosters, T. and Beunen, G. (2005). How to assess physical activity? How to assess physical fitness? *European Journal of Cardiovascular Prevention and Rehabilitation*, **12**, 102-114.

Van Hemelrijck, M., Garmo, H., Holmberg, L., Ingelsson, E., Bratt, O., Bill-Axelson, A., Lambe, M., Stattin, P. and Adolfsson, L. (2010). Absolute and relative risk of cardiovascular disease in men with prostate cancer: results from the Population-Based PCBaSe Sweden. *Journal of Clinical Oncology*, **20**, 3448-3456.

Vanhoutte, P.M. (1996). Endothelial dysfunction in hypertension. *Journal of Hypertension*, **14**, S83-S93.

van Londen, G.J., Levy, M.E., Perera, S., Nelson, J.B. and Greenspan, S.L. (2008). Body composition changes during androgen deprivation therapy for prostate cancer: A 2-year prospective study. *Critical Reviews in Oncology/Hematology*, **68**, 172-177.

Vaziri, N.D. (2008). Causal link between oxidative stress, inflammation, and hypertension. *Iranian Journal of Kidney Diseases*, **2**, 1-10.

Vermeulen, A., Verdonck, L. and Kaufman, J.M. (1999). A critical evaluation of simple methods for the estimation of free testosterone in serum. *The Journal of Clinical Endocrinology and Metabolism*, **84**, 3666-3672.

Vermeulen, A. (2000). Andropause. *Maturitas*, **34**, 5-15.

Vermeulen, A., Kaufman, J.M., Goemaere, S and Van Pottelberg, I. (2002). Estradiol in elderly men. *Aging male*, **5**, 98-102.

Virally, M., Blicklé, J.F., Girard, J., Halimi, S., Simon, D. and Guillausseau, P.J. (2007). Type 2 diabetes mellitus: epidemiology, pathophysiology, unmet needs and therapeutical perspectives. *Diabetes and Metabolism*, **33**, 231-244.

Vita, J.A. and Keaney, J.F. (2002). Endothelial function. A barometer for cardiovascular risk? *Circulation*, **106**, 640-642.

Vladimirova-Kitova, L., Terzieva, D. and Marinov, B. (2009) Intima-media thickness and flow-mediated vasodilation in asymptomatic subjects with newly detected severe hypercholesterolemia. *Echocardiography*, **26**, 1060-1068.

Vogel, R.A., Corretti, M.C. and Plotnick, G.D. (2000). A comparison of brachial artery flow-mediated vasodilation using upper and lower arm arterial occlusion in subjects with and without coronary risk factors. *Clinical Cardiology*, **23**, 571-575.

Völgyi, E., Tylavsky, F.A., Lyytikäinen, A., Suominen, H., Alén, M. and Cheng, S. (2008). Assessing body composition with DXA and bioimpedance: Effects of obesity, physical activity, and age. *Obesity*, **16**, 700-705.

Volpe, H. and Watkins, S.V. (2006). Radiation therapy. In *Contemporary issues in prostate cancer. A nursing perspective. Second Edition* (edited by J.Held-Warmkessel), pp. 202-228. Sudbury, MA: Jones and Bartlett Publishers.

Waldman, A.R. (2006). Screening and early detection. In *Contemporary issues in prostate cancer. A nursing perspective. Second Edition* (edited by J.Held-Warmkessel), pp. 44-59. Sudbury, MA: Jones and Bartlett Publishers.

Walker, L.M. and Robinson, J.W. (2010). The unique needs of couples experiencing androgen deprivation therapy for prostate cancer. *Journal of Sex and Marital Therapy*, **36**, 154-165

Wallace, I.R., McKinley, M.C., Bell, P.M. and Hunter, S.J. (2013). Sex hormone binding globulin and insulin resistance. *Clinical Endocrinology*, **78**, 321-329.

Wallner, K.E. (2000). Prostate Brachytherapy. In *Radiotherapy of Prostate Cancer* (edited by C. Greco and M.J. Zelefsky). pp.267-278. Amsterdam: Harwood Academic Publishers.

Wang, Y-X. (2007). Do measures of vascular compliance correlate with endothelial function? *Current Diabetes Reports*, **7**, 265-268.

Wang, C., Nieschlag, E., Swerdloff, R., Behre, H.M., Hellstrom, W.J., Gooren, L.J., Kaufman, J.M., Legros, J-J., Lunenfeld, B., Morales, A., Morley, J.E., Schulman, C., Thompson, I.M., Weidner, W. and Wu, F.C.W. (2008). Investigation, treatment and monitoring of late-onset hypogonadism in males. *European Journal of Endocrinology*, **159**, 507-514.

Warburton, D.E.R., Nicol, C.W. and Bredin, S.S.D. (2006). Health benefits of physical activity: the evidence. *Canadian Medical Association Journal*, **174**, 801-809.

Ward, K.K., Shah, N.R., Saenz, C.C., McHale, M.T., Alvarez, E.A. and Plaxe, S.C. (2012). Cardiovascular disease is the leading cause of death among endometrial cancer patients. *Gynecologic Oncology*, **126**, 176-179.

Weaver, K.E., Foraker, R.E., Alfano, C.M., Rowland, J.H., Arora, N.K., Bellizzi, K.M., Hamilton, A.S., Oakley-Girvan, I., Keel, G. and Aziz, N.M (2013). Cardiovascular risk factors among long-term survivors of breast, prostate, colorectal, and gynecologic cancers: a gap in survivorship care? *Journal of Cancer Survivorship*, **7**, 253-261.

Webb, C.M., McNeill, J.G., Hayward, C.S., de Zeigler, D. and Collins, P. (1999). Effects of testosterone on coronary vasomotor regulation in men with coronary heart disease. *Circulation*, **100**, 1690-1696.

Weir, J.P. (2005). Quantifying test-retest reliability using the intraclass correlation coefficient and the SEM. *Journal of Strength and Conditioning Research*, **19**, 231-240.

Weiss, J.M., Huang, W.Y., Rinaldi, S., Fears, T.R., Chatterjee, N., Hsing, A.W., Crawford, E.D., Andriole, G.L., Kaaks, R. and Hayes, R.B. (2008). Endogenous sex hormones and the risk of prostate cancer: A prospective study. *International Journal of Cancer*, **122**, 2345-2350.

