DOCTOR OF PHILOSOPHY

The role of adipokines (leptin and adiponectin) and lipids in the interaction between obesity and prostate cancer

Nugroho, Fajar

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The role of adipokines (leptin and adiponectin) and lipids in the interaction between obesity and prostate cancer

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Fajar Ari Nugroho

BSHN., M.Kes.

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QUEEN'S UNIVERSITY BELFAST

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The role of adipokines (leptin and adiponectin) and lipids in the interaction between obesity and prostate cancer

Summary: (max. 300 words)

This thesis has been structured with the main objective of providing an overview of how the adipokines (leptin and adiponectin) and lipid profiles contribute to the interaction between obesity and prostate cancer, with each chapter using a different study design and research question in order to get a more complete picture of how obesity is linked to prostate cancer. While obesity has been related to prostate cancer, the results from this thesis have shown the role for adipokines in terms of risk, aggressiveness and progression of prostate cancer is still uncertain, with the work conducted in this thesis systematically reviewing the literature and highlighting weaknesses within that literature, which new analysis of an available prospective cohort study, the PRIME study, attempted to rectify. Ultimately, findings from this survival analysis suggested trends in terms of associations between adipokines and prostate cancer mortality, but results were not statistically significant, likely due to a low number of cases, and therefore further robust studies are required considering the method of assessment of adipokine exposure and development of robust models using appropriate confounders, which will allow conclusions regarding this potential association. Post-hoc analysis of a diet and lifestyle intervention has demonstrated that, although previously analysed anthropometric outcomes and dietary intake were altered, there was no significant effect on lipid profile and CVD risk outcomes, while level of adherence also did not seem to be associated with these secondary outcomes, although adherence was associated with the primary anthropometry outcome. As for the survival analysis, a lack of statistical power is likely to have been an issue for the secondary lipid outcomes, and a retrospective power calculation confirmed this.

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Much obliged.

Abbreviation

AdipoR 1/2	Adiponectin Receptor ½
ADT	Androgen Deprivation Therapy
ADIPOQ	Adiponectin
AKT	Protein Kinase B
AMPK	Activated Protein Kinase
ASR	Age-Standardized Rate
BIA	Bio Impedance Analysis
BRCA 1/2	Breast Cancer Gene 1/2
BMI	Body Mass Index
BPH	Benign Prostate Hyperplasia
CT	Computerized Tomography
CZ	Central Zone
DEXA	Dual Energy X-ray Absorption
DHT	Dihydrotestosterone
DNA	Deoxyribonucleic Acid
DRE	Digital Rectal Exam
EUROCARE	European Cancer Registry
FFA	Free Fatty Acids
FGF2	Fibroblast Growth Factor
GLP-1	Glucagon like Peptide 1
HDL	High Density Lipoprotein
HIF1	Hypoxia Inducible Factor 1
HMW	High Molecular Weight
HPC1	Hereditary Prostate Cancer 1
HR	Hazard Risk
IL-1β	Interleukin-1β
IGF	Insulin-like Growth Factor
IRS	Insulin Receptor Substrate
LDL	Low Density Lipoprotein

LEP	Leptin
LEPR	Long-form Leptin Receptor
LMW	Low Molecular Weight
MAPK	Mitogen Activated Protein Kinase
MCP	Monocyte Chemoattractant Protein
MESH	Medical Subject Heading
MMW	Medium Molecular Weight
MRI	Magnetic Resonance Imaging
NOS	Newcastle-Ottawa Scale
OR	Odd Ratio
PCA	Prostate Cancer
PI3K	Phosphoinositide 3-Kinase
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analysis
PSA	Prostate Specific Antigen
PYY	Peptide YY
PZ	Peripheral Zone
RR	Relative Risk
SEER	Surveillance, Epidemiology, and End Results
TG	Triglyceride
TNF-α	Tumour Necrosis Factor α
TNM	Tumour Nodes Metastasis
TMPRSS2	Transmembrane Protease Serine 2
TSP-1	Thrombospondin 1
TZ	Transitional Zone
VEGF/VEGFR	Vascular Endothelial Growth Factor
VLDL	Very Low-Density Lipoprotein
WAT	White Adipose Tissue
WCRF-CUP	World Cancer Research Fund International-Continuous Update Project
WHO	World Health Organization

Abstract

The incidence of prostate cancer is estimated to continue to increase. However, Prostate cancer is cancer with an aetiology that is still not well understood at present due to the complexity of the factors involved. Obesity has been identified as a contributing factor to at least twelve types of cancer, including prostate cancer.

This thesis has been structured with the main objective of providing an overview of how the adipokines (leptin and adiponectin) and lipid profiles contribute to the interaction between obesity and prostate cancer, with each chapter using a different study design and research question in order to get a more complete picture of how obesity is linked to prostate cancer.

While obesity has been related to prostate cancer, the results from this thesis have shown the role for adipokines in terms of risk, aggressiveness and progression of prostate cancer is still uncertain, with the work conducted in this thesis systematically reviewing the literature and highlighting weaknesses within that literature, which new analysis of an available prospective cohort study, the PRIME study, attempted to rectify.

Ultimately, findings from this survival analysis suggested trends in terms of associations between adipokines and prostate cancer mortality, but results were not statistically significant, likely due to a low number of cases, and therefore further robust studies are required considering the method of assessment of adipokine exposure and development of robust models using appropriate confounders, which will allow conclusions regarding this potential association.

Post-hoc analysis of a diet and lifestyle intervention has demonstrated that, although previously analysed anthropometric outcomes and dietary intake were altered, there was no significant effect on lipid profile and CVD risk outcomes, while level of adherence also did not seem to be associated with these secondary outcomes, although adherence was associated with the primary anthropometry outcome. As for the survival analysis, a lack of statistical power is likely to have been an issue for the secondary lipid outcomes, and a retrospective power calculation confirmed this.

1. Intro: the role of adipokines (leptin and adiponectin) and lipids as potential contributors to the interaction between obesity and prostate cancer.

1.1. Obesity

Obesity is a state of excess fat caused by an imbalance between energy intake and expenditure. Imbalanced energy intake can be caused by multiple factors, including increased consumption of energy-dense foods and decreased physical activity (WHO, 2019b). The excess energy will be converted to triglycerides that accumulate as body fat reserves, which increase body weight and, ultimately, the risk of health problems (Chooi et al., 2019). The number of people with obesity and overweight has increased since 1980 (Ng et al., 2014) and these conditions are estimated to have caused more deaths than underweight globally (WHO, 2019b).

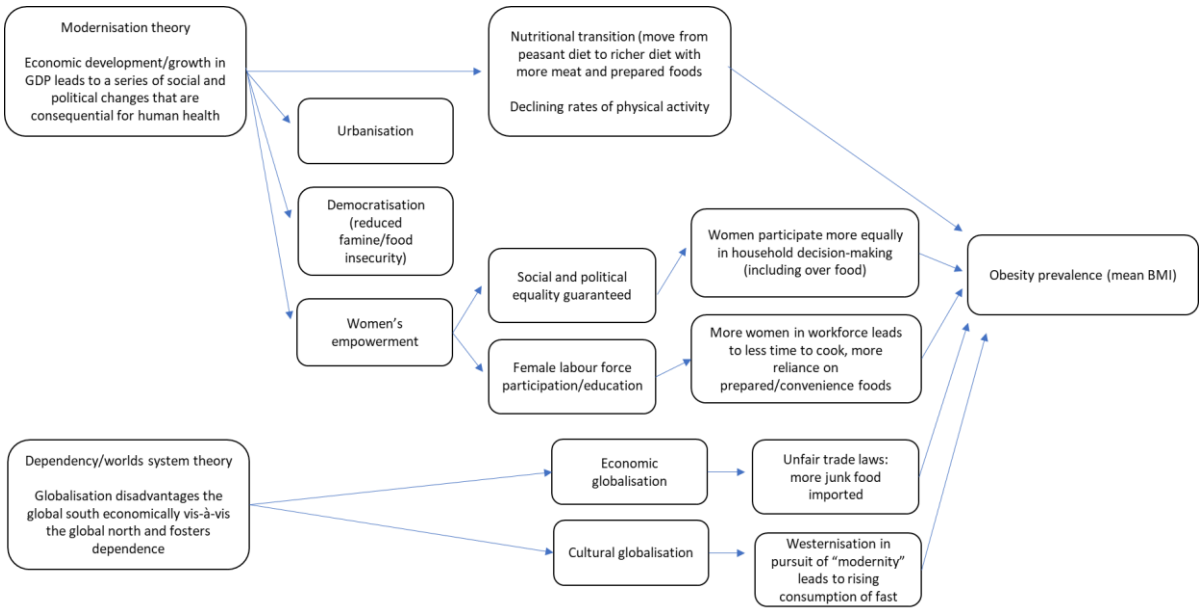
According to the opinions of experts cited by Fox et al (2019), there are two basic theories (modernization theory and dependency-world system theory) which explain the obesity pandemic in a society where it is closely related to prosperity (Fox et al., 2019) (**Figure 1**). Modernization theory is a concept that explains the shift of society from a 'traditional' to a 'modern' stage which was initiated by the German sociologist Max Webber, which was later refined by the Harvard sociologist Talcott Parson (Knöbl, 2003). The theory stated that a positive change in economic, social, cultural and political will result in a virtuous cycle of increasing living standards, social movements and democratic growth (Fox et al., 2019). These changes then induce an epidemiological transition from infectious disease to chronic degenerative disease-related obesity in society (Fox et al., 2019). Other than that, modernization theory also predicts a fluctuation of Body Mass Index (BMI) from additional potential mechanisms such as urbanization, women's empowerment and democratisation (Fox et al., 2019).

Urbanization has been reported to be associated with increasing obesity (Fox et al., 2019). Urbanization has resulted in a change in the diet of urban communities from a plant-based diet to a diet with high energy and high fat density (Chooi et al., 2019, Fox et al., 2019). In addition, many urban people also switch from physically demanding to mental challenging work, where according to Huneault et al. (2010), this type of work often results in changes in sleep hours and has more stressors. Activity that requires mental performance is related to neurons and increased glucose requirements which often result in fluctuations in insulin and blood glucose levels (Huneault et al., 2011). This phenomenon might associate with changes in eating habits and weight gain pattern that lead to obesity (Huneault et al., 2011).

As shown in **Figure 1**, the role of democratization in the obesity trend remains unclear (Fox et al., 2019). Democratic countries may tend to adopt policies that protect their people from obesogenic foods but, this is often not the case (Fox et al., 2019). On the other hand, the effect of women's empowerment is also still being discussed (Fox et al., 2019). In general, the concept of broader involvement of women in the workplace is often found to reduce their involvement in preparing healthy meals in the family (Fox et al., 2019). Although these two things are still being studied, the impact of both is considered to have potentially contributed to the increase in obesity levels by modernization theory (Fox et al., 2019).

Meanwhile, the dependency and world-system theory are a 'radical' theory of development in which poverty and underdevelopment occur not entirely from society itself but because of external exploitation (Fox et al., 2019). This theory illustrated that groups of developing countries have been and continue to be controlled economically and politically by external powers (Fox et al., 2019). Control was carried out through activities of accounts payable, trade and foreign investment which indirectly affect the level of prosperity and health of the people (Fox et al., 2019). The diffusion of obesogenic food products in low and middle income countries markets was a clear example that fits this theory (Fox et al., 2019). Developing countries

have become 'forced' unconsciously to adopt obesogenic food and face the threat of obesity (Fox et al., 2019) **(Figure 1.1)**.



Source: adapted from Fox et al (2019).

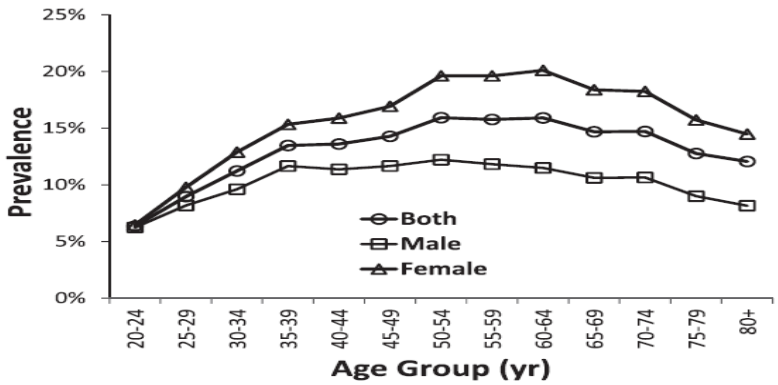
Figure 1.1. Theoretical framework: how different variables might affect obesity

According to the World Health Organization (WHO), obesity is not only faced by developed countries but also by developing countries. Poor nutritional quality during prenatal, infancy and childhood and exposure to unhealthy foods triggers the emergence of obesity early in developing countries (WHO, 2019b). WHO has established strategies to combat obesity through improved dietary habits and physical activity that were being carried out with, firstly, the WHO's Global Strategy on Diet, Physical Activity and Health-related to policies in promoting healthy diets and physical activity at the community level that is targeting significant changes by 2030 (WHO, 2019b). Secondly, the WHO is attempting to combat obesity through the Global Action Plan for the Prevention and Control of Non-Communicable Diseases 2013-2030, which is acting by involving all heads of state together to reduce the world obesity curve (WHO, 2019b). Thirdly, through the World Health Assembly, the WHO introduced the Commission on Ending Childhood Obesity (2016) which produced recommendations related to the obesogenic environment and the critical period in overcoming obesity in children (WHO, 2019b).

1.2. Obesity statistic

1.2.1. Prevalence rates

Globally, it is estimated that 39% of the population was overweight and obese in 2015 (Chooi et al., 2019). The prevalence of overweight in young women is lower than that of men of the same age (20-44 years) but this condition is reversed at a later age where menopause may be the reason for the higher prevalence of female overweight than men (45-49 years) (Chooi et al., 2019). In contrast to overweight, the prevalence of obesity in women is higher than men at all ages (Chooi et al., 2019). The peak prevalence of both overweight and obesity in both sexes is recorded in the age range of 50-65 years (Chooi et al., 2019) (**Figure 1.2**).

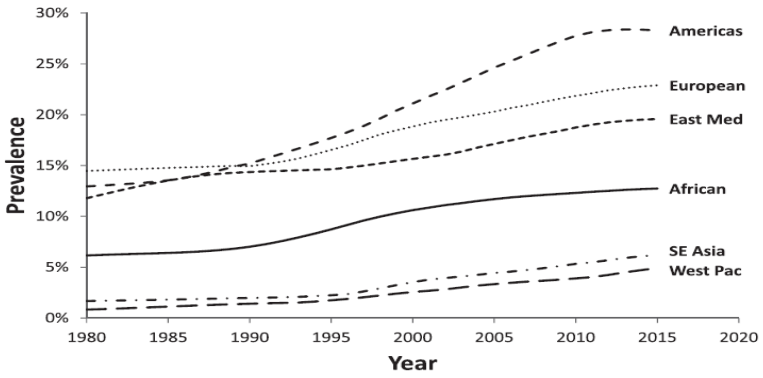


Source: Chooi et al (2019).

Figure 1.2. Prevalence of obesity in adults > 20 years old by age group and sex worldwide (2015)

1.2.2. Regional trend

The United States and Europe were the two continents with the highest prevalence of obesity globally (**Figure 1.3**). The United States experienced an increase in obesity prevalence of about 28.3% from 1980 to 2015 while Europe came in the second position, with a 22.9% prevalence increase (Chooi et al., 2019). This was followed by the Eastern Mediterranian region (19.6%), the Africa region (12.7%) and the Southeast Asian region (6.2%). The West Pacific region was last in the list (4.9%), although China is a notable country in this region with the highest prevalence rate (29.9%) (Chooi et al., 2019).



Source: Chooi et al (2019).

Figure 1.3. Age-standardised prevalence of obesity in adults > 20 years old by geographical region (1980-2015)

Trends in increasing obesity prevalence were also reported by the Northern Ireland Health Survey (HSNI) 2010/2011. A total of 59% of surveyed adults were reported as overweight (36%) or obese (23%) (HSNI, 2011). In the latest 2017/2018 survey, both numbers significantly increased, becoming 37% for overweight and 27% for obesity, which represented a 23% increase in the obesity trend (HSNI, 2018). This survey found obesity was less common in younger ages but high in middle-aged (25%) or older (30%). Furthermore, the obesity group was also reported to have greater morbidity (50%) than the non-obese group (27%) (HSNI, 2011).

1.3. Aetiology obesity

Energy balance has been associated with the aetiology of obesity. A study by Weinsier et al (1998) reached a conclusion that the total expenditure of resting energy has a dominant role in energy balance (60%) and proposed to use this as the main strategy for targeting obesity (Weinsier et al., 1998). However, this strategy was considered ineffective to overcome obesity without the support of a reduction in energy intake (Hill et al., 2012). Moreover, other studies noted that both energy balance and sedentary behaviour play important parts in energy storage augmentation and weight gain mechanisms associated with the obesity pandemic (Pereira-Lancha et al., 2012, Racette et al., 2003). Furthermore, the technological expansion and

modernisation connected with sedentary lifestyles and decreased physical activity (Ng et al., 2014, Wiklund, 2016) have been reported to increase 3.9 times the risk of obesity (Pietililainen et al., 2008).