Welsch, M.A., Allen, J.D. and Geaghan, J.P. (2002). Stability and reproducibility of brachial artery flow-mediated dilation. *Medicine and Science in Sports and Exercise*, **34**, 960-965.

Werns, S. W., Walton, J.A., Hsia, H.H., Nabel, E.G., Sanz, M.L. and Pitt, B. (1989). Evidence of endothelial dysfunction in angiographically normal coronary arteries of patients with coronary artery disease. *Circulation*, **79**, 287-291.

Whelton, S.P., Chin, A., Xin, X. and He, J. (2002). Effect of aerobic exercise on blood pressure: a meta-analysis of randomised, controlled trials. *Annals of Internal Medicine*, **136**, 493-503.

Wilkinson, I.B., MacCallum, H., Rooijmans, D.F., Murray, G.D., Cockcroft, J.R., McKnight, J.A. and Webb, D.J. (2000). Increased augmentation index and systolic stress in type 1 diabetes mellitus. *QJM*, **93**, 441-448.

Wilkinson, I.B., Prasad, K., Hall, I.R., Thomas, A., MacCallum, H., Webb, D.J., Frenneaux, M.P. and Cockcroft, J.R. (2002). Increased central pulse pressure and augmentation index in subjects with hypercholesterolemia. *Journal of the American College of Cardiology*, **39**, 1005-1011.

Williams, C.D., Whitley, B.M., Hoyo, C., Grant, D.J., Schwartz, G.G., Presti, J.C., Iraggi, J.D., Newman, K.A., Gerber, L., Taylor, L.A., McKeever, M.G. and Freedland, S.J. (2012). Dietary calcium and risk for prostate cancer: A case-control study among US veterans. *Preventing Chronic Disease*, **9**, 1-9.

Wilt, T.J., Nair, B., MacDonald, R. and Rutks, I. (2001). Early versus deferred androgen suppression in the treatment of advanced prostatic cancer. *Cochrane Database of Systematic Reviews*, **1**, CD003506.

Winnick, J.J., Sherman, M., Habash, D.L., Stout, M.B., Failla, M.L., Belury, M.A. and Schuster, D.P. (2008). Short-term aerobic exercise training in obese humans with type 2 diabetes mellitus improves whole-body insulin sensitivity through gains in peripheral, not hepatic insulin sensitivity. *Journal of Clinical Endocrinology and Metabolism*, **93**, 771-778.

Winter, E.M. and Fowler, N. (2009). Exercise defined and quantified according to the Système Internatinal d'Unités. *Journal of Sports Science*, **27**, 447-460.

Wirth, M.P., Weissbach, L., Marx, F.J., Heckl, W., Jellinghaus, W., Reidmiller, H., Noack, B., Hinke, A. and Froehner, M. (2004). Prospective randomized trial comparing flutamide as adjuvant treatment versus observation after radical prostatectomy for locally advanced, lymph node-negative prostate cancer. *European Urology*, **45**, 267-270.

Wolin, K.Y., Patel, A.V., Campbell, P.T., Jacobs, E.J., McCullough, M.L., Colditz, G.A. and Gapstur, S.M. (2010). Change in physical activity and colon cancer incidence and mortality. *Cancer Epidemiology, Biomarkers and Prevention*, **19**, 3000-3004.

World Health Organization, International Society of Hypertension Writing Group. (2003). 2003 World Health Organization/International Society of Hypertension statement on management of hypertension. *Journal of Hypertension*, **21**, 1983-1992.

World Health Organisation. (2009). Global health risks: mortality and burden of disease attributable to selected major risk factors. *World Health Report*, May/13, http://www.who.int/healthinfo/global_burden_disease/global_health_risks/en/

World Health Organization. (2011). Global status report on noncommunicable diseases 2010. Aug/13. http://www.who.int/nmh/publications/ncd_report2010/en/

World Health Organization (2013). Cardiovascular disease. Fact sheet No 317. Aug/13. http://www.who.int/mediacentre/factsheets/fs317/en/index.html

World Heart Federation (2013). Cardiovascular disease risk factors. Family history and cardiovascular disease. Aug/13. http://www.world-heart-federation.org/cardiovascular-health/cardiovascular-disease-risk-factors/family-history/

Yaron, M., Greenman, Y., Rosenfeld, J.B., Izkhakov, E., Limor, R., Osher, E., Shenkerman, G., Tordjman, K. and Stern, N. (2009). Effect of testosterone replacement therapy on arterial stiffness in older hypogonadal men. *European Journal of Endocrinology*, **160**, 839-846.

Yeboah, J., Folsom, A.R., Burke, G.L., Johnson, C., Polak, J.F., Post, W., Lima, J.A., Crouse, J.R. and Herrington, D.M. (2009). Predictive value of brachial flow-mediated dilation for incident cardiovascular events in a population-based study. The multi-ethnic study of atherosclerosis. *Circulation*, **120**, 502-509.

Yeh, E.T.H. and Bickford, C.L (2009). Cardiovascular complications of cancer therapy. Incidence, pathogenesis, diagnosis, and management. *Journal of the American College of Cardiology*, **53**, 2231-2247.

Yellen, S.B., Cella, D.F., Webster, K., Blendowski, C. and Kaplan, E. (1997). Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. *Journal of Pain and Symptoms Management*, **13**, 63-74.

Yialamas, M.A., Dwyer, A.A., Hanley, E., Lee, H., Pitteloud, N. and Hayes, F.J. (2007). Acute sex steroid withdrawal reduces insulin sensitivity in healthy men with idiopathic hypogonadotropic hypogonadism. *The Journal of Clinical Endocrinology and Metabolism*, **92**, 4254-4259.

Yilmaz, M.I., Sonmez, A., Qureshi, A.R., Saglam, M., Stenvinkel, P., Yaman, H., Eyileten, T., Caglar, K., Oguz, Y., Taslipinar, A., Vural, A., Gok, M., Unal, H.U., Yenicesu, M. and Carrero, J.J. (2011). Endogenous testosterone, endothelial dysfunction and cardiovascular events in men with nondialysis chronic kidney disease. *Clinical Journal of the American Society of Nephrology*, **6**, 1617-1625.