The role of hormones involved in energy balance is also likely to be important in obesity. Leptin, discussed in more detail in a subsequent section, is one of the hormones that has been widely linked to obesity. In the early 90s, the leptin gene and the association of its receptor with energy balance regulation were identified in people with extreme obesity (Weinsier et al., 1998). Leptin has been suggested to have a role in obesity since then, but the results of many studies regarding the role of leptin and leptin resistance in satiety response and energy balance were mixed at that time (Weinsier et al., 1998). This diversity encourages further study of the role of leptin in obesity, as well as other hormones that work with leptin in regulating energy balance, such as glucagon-like peptide 1 (GLP-1), peptide YY (PYY), pancreatic polypeptides, cholecystokinin, ghrelin, insulin and adiponectin (Lean and Malkova, 2016, Nigro et al., 2014).

Dietary intake is also an important factor in the aetiology of obesity. Diet can be a protective factor or can also be a risk factor for obesity (Swinburn et al., 2004). Jeon (2011) reported that the nutrient intake of people with obesity was higher than those who were normal weight. The imbalance in dietary intake may also be related to a poor lipid profile in obesity (Jeon et al., 2011). A recent review reported an increased risk of overweight and obesity for people in the highest compared to the lowest category of unhealthy dietary intake (OR 1.65 95% CI 1.45-1.87, $p < 0.0001$) (Mu et al., 2017).

Apart from behavioural and biological factors, the aetiology of obesity also involves obesogenic environment factors. The obesogenic environment, the opposite of leptogenic or weight-loss inducing environment, is the surroundings, opportunities or living conditions that promote obesity in an individual or population (Swinburn et al., 2004). There are various potential factors in the obesogenic environment, but they can be grouped into two main categories,

namely food and physical activity (Mackenbach et al., 2014). Food consumption and production is a complex system in obesity (NHS 2018). Food, including drinks consumed, greatly determines a person's weight, in which there is an interaction of how food is produced, price, promotion and availability (NHS 2018). On the other hand, physical activity also has a significant effect on a person's body weight (NHS 2018). An environment that is not designed to support physical activity such as those with limited access and poor safety to be active are examples of conditions that prevent a person from having a healthy weight (NHS 2018).

Based on these facts, obesity can be considered a multifactorial health problem that involves not only energy balance but also biological, environmental, and obesogenic behaviours (Kadouh and Acosta, 2017).

1.4. Measuring obesity

Measuring obesity can be done in various ways. The main ones are presented below:

1.4.1. Fat mass

Fat mass can be used to measure overweight and obesity. Measurement of fat mass with high accuracy can use imaging technologies such as Dual-Energy X-ray Absorption (DEXA), Computerized Tomography (CT) scans, and Magnetic Resonance Imaging (MRI), but these methods are impractical and high-cost for general use (Purnell, 2018). Another alternative measurement is underwater weighing or air transfer using Air Displacement Plethysmograph (BOD POD) or Bio Impedance Analysis (BIA) (Purnell, 2018). BOD POD and BIA are the two methods most often used by obese specialist clinics and fitness centres; however, they are not always recommended because their accuracy is often obscured by obesity complications such as congestive heart failure or chronic kidney failure (Purnell, 2018).

1.4.2. Body mass index, waist circumference (WC) and waist to hip ratio (WHR)

The World Health Organization uses Body Mass Index (BMI) as a simple indicator in classifying underweight, overweight and obesity in adults. BMI is calculated from body weight in kilograms divided by the square of height in metres (kg/m^2) (**Table 1.1**) (WHO, 2019a). Its value is age-independent, the same for both sexes and may not be able to describe differences in body fat distribution (WHO, 2019a). In general, a high BMI value is stated to indicate excess body fat (Han et al., 2006). BMI may also differently associate with health risks in certain populations for example, in one area it was linked to health problems related to undernutrition and in another to overweight and obesity (WHO, 2019a).

Furthermore, to achieve optimal health, the average body mass index for the adult population should be in the range of 21 to 23 kg / m^2, while for individuals it is necessary to maintain body mass index in the range of 18.5 to 24.9 kg / m^2. There is an increased risk of comorbidity for a body mass index of 25.0 to 29.9, and the risk of moderate to severe comorbidity for a body mass index of more than 30 (WHO, 2019a). However, BMI is a substandard as an indicator of body fat percentage and also does not capture information on the distribution of fat mass in different parts of the body compared to other measurements such as the waist or waist-hip ratio (Nuttall, 2015). According to Nuttall (2015) this is caused by squaring the height which results in a decrease in the effect of height variations related to body weight on height because most of the body fat is in the trunk.

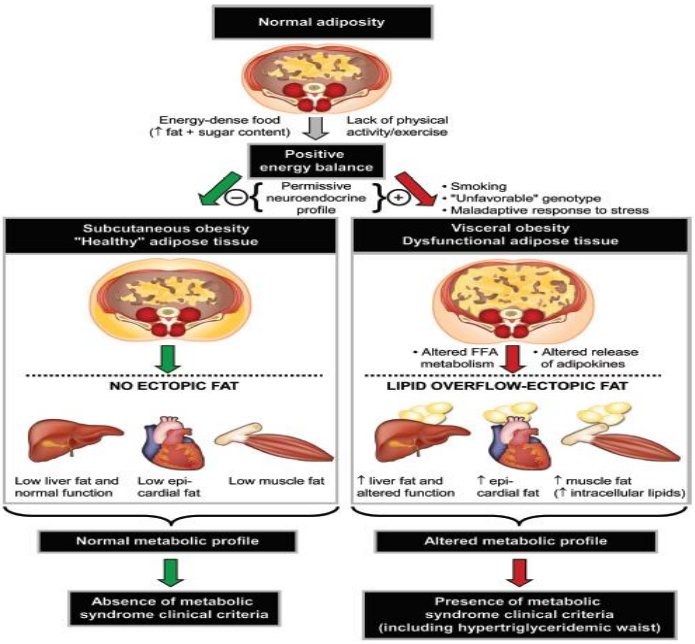
In addition to the use of BMI, waist circumference and waist to hip ratio (WHR) are also used as indicators of obesity. BMI and waist circumference can both be used as indicators at the population level, while waist circumference, in particular, is also an anthropometric marker of visceral adiposity (Despres, 2012). A person who has increased fat around the abdomen or has decreased major muscle mass will have a larger waist circumference as well as an increased waist to hip ratio (Han et al., 2006).

Table 1.1. The international BMI and WC classification

Classification	BMI (kg/m²)		Classification	High-risk WC (cm or inches)
	Principal cut-off points	Additional cut-off points		
Underweight	<18.50	<18.50	Men	
Severe thinness	<16.00	<16.00	US criteria	> 102 or 40
Moderate thinness	16.00-16.99	16.00-16.99	European criteria	> 94 or 37
Mild thinness	17.00-18.49	17.00-18.49	South Asian, Japanese, and Chinese criteria	> 90 or 35.5
Normal range	18.50-24.99	18.50-22.99	Women	
		23.00-24.99	US criteria	> 88 or 35
Overweight	≥ 25.00	≥ 25.00	European criteria	> 80 or 31.5
Pre-obese	25.00-29.99	25.00-27.49	South Asian, Japanese and Chinese criteria	> 80 or 31.5
		27.50-29.99		
Obese	≥ 30.00	≥ 30.00		
Obese class I	30.00-34.99	30.00-32.49		
		32.50-34.99		
Obese class II	35.00-39.99	35.00-37.49		
		37.50-39.99		
Obese class III	≥ 40.00	≥ 40.00		

Source: Adapted from WHO, 1995, WHO, 2000 and WHO 2004; Purnell et al (2018)The WHR or waist circumference is also used to identify obesity by measuring the proportion of fat in the abdomen at the level of the waist or hips (Purnell, 2018). Furthermore, someone who has a normal BMI and is therefore considered to be of normal weight can have a high waist circumference and a higher risk of developing metabolic syndrome compared to obese people classified according to the BMI index but with normal waist circumference (Alvarez-Cubero et al., 2013).

It has further reported by a study that health problems related to visceral obesity, especially CVD, are most closely related to the WHR, followed by waist circumference and BMI (Czernichow et al., 2011). Another study reported at the population level WHR showed a significant association with at least one type of cardio metabolic risk for each 0.1 increment (OR 1.40 95% CI 1.15-1.70) (Elffers et al., 2017). Meanwhile, waist circumference was related to cardio metabolic risk every 11 cm increments (OR 1.29 95% CI 1.05-1.59) (Elffers et al., 2017). In simple terms, an overview of the relationship between visceral adiposity and health problems including CVD is presented in **Figure 1.4**.



Source: Despres (2012)

Figure 1.4. The lipid overflow-ectopic fat model

On the other hand, the role of waist circumference and waist to hip ratio in reflecting on obesity has a close relationship with leptin and adiponectin. Abdominal subcutaneous adipose tissue and visceral adipose tissue are also the main depots for storing white adipose tissue (WAT) (Bjorndal et al., 2011) which actively act as an integral part of the endocrine organs that secrete adipokines (leptin and adiponectin) (Khan and Joseph, 2014). Therefore,

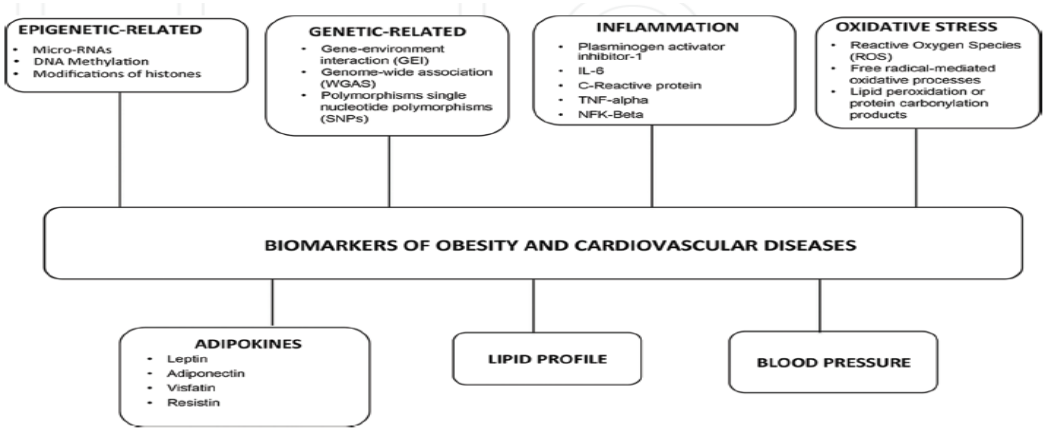
the measurement of waist or waist to hip ratio is important in predicting the consequences of health problems related to excess fat besides BMI (Nuttall, 2015).

1.4.3. Dietary assessment

In measuring background factors related to obesity, dietary assessment has an important role in providing information on initial eating patterns, changes that occur and establishing the necessary feedback (O'Neill, 2001). However, there are biases that should be considered when carrying out dietary assessments (Archundia Herrera and Chan, 2018). It is necessary to have an ongoing evaluation of tools to maximise the effectiveness, acceptance and validity of measurements to detect dietary patterns (Archundia Herrera and Chan, 2018). Furthermore, biases can be enhanced or differ depending on level of overweight or obesity. This bias is particularly commonly found when reporting about fats and carbohydrates (Swinburn et al., 2004). However, under-reporting should be a concern since this can make measuring accurate dietary patterns in obesity difficult (Weinsier et al., 1998).

1.5. Metabolic changes in obesity

In conditions of obesity, there are several changes in metabolism. The changes of leptin, adiponectin and lipid profiles will be explored in this thesis. In general, here are some of the metabolic changes in obesity:



Source: Meza et al 2016.

Figure 1.5. General metabolic changes biomarker of obesity and cardiovascular disease

1.5.1. Insulin resistance

Insulin secretion is enhanced in the fed state and prolonged exposure to high levels of insulin can lead to insulin resistance. Insulin resistance is a condition of compensation which occurs in hyperinsulinemia due to impaired interaction of complex feedback interactions between sensitivity and secretion of insulin (Petersen and Shulman, 2018). It affects the utilization of blood glucose (glycolysis) and the regulation of blood glucose production from sources other than carbohydrates (gluconeogenesis) (Petersen and Shulman, 2018). This feedback disorder is mainly caused by a decrease in the function of the pancreas and/or a decrease in the number of insulin receptors (Petersen and Shulman, 2018).

According to Kahn (2000), the association between obesity and insulin resistance has been found in all ethnic groups and is associated with increased body fat (Kahn and Flier, 2000). A narrative review revealed that the main mediator of obesity-related insulin resistance was a higher level of circulating free fatty acids (FFA) in people with obesity (Guilherme et al., 2008). Other studies have also reported that adipose tissue abnormalities in people with obesity cause a disruption in the secretion of leptin and adiponectin that play an important role in insulin sensitivity, satiety control and reducing FFA and triglycerides (Antuna-Puente et al., 2008, Martyn et al., 2008).

1.5.2. Lipid metabolism

Almost 70% of people with obesity have dyslipidaemia or impaired lipid profiles (Uranga and Keller, 2019). Triglycerides (TG), free fatty acids, Very Low Density Lipoprotein (VLDL), Apo B, and non-High Density Lipoprotein (HDL)-cholesterol tend to increase in obesity, whereas total HDL serum levels and HDL function decrease (Uranga and Keller, 2019). Low

Density Lipoprotein (LDL) levels seem to remain normal but pro-atherogenic components of LDL may increase (Uranga and Keller, 2019). These abnormalities have been frequently noticed in metabolic syndrome and linked with insulin resistance-related inflammation in obesity (Uranga and Keller, 2019).

Furthermore, Uranga and Keller (2019) suggested that the increase in free fatty acids in obesity also has a role in insulin resistance. The enlargement of adipose tissue in obesity contributes to increasing free fatty acids. It is related to the disruption of antilipolytic (the inhibition of lipolysis) effect of insulin, increased de novo fatty acid synthesis and increased absorption of triglyceride-rich proteins in the liver (Uranga and Keller, 2019). Ultimately this process will cause ectopic lipid deposition (i.e. storage of fat on abnormal sites such as liver, muscle, heart), which may be cytotoxic and trigger health problems (Uranga and Keller, 2019).

1.5.3. Satiety hormone

1.5.3.1. Satiety hormones in general

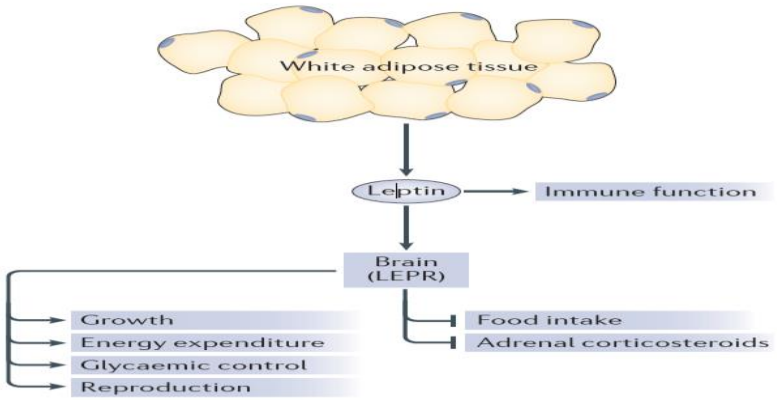
The biological effect of appetite generates from the complex concept of energy balance that involves energy intake, expended energy, thermic effects of food, exercise activity thermogenesis, resting energy expenditure, and resting metabolic rate (MacLean et al., 2017). A satiety response is regulated by several hormones that work synergistically such as Glucagon-like Peptide 1 (GLP 1), Peptide YY (PYY), pancreatic polypeptide, cholecystokinin, ghrelin, insulin, leptin and adiponectin (Lean and Malkova, 2016). Leptin and adiponectin are the two satiety hormones that will be discussed in chapter 2.

1.5.3.2. Leptin

Leptin is a hormone produced mainly by white adipose tissue (Kelesidis et al., 2010, Lean and Malkova, 2016). This hormone is secreted in a pulsatile fashion (regular pattern) but has a diurnal variation (Kelesidis et al., 2010). Leptin is produced proportionally based on the

body's energy reserve status (triglycerides) (Lean and Malkova, 2016, Pan and Myers, 2018). Circulating leptin is bound to long-form leptin receptors (LEPR) in the brain and plays several roles in growth, energy expenditure, glycaemic control, reproduction, food intake inhibition, adrenal production of corticosteroids, and having a role in the production and function of immune cells (**Figure 1.6**) (Pan and Myers, 2018).

Furthermore, a study reported that people with obesity have higher circulating leptin when compared to normal-weight people, however, this increased leptin resulted in leptin resistance and thus did not inhibit appetite (Lean and Malkova, 2016). On the other hand, leptin signalling is also altered due to increased adiposity in obesity (Pan and Myers, 2018).