Yu, C., Chen, Y., Cline, G.W., Zhang, D., Zong, H., Wang, Y., Bergeron, R., Kim, J.K., cushman, S.W., Cooney, G.J., Atcheson, B., White, M.F., Kraegen, E.W. and Shulman, G.I. (2002). Mechanism by which fatty acids inhibit insulin activation of insulin receptor substrate-1 (IRS-1)- associated phosphatidylinositol 3-kinase activity in muscle. *The Journal of Biological Chemistry*, **277**, 50230-50236.

Yusuf, S., Hawken, S., Ounpuu, S., Dans, T., Avezum, A., Lanas, F., McQueen, M., Budaj, A., Pais, P., Varigos, J. and Lisheng, L. (2004). Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *The Lancet*, **364**, 937-952.

Yusuf, S.W., Razeghi, P. and Yeh, E.T. (2008). The diagnosis and management of cardiovascular disease in cancer patients. *Current Problems in Cardiology*, **33**, 163-196.

Zagars, G.K., Johnson, D.E., Von Eschenbach, A.C. and Hussey, D.H. (1988). Adjuvant estrogen following radiation therapy for stage C adenocarcinoma of the prostate- Long term results of a prospective randomized study. *International Journal of Radiation, Oncology, Biology, Physics*, **14**, 1085-1091.

Zamboni, M., Mazzali, G., Fantin, F., Rossi, A. and Di Francesco, V. (2008). Sarcopenic obesity: a new category of obesity in the elderly. *Nutrition, Metabolism and Cardiovascular Diseases*, **18**, 388-395.

Zgliczynski, S., Ossowski, M., Slowinska-Srzednicka, J., Brzezinska, A., Zgliczynski, W., Soszynski, P., Chotkowska, E., Srzednicki, M. and Sadowski,

Z. (1996). Effect of testosterone replacement therapy on lipids and lipoproteins in hypogonadal and elderly men. *Atherosclerosis*, **121**, 35-43.

Zieman, S.J., Melenovsky, V. and Kass, D.A. (2005). Mechanisms, pathophysiology, and therapy of arterial stiffness. *Arteriosclerosis, Thrombosis and Vascular Biology*, **25**, 932-943.

Zierath, J.R. (2002). Invited Review: Exercise training-induced changes in insulin signalling in skeletal muscle. *Journal of Applied Physiology*, **93**, 773-781.

Zitzmann, M., Brune, M. and Nieschlag, E. (2002). Vascular reactivity in hypogonadal men is reduced by androgen substitution. *The Journal of Clinical Endocrinology and Metabolism*, **87**, 5030-5037.

Zitzmann, M. and Nieschlag, E. (2007). Androgen receptor gene CAG repeat length and body mass index modulate the safety of long-term intramuscular testosterone undecanoate therapy in hypogonadal men. *The Journal of Clinical Endocrinology and Metabolism*, **92**, 3844-3853.

Zöller, B., Ji, J., Sundquist, J. and Sundquist, K. (2012). Risk of coronary heart disease in patients with cancer: A nationwide follow-up study from Sweden. *European Journal of Cancer*, **48**, 121-128.

Zurio, F., Larson, K., Bogardus, C. and Ravussin, E. (1990). Skeletal muscle metabolism is a major determinant of resting energy expenditure. *Journal of Clinical Investigation*, **86**, 1423-1427.

APPENDIX 1

Faculty of Health and Wellbeing Research Ethics Committee
Report Form

Principal Investigator: Stephen Gilbert

Title: Endothelial function and cardiovascular health in healthy elderly men.

Checklist:

Application form	✓
Informed consent form	✓
Participant information sheet	✓
Risk assessment form	✓
Pre-screening form	✓
Pre-screening form (under 18)	n/a
Collaboration evidence/support	n/a
CRB Disclosure certificate	✓

Recommendation:

Acceptable:	
Not acceptable, see comments:	
Acceptable, but see comments:	✓

Comments:

Please provide a written response to the reviewer's comments (attached).

Signature : ..... Date: N/a Jan 2010

Professor Edward Winter, Chair
Faculty of Health and Wellbeing Research Ethics Committee

Note: *Approval applies until the anticipated date of completion unless there are changes to the procedures, in which case another application should be made.*

Sheffield Hallam University

SHARPENS YOUR THINKING

Direct dial +44 (0) 114 225 5679

20 August 2010

fao Stephen Gilbert

Dear Stephen

Title of research: Endothelial function and cardiovascular health in healthy elderly men.

Thank you for informing me of the amendments to your study.

I am pleased to inform you that this is acceptable.

Yours sincerely

D.M. Binney

David Binney
Chair, Sport & Exercise Research Ethics Review Group

cc Edward Winter

From the Office of the Pro Vice-Chancellor
Sheffield Hallam University Collegiate Crescent Campus Sheffield S10 2BP UK
Telephone +44 (0)114 225 4384 Fax +44 (0)114 225 5775
E-mail r.billingsley@shu.ac.uk www.shu.ac.uk
Pro Vice-Chancellor, Health and Wellbeing **Professor Rhiannon Billingsley** *BA MA Econ CQSW*

APPENDIX 2

NHS

National Research Ethics Service

Sheffield Research Ethics Committee
Yorkshire and the Humber REC Office
First Floor, Millside
Mill Pond Lane
Meanwood
Leeds
LS6 4RA

Tel: 0113 3050160

16 December 2010

Mr. Derek Rosario
Senior Clinical Lecturer, Honourary Consultant in Urology
STH Teaching Hospitals
Academic Urology Unit
K Floor, Royal Hallamshire Hospital
Glossop Road
Sheffield
S10 2JF

Dear Mr. Rosario

Study title:	**The feasibility of a combined programme of exercise and dietary advice in the treatment of prostate cancer patients.**
REC reference:	**07/Q2305/3**
Amendment number:	
Amendment date:	**26 November 2010**

The above amendment was reviewed at the meeting of the Sub-Committee held on 16 December 2010 by the Sub-Committee in correspondence.