Source: Pan et al (2018)

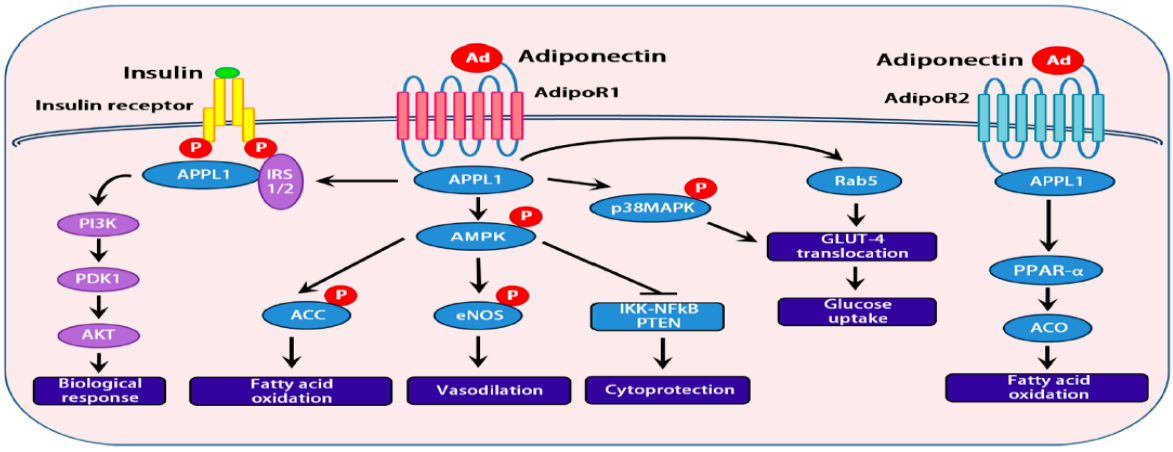
Figure 1.6. The action of leptin

1.5.3.3. Adiponectin

Adiponectin is produced by adipose tissue (Kelesidis et al., 2010, Nigro et al., 2014) mainly secreted by white adipose tissue (WAT) (Achari and Jain, 2017). Adiponectin consists of variants composed of homo-oligomers with various weights. The three main forms of adiponectin are the Low Molecular Weight trimers (LMW), the Moderate Molecular Weight hexamers (MMW), and the High Molecular Weight oligomers/multimers (HMW) and also, a globular form (Achari and Jain, 2017, Iwabu et al., 2019, Nigro et al., 2014). The HMW is the most active form (Nigro et al., 2014) while it also has an insulin-sensitizing role and has a

cardiovascular protective effect (Achari and Jain, 2017, Iwabu et al., 2019). Lower levels of active oligomer might be associated with a risk of obesity-related diseases such as diabetes mellitus, cardiovascular disorders and metabolic syndrome (Iwabu et al., 2019, Nigro et al., 2014).

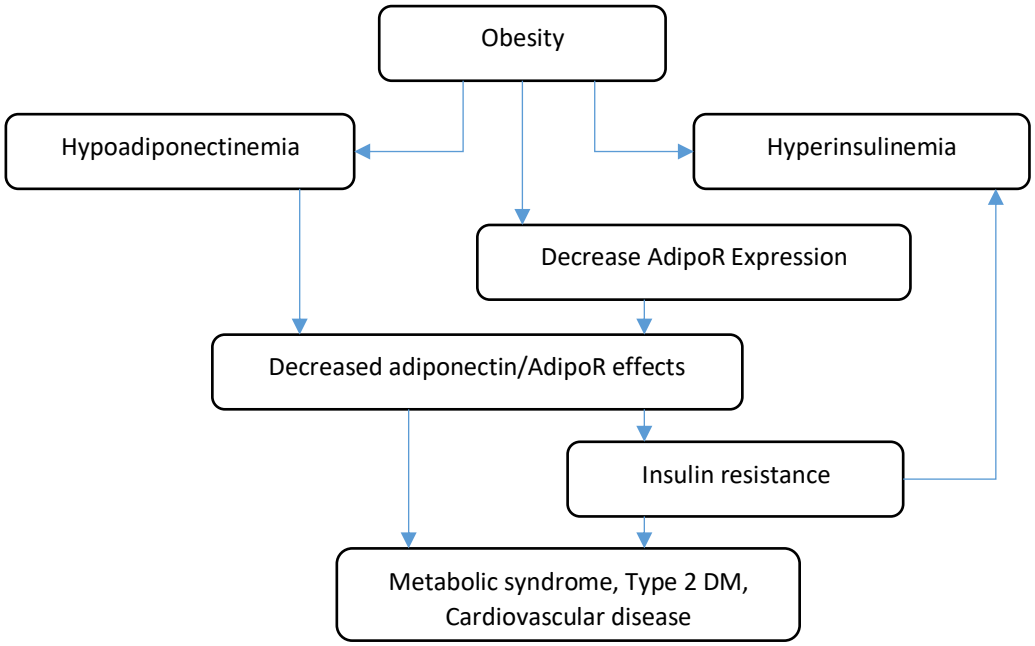
Furthermore, similar to leptin, adiponectin is also involved in regulating energy homeostasis through the mechanism of glucose uptake and oxidation of fatty acids along with insulin (**Figure 1.7**) (Achari and Jain, 2017). Adiponectin and insulin interact through each of the receptors to induce a cascade signalling activity. Adiponectin communicates with its receptors (AdipoR1/2) to activate multiple signalling pathways such as Insulin Receptor Substrate (IRS) 1/2, Adenosine Monophosphate-activated Protein Kinase (AMPK) and p38 Mitogen-activated Protein Kinase (MAPK) pathways (Achari and Jain, 2017, Nigro et al., 2014). IRS 1/2 pathway activation will activate insulin sensitization in the tissues. Furthermore, insulin will initiate metabolic action carried out by the Phosphatidylinositol 3-Kinase/protein kinase B (PI3K/AKT) pathway to drive protein synthesis, lipogenesis, uptake and use of glucose, glycogen synthesis, and decrease lipolysis and gluconeogenesis (Achari and Jain, 2017).



Source: Achari and Jain (2017)

Figure 1.7. Adiponectin signal transduction crosstalk with insulin

However, in conditions of obesity, Iwabu et al (2019) stated that the amount and function of adiponectin and its receptor is decreased. This alteration induces the emergence of insulin resistance and hyperinsulinemia that disrupts energy homeostasis (Iwabu et al., 2019). This process becomes a sequence of causes and effects in which hypoadiponectinemia and insulin resistance aggravate each other, leading inexorably to poorer metabolic outcomes (**Figure 1.8**) (Iwabu et al., 2019).



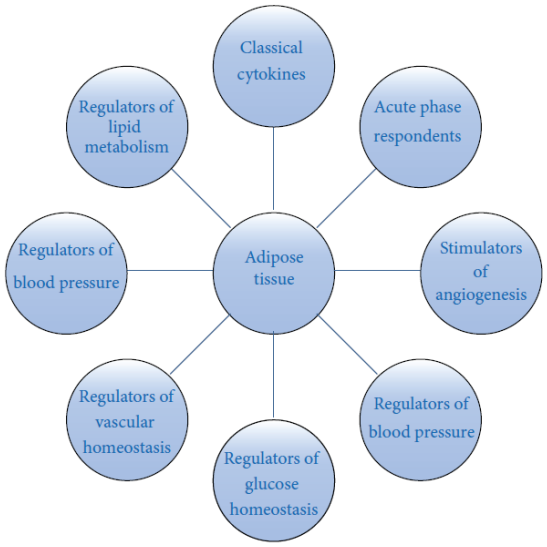
Source: modified from Iwabu et al (2019)

Figure 1.8. The roles of decreased adiponectin and AdipoR effects in obesity-related diseases

1.5.4. Obesity and adiponectin

According to Khan and Joshep (2014), the role of adipokines (leptin and adiponectin) in the endocrine system starts from the action of adipose tissue elements, especially white adipose tissue (WAT) as endocrine organs. WAT secretes active polypeptides known as adipokines which act locally, systematically, and express on various metabolic receptors. The role of adipokines acting through these receptors influences both hormonal networks and communication in the central nervous system (CNS). So indirectly adipose tissue through

adipokines can also cross-communicate with various organs throughout the body via the CNS. The general physiological roles of adipokines are shown in the figure below.



Source: Khan and Joseph (2014)

Figure 1.9. The overview of the various physiological function of adipokines expressed and secreted from adipose tissue

1.5.5. Adipokines measurement

Generally, the increase in adipokines is influenced by energy balance, lipid metabolism, immunity, insulin sensitivity, cancer, and cardiovascular disease. According to Hill et al (2009) secretion of adipokines varies depending on the depots and relative inclusion of non-adipocytes (vascular-stromal cells, endothelial cells, and macrophage). Leptin and adiponectin are the most abundant circulating adipokines. The most commonly used examination and measurement of adipokines is serum, plasma, or cerebrospinal fluid (CFS) concentrations with the ELISA method, where this method compares the antibody/antigen interactions on the target protein from the prepared standard curve (Hill et al., 2009). This method is still being carried out today, although at present a more advanced multiplexing assay technology has been developed but is not yet widely used.

The challenges in examining adipokines are influenced by, first, the complexity possessed by adipokines e.g., the different oligomers found in adiponectin. Second, the type of sample; although serum and plasma are the most commonly used forms, however, commercial assays are validated using healthy humans that often present a challenge when these assays are used in patients with obesity-related diseases. Third, the time of examination is important: leptin, and adiponectin have diurnal/rhythm variation. Although the changes are not large, the time of sampling still needs attention. Fourth, factors that may also influence the results such as sample preparation, use of appropriate assay validation, BMI, nutritional status, gender, disease risk, and ethnicity), need to be considered when planning studies and consider interpretation appropriately.

1.6. Obesity and health problems

Overweight and obesity have linked to several health problems including insulin resistance and diabetes mellitus, cardiovascular disease, metabolic syndrome and cancer (Bays et al., 2013). Obesity has been associated with insulin resistance that induces metabolic syndrome, cardiovascular disease and diabetes mellitus (Perry and Wang, 2012). According to Al-Goblan (2014), insulin resistance is a condition commonly experienced by people with obesity and is a link that connects between obesity and diabetes mellitus. The inability of pancreatic beta cells to respond to insulin resistance in people with obesity is the cause of the emergence of diabetes mellitus (Al-Goblan et al., 2014). According to WHO, in line with the increasing prevalence of people with obesity in the world, the incidence of diabetes in adults also increased from 4.7% in 1980 to 8.5% in 2014 (WHO, 2019b).

Obesity is also a risk factor for the development of cardiovascular disorders, where about 32%-49% of cardiovascular disease cases were experienced by people with obesity (Csige et al., 2018). According to this review, obesity has played the role in various types of cardiovascular

disorders such as atherosclerosis, coronary artery disease, heart failure, cardiac arrhythmias, and sudden cardiac death (Csige et al., 2018).

The metabolic syndrome, which is a collection of abnormal cardio metabolic conditions that together increase the risk of cardiovascular disorders and type 2 diabetes mellitus, has been also associated with obesity (Gregory, 2019). The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATPIII) defines the metabolic syndrome as having any three of the following five criteria: waist circumference more than 40 inches (men) or 35 inches (women), blood pressure over 130/85 mmHg, fasting triglycerides over 150 mg/dl, fasting high-density lipoprotein (HDL) cholesterol level less than 40 mg/dl (men) or 50 mg/dl (women) and fasting blood sugar levels greater than 100 mg/dl (NCEP, 2002). The increased free fatty acid turnover (FFA) in obesity is thought to increase the risk of metabolic syndrome (Han and Lean, 2016). A study reported that about 31% of obese people experienced metabolic syndrome (Engin, 2017) while another study even reported a higher percentage (26% to 50%) (Gregory, 2019). The risk of mortality caused by metabolic syndrome in people with obesity was also said to be 1.5 times higher than people with normal weight (Engin, 2017).

1.7. Obesity and cancer

1.7.1. A general association of obesity and cancer

There is an ongoing program of research which analyses global research studies to assess the role of diet, nutrition, physical activity, and weight in cancer risk and survival [World Cancer Research Fund International Continuous Update Project (WCRF-CUP)] (WCRF, 2018). This report clearly shows an association between obesity and cancer at twelve sites namely bowel, breast (postmenopausal), gallbladder, kidney, liver, mouth-pharynx-larynx, oesophagus (adenocarcinoma), ovary, pancreas, prostate (advanced), stomach (cardia), and womb (WCRF, 2018).

According to the WCRF (2018), high body fat stores can cause insulin resistance and encourage the body to produce growth hormone. Higher growth hormone levels can encourage the growth of cancer cells (WCRF, 2018). In addition, body fat also stimulates the inflammatory response (WCRF, 2018). Inflammation can increase cancerous growth by encouraging cancer cells to divide. It is thought that this inflammatory response is the biological mechanism which is a key contributor to the association between obesity and cancer (WCRF, 2018).

Maintaining a healthy weight is one of the key recommendations set forth by the WCRF to prevent cancer. The WCRF-CUP suggests that a balanced diet and regular physical activity could help maintain a healthy body weight. Further suggestions related to weight in terms of cancer prevention include maintaining a BMI between 21 kg/m^2 to 23 kg/m^2, maintaining a normal body weight from age 21, and avoidance of weight gain and avoidance of an increased waist circumference in adulthood (WCRF, 2018).

1.7.2. Biological mechanism of obesity and cancer

Several pathways have been described to explain the association between obesity and cancer. These include angiogenesis, chronic inflammation, vascularization of and oxygen supply to the tumour, attachment and maturity, and macrophage infiltration (Hida et al., 2016, Tahergorabi et al., 2016). Angiogenesis is a complex process consisting of vascular re-arrangement, matrix degradation, endothelial propagation, cell migration, and anastomosis in cell development (Tahergorabi et al., 2016). Angiogenesis induces endothelial tissues to produce angiogenic and angiostatic factors needed such as placental growth factor, fibroblast growth factor (FGF2), angiopoietin-2, angiostatin, leptin, thrombospondin (TSP-1), resistin, insulin-like growth factor (IGF), hepatocyte growth factor (Tahergorabi et al., 2016) and vascular endothelial growth factor (VEGF/VEGFR) (Hida et al., 2016).

Obesity is a chronic inflammatory state inducing multiple stress signals and causing adipose tissue remodelling (Louie et al., 2013). The excess storage of lipid within the adipose tissue will then result in higher circulating concentrations of FFAs and the enzyme Fatty Acid Synthase (Louie et al., 2013). In addition, adipose tissue remodelling increases oxidation and promotes insulin resistance in muscle and liver, creating more aggressive cancer phenotypes, and functioning as oncogenic signalling (Perez-Hernandez et al., 2014).

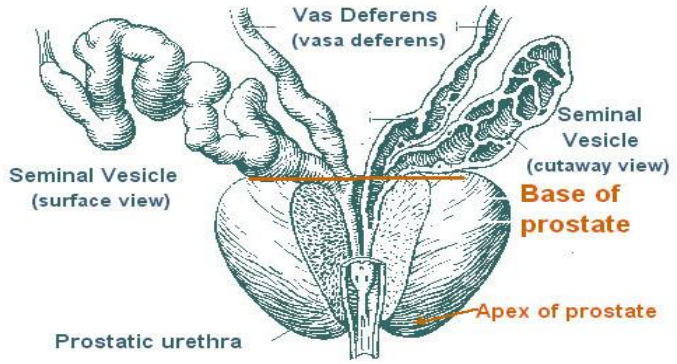
Moreover, inflammation reduces vascularization and as a result oxygen supply for the cell (hypoxia) via activation of hypoxia-inducible factor 1 (HIF1) (Perez-Hernandez et al., 2014). HIF1 and angiogenesis together support the cancer cells' growth and suppress normal cell development. Furthermore, this process is results in activation of inflammatory cytokines such as interleukin 1-β (IL-1β), TNF-α and monocyte chemoattractant protein (MCP) and induces fibrosis (Perez-Hernandez et al., 2014). Fibrosis, local inflammation and insulin resistance together encourage cell growth and inhibit apoptosis (Tahergorabi et al., 2016) providing a rich microenvironment for cancer growth (Perez-Hernandez et al., 2014).

Obesity, which is also related to macrophage infiltration during inflammation promotes cancer attachment and maturity (Cho et al., 2007). In addition, adipose tissue remodelling results in a disruption of energy homeostasis through increased demand for adipogenesis (Stephens, 2012). Increased adipogenesis results in an increase in pro-inflammatory factors such as tumour necrosis factor (TNF)-α, interleukin (IL)-6, and C-reactive protein (Tahergorabi et al., 2016) which in turn induces macrophage infiltration and initiates cancer cell growth (Harvey et al., 2011).

1.8. Prostate cancer

1.8.1. Anatomy, structure, and function of the prostate

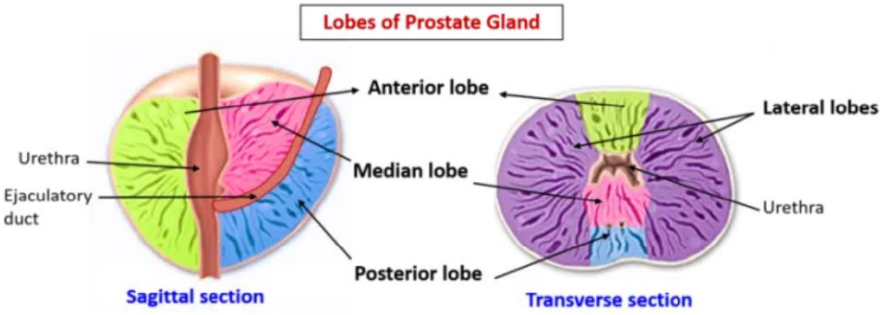
The prostate is a gland of the male reproductive system located in front of the rectum and just below the bladder (NCI, 2008). This gland is about the size of a chestnut and somewhat conical in shape, and consists of a base, an apex, an anterior, a posterior and two lateral surfaces (NCI, 2008). The main function of the prostate is to produce fluid for semen, which transports sperm during the male orgasm (NCI, 2008) (**Figure 1.10**).



Source: National Cancer Institute (2008)
Figure 1.10. Anatomy of prostate

The prostate consists of a base (the base is directed upward near the inferior surface of the bladder where the most part of this surface is directly continuous with the bladder wall), an apex (the apex part is directed downward and is in contact with the superior fascia of the urogenital diaphragm), an anterior, a posterior and two lateral surfaces (NCI, 2008).