Ethical opinion

There were no ethical issues.

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Participant Information Sheet	6	19 November 2010
Notice of Substantial Amendment (non-CTIMPs)		26 November 2010
Covering Letter		26 November 2010

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

07/Q2305/3:	Please quote this number on all correspondence

Yours sincerely

Mr John Robinson
Committee Co-ordinator

E-mail: john.robinson@leedspft.nhs.uk

Enclosures: *List of names and professions of members who took part in the review*

Copy to: *Dr. John Saxton, Sheffield Hallam University*
Ms Marica Brozicevich, Sheffield Teaching Hospitals NHS Foundation Trust

APPENDIX 3

Sheffield Teaching Hospitals NHS
NHS Foundation Trust

Sheffield Hallam University
SHARPENS YOUR THINKING

Participants needed...

Participants needed for a research study undertaken by Sheffield Hallam University in collaboration with Sheffield University and Sheffield Teaching Hospitals.

Men aged 60 years or older are needed to form part of a control group, whose results will be compared to patients with prostate cancer.

The study aims to investigate cardiovascular health in men with prostate cancer on androgen deprivation therapy. This study hopes to advance knowledge on the cardiovascular effects of treatment options for prostate cancer patients.

Men willing and eligible to take part will be required to attend 1 testing session lasting approximately 90 minutes. During this session your vascular function will be assessed and a venous blood sample will be taken.

Testing will take place at the Centre for Sport and Exercise Science, Sheffield Hallam University, Collegiate Campus, Ecclesall Road, Sheffield.

If you are interested in volunteering to take part in this project, or would like any further information, please contact Stephen Gilbert, study researcher.

Telephone: 0114 225 5413

Email: s.gilbert@shu.ac.uk

APPENDIX 4

Sheffield Hallam University

Participant Information Sheet- Controls

Version 1: 8th June 2010

Cardiovascular health in prostate cancer patients on androgen deprivation therapy

Q: What is the main purpose of this study?

A: Men with prostate cancer often have treatment to reduce the level of testosterone (male hormones) in their blood (Androgen Deprivation Therapy). Some men who are receiving this treatment experience side effects such as deterioration of cardiovascular health. The aim of this study is to see whether men receiving androgen deprivation therapy experience decreased arterial function which might be associated with increased risk of cardiovascular events.

Q: Why have I been approached about this study?

A: To investigate the effects prostate cancer and its drugs on cardiovascular health a group of participants without these conditions are required to act as controls. You have been approached to be a member of this control group.

Q: What does being in the 'control group' mean?

A: Being in the 'control group' simply means your results will be compared against those of patients who have prostate cancer and are on androgen deprivation therapy. This will allow us to assess differences in results brought about by cancer or by the type of treatment.

Q: What is required of me if I decide to take part in this study?

A: All participants who are interested in entering the study will be invited to meet a researcher from The Centre for Sport and Exercise Science at Sheffield Hallam University. You will have the opportunity to go through this information sheet again and ask any questions you might have about the study. You will be given a consent form to take home and complete. This is so you can take time to decide whether or not you want to take part in the study.

The assessment:

If you decide to take part you will be asked to attend the assessment session which will be held at The Centre for Sport and Exercise Science at Sheffield Hallam University, Collegiate Crescent, Sheffield. You should bring your completed consent form with you. The researcher will take your medical history and your vascular function will be examined. You will be asked to come to this session in the morning, following an overnight fast and having avoided products containing vitamin C, tobacco and caffeine for 6 hours beforehand. Assessment of vascular function requires a pneumatic blood pressure cuff to be inflated around the forearm for 5 minutes and then released. For 1 minute before cuff inflation, and 5 minutes after cuff deflation, an ultrasound probe will be placed on the skin just above the elbow to image the artery inside the upper arm. Inflation of the

cuff around the arm can result in a 'pins and needles' sensation in the fingers, but once the cuff is released this feeling quickly goes away. After 15 minutes of rest a second scan will be performed for 7 minutes. This time the cuff will not be used, but after the first minute of scanning you will be asked to take 400 µl of glyceryl trinitrate (GTN). GTN is taken via a spray under the tongue and may cause slight feelings of nausea or light headedness, but these feelings should go away within 10 minutes. Throughout the vascular function tests blood pressure will be taken from an additional cuff around the opposite arm.
After the vascular function testing a venous blood sample will be drawn from your arm and a finger tip sample will also be taken for analysis of biomarkers of cardiovascular health. Additionally your body composition, body weight and height will also all be assessed.

Q: How long will the study last?
A: The study will only require the one assessment visit. This assessment will take approximately 90 minutes to complete.

Q: What are the possible benefits of taking part in this study?
A: We cannot promise that the study will help you, but the information which we obtain might help improve the rehabilitation of prostate cancer patients.

Q: Are there any side-effects of taking part?

A: Taking glyceryl trinitrate during the assessment visit can make some people feel light headed or nauseous for around 10 minutes afterwards. However, we will ensure you are lying down when you take this and stay lying down until the symptoms have subsided.
Blood sampling can also make some people feel light headed, but you will remain lying down until this process has been completed. Venous blood sampling can result in bruising in some people but this will be minimised through maintaining pressure on the site after sampling.

Q: What are the possible disadvantages and risks of taking part?

A: The potential for risks to occur will be minimised.

In the event that something does go wrong during the research study, there are no special compensation arrangements. If you are harmed then you would have access to the normal university complaints mechanism (see below).
If you are harmed and this is due to someone's negligence then you might have grounds for legal action for compensation, but you could have to pay your legal costs.

Q: Do I have to take part?
A: It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form.

Q: What if I do not wish to take part?
A: Your participation is entirely voluntary. If you decide not to take part, this will not affect the standard of care you receive from any other health professional.

Q: What if I change my mind during the study?
A: You are free to withdraw from the study at any time without giving a reason.

Q: What will happen to the information from the study?
A: The overall conclusions of the study will be available to you, however it will not be possible to produce an individualised report of your results.