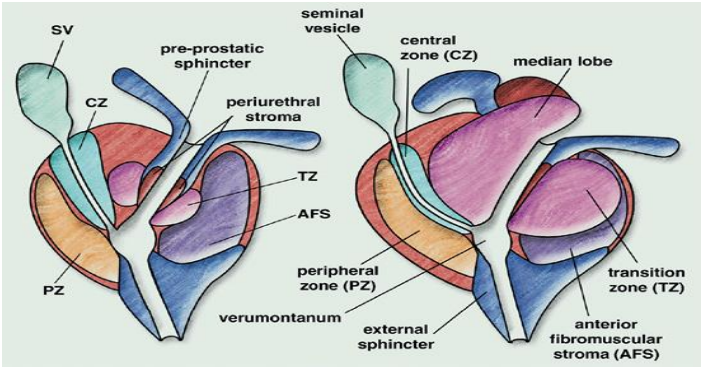
The prostate also is divided into several lobes. The anterior lobe lies in front of the urethra and is composed of fibromuscular tissue. The median lobe, which is cone-shaped, sits between the two ejaculatory ducts and the urethra. The lateral lobes (right and left) form the main mass of the gland and are separated by the urethra. The posterior lobe is the posteromedial part of the lateral lobes and can be palpated through the rectum during the digital rectal exam (DRE) (**Figure 1.11**) (NCI, 2008).



Source: https://anatomyqa.com/prostate-gland-anatomy/

Figure 1.11. The lobes of prostate

The prostate can also be divided according to function and includes the central (CZ), peripheral (PZ) and transitional (TZ) zones. Prostate cancer can spread from one of these zones, and most prostate cancers start in the peripheral zone (**Figure 1.12**) (NCI, 2008).



Source: https://www.pinterest.co.uk/pin/53128470579163442/

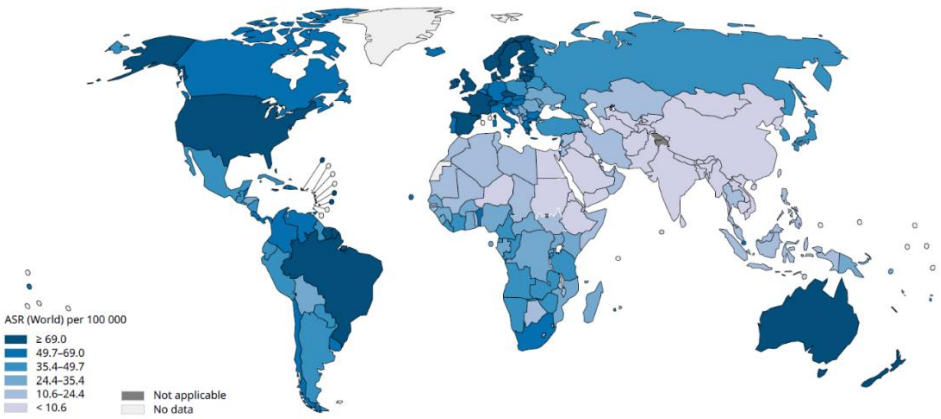
Figure 1.12. The zones of the prostate gland

1.8.2. Prostate cancer statistics

1.8.2.1. Incidence

According to the 2018 Globocan report using data from the International Agency for Research on Cancer (IARC), prostate cancer incidence was estimated at 1,276,106 new cases worldwide accounting for 7.1% of all cancers in men (Bray et al., 2018). There is however large geographical variation in the age-standardized rate (ASR) per 100,000 people (2018). The highest incidence was reported in Oceania (79.1/100,000), followed by North America

(73.7/100,000), and Europe (62.1/100,000). While the lowest incidence was recorded in Africa (26.6/100,000) and Asia (11.5/100,000) (Rawla, 2019) (**Figure 1.13**).



Source: IARC (2020)

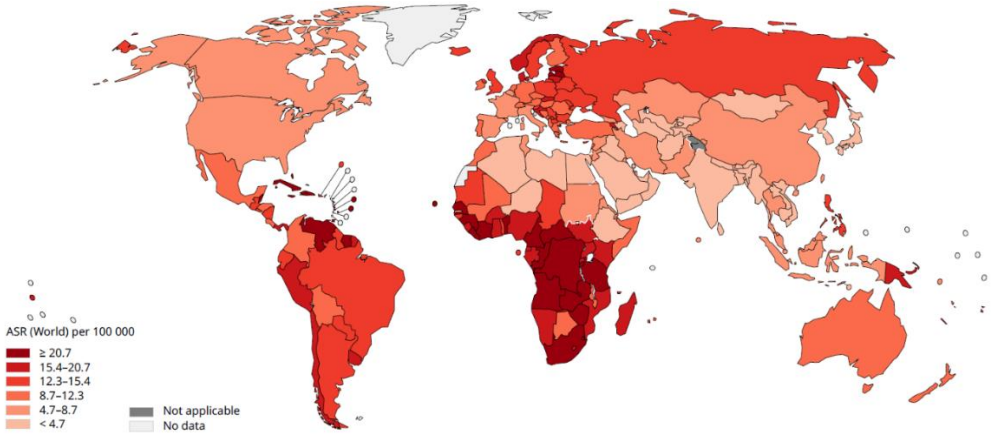
Figure 1.13. Estimated age-standardized incidence rates of prostate cancer worldwide in 2018

The incidence of prostate cancer increases with age, it was estimated that 1 in 350 men under the age of 50 were diagnosed with prostate cancer and this number increased in the age group between 50-59 years with the peak incidence of prostate cancer found in groups of men over 65 years old (60% of all incident cases) (Rawla, 2019). Based on the review by Rawla (2019), it was reported that African Americans have the highest incidence of prostate cancer. This review also reveals that the incidence of prostate cancer was not only high in the African American group but also in the Caribbean, and black men in Europe which reinforces the assumption of a genetic predisposition to the disease (Rawla, 2019).

1.8.2.2. Mortality

Prostate cancer mortality rates per 100,000 recorded in 2018 were highest in South America and Southern Africa, as well as in Northern and Eastern Europe. Mortality statistics from 2018 were reported in Central America (10.7) followed by New Zealand (10.2) and Western Europe (10.1) (IARC, 2020b). Conversely, a low mortality rate was reported by Asia (South-central 3.3, Eastern 4.7 and South-east 5.4) and Northern Africa (5.8) (IARC, 2020b). On the other hand, the largest percentage of deaths from prostate cancer was recorded by

Asia (33.33%) followed by Europe (29.9%) where most of the deaths (55%) were associated with age particularly in the over 65 year age group (IARC, 2020b) (**Figure 1.14**).



Source: IARC (2020)

Figure 1.14. Estimated age-standardized mortality rates of prostate cancer worldwide in 2018

1.8.2.3. Trends

The trend of increasing prostate cancer incidence is expected to continue from 2018 to 2040 (Rawla, 2019). In 2040 it is estimated that there will 1,017,712 new cases (+ 79.8% overall change) worldwide (IARC, 2020c). It is estimated that in 2040, the highest incidence of prostate cancer will be recorded in Africa (+120.6%), followed by Latin America and the Caribbean (+ 101.1%) and Asia (+ 100%) while vice versa will be reported to decrease in Europe (- 30.1%) (Rawla, 2019). The expected increase in incidence is related to increased life expectancy and greater access to health care and prostate cancer screening (Rawla, 2019). Mortality rates are thought to increase by 92% by 2040 resulting in 720,661 deaths worldwide (IARC, 2020d). The highest mortality increase is expected in Africa (+ 124.4%) followed by Asia (116.7%) while the lowest is expected in Europe (58.3%) (Rawla, 2019). The distribution of mortality is thought to be related to screening capabilities, the availability of supporting health services which may still be a problem both in Africa and parts of Asia (Rawla, 2019) (**Table 1.2**).

Table 1.2. Estimated number of incidence and mortality from 2018 to 2040, prostate cancer, males, all ages

		2018			2040	
		Number	Number	Demographic change	Change in risk	Overall change
Incidence						
Africa	Males APC (0%)	80,791	178,634	97,663 (120.6%)	97,663 (+120.6%)	97,663 (+120.6%)
Latin America and the Caribbean	Males APC (0%)	190,385	382,808	192,423 (+101.1%)	192,423 (+101.1%)	192,423 (+101.1%)
North America	Males APC (0%)	234,278	312,901	78,623 (+33.6%)	78,623 (+33.6%)	78,623 (+33.6%)
Europe	Males APC (0%)	449,761	585,134	135,373 (+30.1%)	135,373 (+30.1%)	135,373 (+30.1%)
Asia	Males APC (0%)	297,215	597,180	299,965 (+100.9%)	299,965 (+100.9%)	299,965 (+100.9%)
Mortality						
Africa	Males APC (0%)	42,298	94,909	52,611 (+124.4%)	52,611 (+124.4%)	52,611 (+124.4%)
Latin America and the Caribbean	Males APC (0%)	53,798	124,990	71,192 (+132.3%)	71,192 (+132.3%)	71,192 (+132.3%)
North America	Males APC (0%)	32,686	65,766	33,080 (+101.2%)	33,080 (+101.2%)	33,080 (+101.2%)
Europe	Males APC (0%)	107,315	169,865	62,550 (+58.3%)	62,550 (+58.3%)	62,550 (+58.3%)
Asia	Males APC (0%)	4,465	9,179	4,714 (+105.6%)	4,714 (+105.6%)	4,714 (+105.6%)

Source: modified from Rawla (2019)

1.8.2.4. Survival

The United States of America reported a 5-year survival rate of 98% (SEER cancer statistics review data, 1975-2013) while Europe followed with 83% (EUROCARE-5 data, 1999-

2007) (Rawla, 2019). This relatively high survival rate is associated with early detection (Rawla, 2019). Furthermore, a study reported that prostate cancer recurrence within 10 years could be accompanied by a higher risk of death (Capocaccia et al., 2016).