Q: Will my taking part in this study be kept confidential?
A: The confidentiality of our participants and the data which this study will generate is of utmost importance. All data from this study will be annonymised. In brief, you will be allocated a number during the study. We will need to obtain your permission to allow the research team access to your information collected during the study. This is one of the clauses, which you will sign in agreement on the official consent form.
Our procedures for handling, processing and storage of and destruction of data are compliant with the Data Protection Act 1998.

Q: Who is organising and funding the research?
A: The research is organised and sponsored by The Centre for Sport and Exercise Science, Sheffield Hallam University in collaboration with the University of Sheffield Medical School and Sheffield Teaching Hospitals NHS Foundation Trust.

Q: Who has reviewed this study?
A: The Sheffield Hallam University Research Ethics Committee has reviewed this study.

Q: What if I have further questions?
A: If you have any further questions with regards to this study you may phone:-
Name: Professor Edward Winter (Primary investigator) Tel: 0114 225 4333
Name: Stephen Gilbert (Project co-ordinator) Tel: 0114 225 5413

Q: What if I wish to complain about the way this study has been conducted?
A: If you have any cause to complain about any aspect of the way in which you have been approached or treated during the course of this study, you will be able to contact the normal University complaints procedure
Liz Winders (University Secretary and Registrar) Tel: 0114 225 2051
You can also complain to any individual of the research team
Name: Professor. Edward Winter (Primary investigator) Tel: 0114 225 4333
Name: Stephen Gilbert (Project co-ordinator) Tel: 0114 225 5413

Thank you for taking the time to consider participating in this study
Mr Stephen Gilbert (Project co-ordinator)

Telephone number: 0114 225 5413
Email: s.gilbert@shu.ac.uk

APPENDIX 5

Sheffield Hallam University

PARTICIPANT SCREENING QUESTIONNAIRE

Cardiovascular health in prostate cancer patients on androgen deprivation therapy

Please answer each of the following questions

Name:

_____

Address:_____

_____ Postcode: _____

Telephone:_____ Email:_____

GP: _____ Practice: _____

Date of Birth:_____

Are you currently taking any medication? Yes ☐ No ☐

If yes, please list your medication and dosage in the table below.

Medication name	**Dose**	**Frequency, e.g. times per day/wk/month**	**Duration of medication, e.g. *'initiated 6 months ago'***

Have you ever had?	Y	N	*Have any immediate family had?*	Y	N	*Have you recently had?*	Y	N
High blood pressure	☐	☐	Heart attacks	☐	☐	Chest pain/ discomfort	☐	☐
Any heart trouble	☐	☐	High blood pressure	☐	☐	Shortness of breath	☐	☐
Arterial disease	☐	☐	High Cholesterol	☐	☐	Heart palpitations	☐	☐
Lung disease	☐	☐	Stroke	☐	☐	Dizzy spells	☐	☐
Asthma	☐	☐	Diabetes	☐	☐	Frequent headaches	☐	☐
Diabetes	☐	☐	Early death	☐	☐	Frequent colds	☐	☐
Epilepsy	☐	☐	Other family illness	☐	☐	Back pain	☐	☐
Arthritis	☐	☐				Orthopaedic problems	☐	☐

If you answered **yes** to any of the above, please give brief details _____

_____

Do you currently have any form of muscle or joint injury? Yes ☐ No ☐

If **yes**, please give details _____

_____

Have you ever had an adverse reaction to nitrates? Yes ☐ No ☐

As far as you are aware, is there anything that might prevent you from successfully completing the assessments outlined to you? Yes ☐ No ☐

_____

If blood is being taken please also answer the following questions in the box.

	Yes	No
Are you currently suffering from any known infection or illness?	☐	☐
Have you had jaundice within the previous year?	☐	☐
Have you ever had any form of hepatitis?	☐	☐
Are you HIV antibody positive?	☐	☐
Have you had unprotected sexual intercourse with any person from an HIV high-risk population?	☐	☐
Have you ever been involved in intravenous drug use?	☐	☐
Are you hemophiliac?	☐	☐

3. Do you currently engage in any physical activity?

If yes, what type? _____

On average.. How often? _____ times /week How long? _____ time/ session

4. a. Are you currently a smoker? Yes ☐ No ☐

b. If yes, how many do you smoke? ..... per day

c. If no, are you a previous smoker? Yes ☐ No ☐

d. How long is it since you stopped? ..... years

5. a. Do you drink alcohol? Yes / No
b. If yes, do you usually have?

An occasional drink ☐ A drink everyday ☐ More than one drink a day ☐

As far as I am aware the information I have given is accurate.

Print name: ..... **Date:** ...../...../.....

Signature: .....

APPENDIX 6

Sheffield Hallam University

PARTICIPANT CONSENT FORM

Version 1: 8th June 2010

Cardiovascular health in prostate cancer patients on androgen deprivation therapy.

Participant Identification Number for this study:

Investigators: Mr. Derek Rosario, Professor Edward Winter, Dr Garry Tew, Dr Liam Bourke, Professor John Saxton, Stephen Gilbert

Name of researcher: Mr Stephen Gilbert

Tick box

1. I confirm that I have read and understood the information sheet dated 08/06/2010 (Version 1) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that relevant sections of any of my data collected during the study may be looked at by responsible individuals of the research team, where it is relevant to my taking part in this research. I give permission for these individuals to have access to this data. ☐

4. I agree to take part in the above study. ☐

Name of Participant	Date	Signature
Name of individual taking consent (if not researcher)	Date	Signature
Researcher	Date	Signature

2 copies to be kept: 1 for site file; 1 for participant.

APPENDIX 7

Godin Leisure-Time Exercise Questionnaire

During a typical **7-Day period** (a week), how many times on the average do you do the following kinds of exercise for **more than 15 minutes** during your free time (write on each line the appropriate number).

	Times Per Week
a) STRENUOUS EXERCISE (HEART BEATS RAPIDLY) (e.g., running, jogging, hockey, football, soccer, squash, basketball, cross country skiing, judo, roller skating, vigorous swimming, vigorous long distance bicycling)	_____
b) MODERATE EXERCISE (NOT EXHAUSTING) (e.g., fast walking, baseball, tennis, easy bicycling, volleyball, badminton, easy swimming, alpine skiing, popular and folk dancing)	_____
c) MILD EXERCISE (MINIMAL EFFORT) (e.g., yoga, archery, fishing from river bank, bowling, horseshoes, golf, snow-mobiling, easy walking)	_____

During a typical **7-Day period** (a week), in your leisure time, how often do you engage in any regular activity **long enough to work up a sweat** (heart beats rapidly)?

Often	Sometimes	Rarely/Never
1. ☐	2. ☐	3. ☐

APPENDIX 8

Sheffield Teaching Hospitals NHS
NHS Foundation Trust

Sheffield Hallam

Date

Dear

We would like to inform you about a new research study for men who are undergoing hormonal treatment for prostate cancer. Consultants from the urology unit at The Royal Hallamshire Hospital and health researchers at Sheffield Hallam University are working together to investigate how exercise and diet can affect men's health and quality of life.

This study will be asking men with a diagnosis of prostate cancer to undertake a period of exercise training - under the guidance of a trained exercise specialist. Dietary advice will also be offered. We hope to gain a better understanding of the effects of exercise and diet on prostate cancer related health.

Please find enclosed a patient information sheet, which describes the study in detail and answers the most frequently asked questions.

If you are interested in participating in this study, please return the tear-off slip below, in the envelope provided, as soon as possible. One of the study researchers (Stephen Gilbert 0114 225 5413 or Liam Bourke 0114 225 5865) will then contact you and will gladly answer any further questions you may have.

Yours sincerely,

Mr. Derek Rosario
Consultant Urologist, Academic Urology Unit, The Royal Hallamshire Hospital.

.....

THE FEASIBILITY OF A COMBINED PROGRAMME OF EXERCISE AND DIETARY ADVICE IN THE TREATMENT OF PROSTATE CANCER PATIENTS.

☐ Yes, I am interested in taking part in the above named study. I understand that a member of staff will be contacting me, regarding this study.

☐ No, I am not interested in taking part in the study

Full Name (please print): _____

Telephone Number: _____

APPENDIX 9

Sheffield Teaching Hospitals NHS
NHS Foundation Trust

Sheffield Hallam University

The feasibility of a combined programme of exercise and dietary advice in the treatment of prostate cancer patients.

Patient Information Sheet

Version 6: 19th November 2010

Q: What is the main purpose of this study?

A: The aim of this study is to see whether men receiving androgen deprivation therapy (ADT) for prostate cancer might benefit from a supervised programme of exercise over twelve weeks. We would like to assess the effects of regular exercise on cardiovascular function, general feeling of well-being and on the body's ability to fight off cancer cells.

Q: Why have I been approached about this study?

A: You have been identified by the doctors treating you at the Royal Hallamshire Hospital as a suitable patient for this study because you are being treated for prostate cancer.

Q: What is required of me if I decide to take part in this study?

A: All patients who are interested in entering the study will be invited to meet a researcher from The Centre for Sport and Exercise Science at Sheffield Hallam University. You will have the opportunity to go through this information sheet again and ask any questions you might have about the study. You will be given a consent form to take home and complete. This is so you can take time to decide whether or not you want to take part in the study.

Your initial assessment:

If you decide to take part you will be asked to attend The Centre for Sport and Exercise Science at Sheffield Hallam University on Collegiate Crescent, Sheffield. You should bring your completed consent form with you. The researcher will take your medical history, your vascular function will be examined and a blood sample will be taken. You will be asked to come to this session in the morning, following an overnight fast and having avoided products containing vitamin C, tobacco and caffeine for 6 hours beforehand. During the vascular function tests you will be required to lie as still as possible whilst the ability of the artery in your upper arm to contract and relax is examined. The artery in your upper arm will be imaged using ultrasound whilst a blood pressure cuff is inflated around your forearm for 5 minutes and a small hand-gripping exercise is performed. Inflation of the cuff may result in a 'pins and needles' sensation in the fingers and slight discomfort in the wrist, but this will go away when the cuff is

released. Once the cuff is deflated arterial scanning will be maintained for a further 5 minutes. After a 15 minute rest period a second scan will be performed where you will take 400 µl of glyceryl trinitrate (GTN), followed by a further 6 minutes of arterial scanning. GTN is taken by a spray under the tongue and may cause slight feelings of nausea or light headedness, but these feelings should go away within 10 minutes. Throughout the vascular function tests blood pressure will be taken from an additional cuff around the opposite arm.

You will be asked to attend a second session at the centre within the same week to complete a series of physical tests. These will include walking on a treadmill, performing a sitting-to-standing task, measuring your upper limb strength, taking your blood pressure, body weight, body composition and height. You will be asked to complete a set of questionnaires. Two brief questionnaires will ask you about your physical activity habits. Additionally there will be three questionnaires to complete that will ask about your feelings of fatigue, your quality of life and your physical function at the moment. We will also ask you to complete a questionnaire about your food intake. The questionnaires will take approximately 15 minutes to complete. We will ask you to take home and wear a small device (accelerometer) which measures your level of physical activity throughout the day. It needs no adjustment or setting, you simply wear it on a belt around your waist (from first thing in the morning, until going to bed at night).

Q. What checks take place before I exercise?

A. You will be asked to fill out a medical screening questionnaire before you undergo any assessments or partake in any exercise.

Q. What happens after the initial assessment?

A. Half the men taking part will be allocated to an exercise programme and the other half will be allocated to their 'usual care'. This is a process called 'randomisation' which is routine in such studies. Figure 1 on the last page gives further details of the randomisation process.

Q: What will I have to do if I am allocated to the <u>exercise and dietary advice group</u>?

A: You will be asked to attend The Centre for Sport and Exercise Science at Sheffield Hallam University, Collegiate Crescent Campus (off Ecclesall Road) twice-weekly for six weeks. You will perform a range of aerobic exercises (indoor walking, cycling etc) and resistance exercises under the supervision of a trained therapist. You will also receive information about how to achieve a healthy diet. In addition you will be asked to perform a set of exercises at home once per week during this period. After six weeks, you will attend the centre once per week and to exercise at home twice per week for a further six weeks. You will be asked to wear your accelerometer during certain weeks.

Q: What will I have to do if I am allocated to the usual care group?

A: You will be asked to continue with your usual daily routine. You will only be required to attend the Centre for Sport and Exercise Science for assessment visits which will be at the beginning, middle and end of the 12-week study period and at 27 weeks for a follow up. We will monitor your physical activity by telephoning you a few times and by asking you to wear an accelerometer during certain weeks.

Q: What will the assessment visits entail?

A: All patients will attend regular assessments throughout the study - at the beginning of the study, the 7th and 13th weeks and at follow up. At each assessment we repeat all the measurements that are described in the previous section ***"...your initial assessment"***.

Q: How long will I have to exercise for?

A: Patients randomised to the exercise group will be asked to exercise continuously for up to ten minutes at a time, accumulating thirty minutes of moderate intensity aerobic exercise, plus up to ten minutes of resistance exercise. Each exercise session will last for approximately 40-50 minutes in total. All exercises will be tailored to your level of ability and be carefully supervised and you will be shown how to use the equipment.

Q: How long will the study last?

A: The exercise programme will last for 12 weeks and you will remain in the study for 26 weeks. We will monitor your progress throughout the study with regular assessments.

Q: What are the possible benefits of taking part in this study?

A: We cannot promise that the study will help you, but the information which we obtain might help improve the care of prostate cancer patients.

Q: Are there any side-effects of taking part?

A: If you haven't exercised for a while, exercise might initially make you feel tired and you could feel slightly breathless, but as you do it more regularly you will feel increasingly better. Such exercise might improve your walking ability and quality of life.

Additionally, taking glyceryl trinitrate in the initial assessment can make some people feel light headed or nauseous for around 10 minutes afterwards. However, we will ensure you are lying down when you take this and stay lying down until the symptoms have subsided.

Q: What are the possible disadvantages and risks of taking part?

A: The potential for risks to occur will be minimised by careful assessment before and supervision whilst you exercise. The likelihood of anything untoward happening during the exercise will be minimal. Trained personnel will take a blood sample from you which may cause slight temporary discomfort.

In the event that something does go wrong during the research study, there are no special compensation arrangements. If you are harmed then you would have access to the normal NHS complaints mechanism (see below). If you are harmed and this is due to someone's negligence then you might have grounds for legal action for compensation, but you could have to pay your legal costs.

Q: If I decide to participate, will my GP be notified?

A: With your consent, we will write and inform your family doctor that you are taking part in this study.

Q: What if I do not wish to take part?

A: There is no compulsion on you to take part. Your participation is entirely voluntary. If you decide not to take part, this will not affect the care you receive from the hospital or any other health professional.

Q: What if I change my mind during the study?

A: You are free to withdraw from the study at any time without it affecting your future treatment.

Q: What will happen to the information collected during the study?

A: The overall conclusions of the study will be available to you; however it will not be possible to produce an individualised report of your performance.

Q: Will my taking part in this study be kept confidential?

A: The confidentiality of our patients and the data which this study will generate is of utmost importance. All data from this study will be anonymised. In brief, you will be allocated a number during the study. We will need to obtain your permission to allow the research team access to your medical records and to information collected during the study. This is one of the clauses, which you will sign in agreement on the official consent form.

Our procedures for handling, processing and storage of and destruction of data are compliant with the Data Protection Act 1998.

Q: Who is organising and funding the research?

A: The research is organised and sponsored by The Centre for Sport and Exercise Science, Sheffield Hallam University in collaboration with the University of Sheffield Medical School and Sheffield Teaching Hospitals NHS Foundation Trust.

Q: Who has reviewed this study?

A: The Sheffield Research Ethics Committee has reviewed this study.

Q: What if I have further questions?

A: If you have any further questions with regards to this study then please phone :-

Name: Helen Crank or Stephen Gilbert (Study researchers) tel. 0114 225 5413

Name: Mr. Derek Rosario (Consultant Urologist) Tel: 0114 226 1229

Q: What if I wish to complain about the way this study has been conducted?

A: If you have any cause to complain about any aspect of the way in which you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms are available to you and are not compromised in any way because you have taken part in a research study. The normal hospital complaints procedure applies and you should contact the following person:

Name: Professor Mike Richmond (Medical Director) Tel: 0114 271 1900

You can also complain to any individual of the research team:

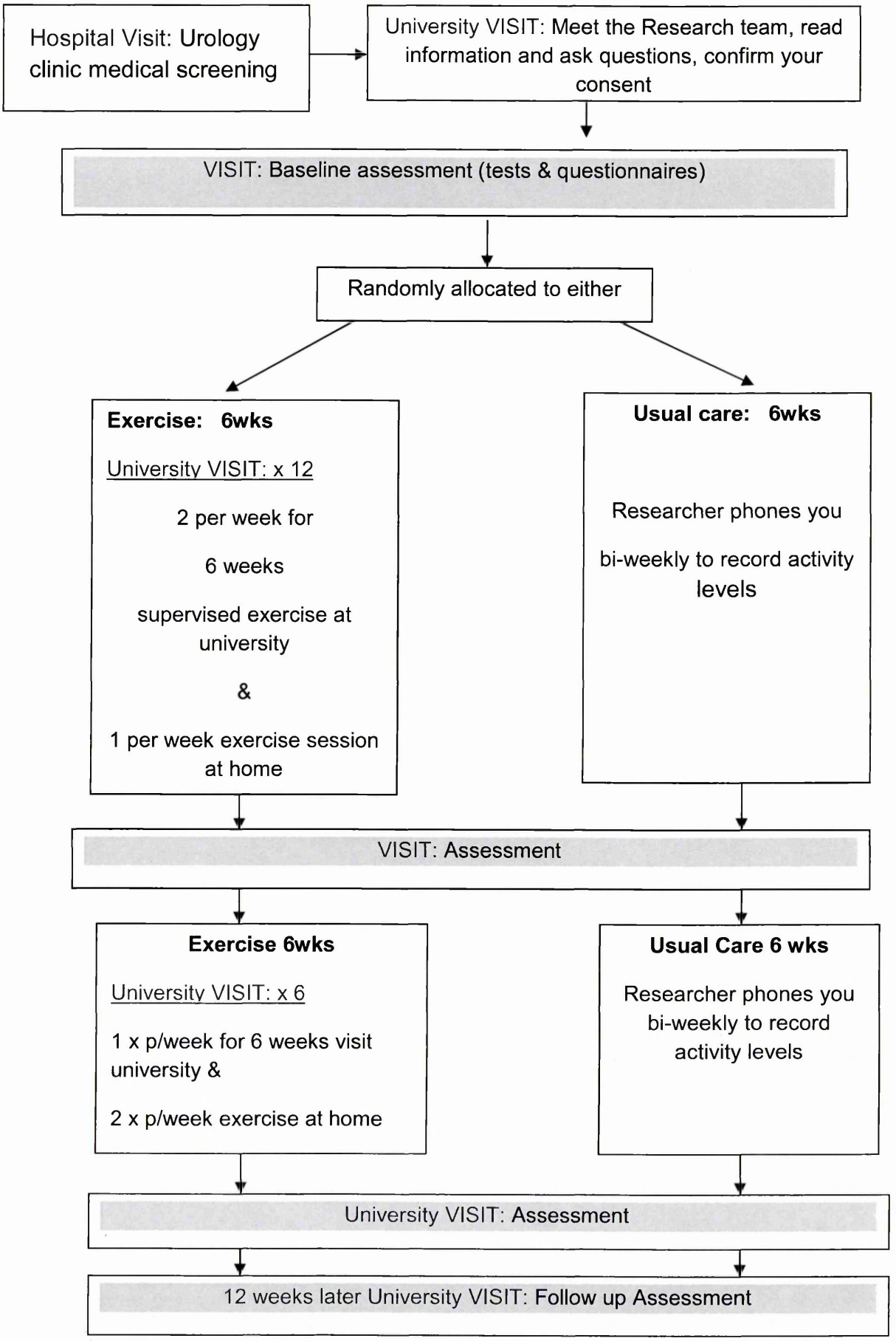
Name: Dr Liam Bourke (Study researcher) tel. 0114 225 5865

Name: Mr. Derek Rosario (Consultant Urologist) Tel: 0114 226 8840

Thank you for taking the time to consider participating in this study

Mr Derek J Rosario (Project co-ordinator)

Figure1 Study flow chart



APPENDIX 10

Sheffield Teaching Hospitals NHS
NHS Foundation Trust

Sheffield Hallam University

PATIENT CONSENT FORM

Version 3: 21st April 2010

Study: The feasibility of a combined programme of exercise and dietary advice in the treatment in prostate cancer patients

Patient Identification Number for this study: .....

Investigators: Mr. Derek Rosario, Dr. John Saxton, Helen Crank, Stephen Gilbert

Please initial the boxes

1. I confirm that I have read and understood the information sheet, version 6 dated 19-11-2010 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that relevant sections of any of my medical notes and data collected during the study may be looked at by responsible individuals of the research team, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I agree to my G.P. being informed of my participation in the study. ☐

5. I agree to take part in the above study. ☐

Name of Patient	Date	Signature
Name of individual taking consent (if not researcher)	Date	Signature
Researcher	Date	Signature

3 copies to be kept; original for site file; 1 for patient; 1 for medical notes

APPENDIX 11

EXERCISE AND DIETARY ADVICE IN THE TREATMENT OF PROSTATE CANCER

STH NUMBER: 07/Q2305/3

Week 1	Date:		
Activity	**Duration**	**RPE Intensity**	**Feelings**
E.g. Hill walking	30 minutes	14	Happy, energetic.

Week 2	Date:		
Activity	**Duration**	**RPE Intensity**	**Feelings**

Week 3	Date:		
Activity	**Duration**	**RPE Intensity**	**Feelings**

Week 4	Date:		
Activity	**Duration**	**RPE Intensity**	**Feelings**

Week 5	Date:		
Activity	**Duration**	**RPE Intensity**	**Feelings**

Week 6	Date:		
Activity	**Duration**	**RPE Intensity**	**Feelings**

APPENDIX 12

Three Day Diet Diary

It is important that you note down everything that you eat and drink in the three days covered by this diary, including things consumed away from home, e.g. snacks or alcohol. This is important because if items are missed out the resulting analysis will not produce a true picture of your diet and we will not be able to compare it to the other diaries you will complete over the course of this study. Try to be as honest as possible, your responses will not be shown to the group.

When recording items in the diary you should enter the type of food or drink consumed and approximate quantity, e.g. two slices of toast or a can of coke. Where possible try to list the different food items separately and in as much detail as possible, e.g. two slices of toast with a thin layer of butter and two teaspoonfuls of jam. Quantities can be reported as common measures where applicable, such as a cup/mug of tea or a spoonful of jam, otherwise please try and estimate the weight, e.g. 8oz steak. For ready meals, please note the pack weight and proportion consumed, e.g. half an 800g lasagne.

Also, please record the approximate time you consumed the item and whether it was a snack or part of a meal. This will help us build a picture of your daily eating pattern.

To save you from having to note down how you take your tea and coffee every time please complete the following two statements:

I usually drink my tea with milk / no milk and ___ teaspoonfuls of sugar

I usually drink my coffee with milk / no milk and ___ teaspoonfuls of sugar

Date	Time	Meal or Snack?	Food Consumed	Quantity

APPENDIX 13

FACT-P (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some -what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box*	☐				
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some -what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some -what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some -what	Quite a bit	Very much
C2	I am losing weight	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
P1	I have aches and pains that bother me	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
P3	My pain keeps me from doing things I want to do..	0	1	2	3	4
P4	I am satisfied with my present comfort level	0	1	2	3	4
P5	I am able to feel like a man	0	1	2	3	4
P6	I have trouble moving my bowels	0	1	2	3	4
P7	I have difficulty urinating	0	1	2	3	4
BL2	I urinate more frequently than usual	0	1	2	3	4
P8	My problems with urinating limit my activities	0	1	2	3	4
BL5	I am able to have and maintain an erection	0	1	2	3	4

APPENDIX 14

FACIT Fatigue Scale (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble <u>starting</u> things because I am tired	0	1	2	3	4
An4	I have trouble <u>finishing</u> things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4