1.8.3. Aetiology of prostate cancer

Although there has been significant progress in prostate cancer therapy, which has resulted in increased survival rates, the aetiology of prostate cancer is still unclear today (Sierra et al., 2016). According to The American Cancer Society (2020), the complexity of prostate cancer aetiology involves multiple factors and this has contributed to the difficulty of understanding the aetiology of prostate cancer (ACS, 2020).

1.8.3.1. Diet

WCRF (2018) has reported several potential studies about a diet that might be associated with prostate cancer such as high energy-dense foods and sugary drinks, low dietary fibre, high red meat and processed meat, drinking alcohol and high salt. Other studies have also stated that high red meat and dairy product, and a lack of fruit and vegetable consumption might be associated with increased risk and progression of prostate cancer (ACS, 2020, Buschemeyer and Freedland, 2007). While others reported a weak association between energy intake imbalance and prostate cancer incidence (ACS, 2020, Mustafa et al., 2016).

1.8.3.2. Obesity

A link between obesity and prostate cancer has been suggested, where obese people may have an increased risk of prostate cancer due to changes in existing metabolism (Bays et al., 2013). Obesity is the only modifiable lifestyle factor that the WCRF has recognized to have a probable role in increasing the risk of advanced prostate cancer. Insulin resistance, changes in lipid profiles and disruption of satiety hormones and their entire process have been suggested as a connector between obesity and prostate cancer. The potential mechanisms

contributing to the association between obesity and cancer were discussed in the previous obesity section.

Epidemiological studies have reported that obesity can have an impact on prostate cancer by reducing the effectiveness of screening thereby causing detection bias, facilitating tumour growth, reducing the effectiveness of treatment, and reducing survival rates through increasing tumour aggressiveness via mechanisms involving insulin, adipokines, and androgens (Wooding and Rehman, 2014). Activation of the intracellular transduction pathway of insulin can promote cell growth, especially when insulin levels are high such as in obesity (Parikesit et al., 2016). When hyperinsulinemia occurs, there is an increase in IGF-1, a recognized growth factor in many cancers, which induces growth and prevents cell apoptosis (Parikesit et al., 2016). On the other hand, high insulin levels also inhibit the production of sex hormone binding globulin (SHBG) which is important for regulating testosterone and dihydrotestosterone which are important in prostate gland development, prostate cancer progression, and early stages of prostate cancer growth (Parikesit et al., 2016).

The association between obesity and prostate cancer has mainly been studied using BMI (Langlais et al., 2019). BMI was stated to be associated with a higher risk tumour at diagnosis as measured by the Cancer of the Prostate Risk Assessment (CAPRA) tool (obese OR 1.32 95% CI 1.07-1.64 and very obese OR 1.68 95% CI 1.21-2.34, p trend = 0.003) as well as upward T-classification between biopsy and surgery (obese OR 1.37 95% CI 1.02-1.82 and very obese OR 1.81 95% CI 1.18-2.75, p trend = 0.018) after adjustment (Langlais et al., 2019). BMI was also associated with increased all-cause mortality both after adjustment for clinical (obese OR 1.26 95% CI 0.94-1.69 and very obese OR 1.76 95% CI 1.14-2.72, p trend <0.001) or surgical features of the tumour (obese OR 1.15 95% CI 0.83-1.59 and very obese 1.52 95% CI 0.93-2.49, p trend = 0.008) (Langlais et al., 2019).

Apart from BMI, obese men are also recognized through the increased distribution of visceral body fat, reflected by an elevated waist circumference and waist to hip ratio (Lavalette et al., 2018). Researchers have reported that the bigger the waist, men have a trend of a higher risk of prostate cancer OR 1.80 (95% CI 1.13-2.88) (p trend = 0.02) likewise if waist to hip ratio > = 1, they will also experience an increased risk of prostate cancer OR 1.56 (95% CI 1.01-2.42) (p trend = 0.04) (Lavalette et al., 2018).

1.8.3.3. Age

The majority of men aged 50 years of more have prostate cancer, however, this cancer rarely found in men below the age of 40 (ACS, 2020). The risk of prostate cancer increased with age (Mustafa et al., 2016). When men are under 65 years of age, it is those with a first-degree family history (father or brother) who have the highest incidence rate of prostate cancer (Kicinski et al., 2011).

1.8.3.4. Family history

Family history was associated with increased prostate cancer risk although many men with prostate cancer also found without this attribute (ACS, 2020, Kicinski et al., 2011, Sierra et al., 2016). Furthermore, various genes have been linked with familial background and prostate cancer such as tumour suppressor genes (BRCA1 and BRCA2), the hereditary prostate cancer gene (HPC1), variants in androgen receptors, vitamin D receptors, and TMPRSS2-ETS gene family fusion (TMPRSS2-ERG or TMPRSS2-ETV 1/4) (ACS, 2020, Kral et al., 2011, Mustafa et al., 2016). However, no single gene with a large effect on prostate cancer risk has yet been identified, and therefore the roles of individual genes might relatively small compared with other factors (Alvarez-Cubero et al., 2013, Di Sebastiano et al., 2017, Kral et al., 2011).

1.8.3.5. Ethnicity

Studies revealed that African and Caribbean men have a higher risk of prostate cancer than men with other ethnic backgrounds. While African American men were reported 60% higher incidence rates of prostate cancer and 2.4-fold greater mortality rates compared with others (ACS, 2020, Mustafa et al., 2016, Odedina et al., 2009, Sierra et al., 2016).

1.8.3.6. Geography

Despite an incomplete understanding of the relationship between geography and prostate cancer development, rates in North America, North-western Europe, Australia and Caribbean-island population tend to be higher than in Asian populations (ACS, 2020). These differences in incidence rates may also be the result from an interaction between geographical factors and differences in genetic background or environmental factors such as lifestyle and dietary practices which may significantly influence prostate cancer development (Alvarez-Cubero et al., 2013, Di Sebastiano et al., 2017).

1.8.4. Symptoms of prostate cancer

Prostate cancer often does not show symptoms until the tumour is large enough to compress the urethra, causing urinary complaints to appear in patients. These complaints are often also found in the condition of benign prostate hyperplasia, so further investigation is needed to ascertain whether these complaints originate from cancer, and these investigations can involve a digital rectal exam (DRE) and/or prostate biopsy to sample the tissue. The following are symptoms of prostate cancer (CRUK, 2019):

a. passing urine more often
b. getting up during the night to empty the bladder (nocturia)
c. difficulty passing urine; this includes a weaker flow, not completely emptying the bladder and straining when starting to empty the bladder

d. urgency

e. blood or semen in the urine

1.8.5. Staging and grading of prostate cancer

1.8.5.1. Stage

Prostate cancer stage is a description of the size and spread of prostate cancer in a person, determined by DRE and imaging techniques. The clinical staging system used in prostate cancer is the Tumour Nodes Metastasis (TNM) staging system. This staging system provides information about whether the tumour has spread to lymph nodes or other parts of the body (metastasis) (Macmillan, 2019).

1.8.5.1.1. Tumour (T)

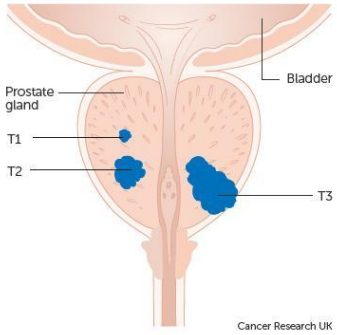
Stage 1 and 2 tumours are known as early (localized) prostate cancer (Macmillan, 2019).

a. Stage T1 is a condition where the prostate cancer is so small that it is not palpable on rectal examination or not visible through a scan. Cancer can be diagnosed by biopsy or PSA (Macmillan, 2019) detection. When prostate cancer is staged based on a tissue biopsy this is referred to as the pathological stage. This stage consists of T1a (the cancer is in less than 5% of removed tissue) stage, T1b (the cancer is ≥ 5% of removed tissue) and T1c (cancer is found by biopsy) (CRUK, 2019).

b. Stage T2 is a condition where the tumour is still inside the prostate and is detected by rectal examination (Macmillan, 2019, CRUK, 2019). Stage T2 consists of T2a (the cancer is in only half on one side of the prostate gland), T2b (the cancer is in more than half of the side of the prostate gland, but not both sides) and T2c (the cancer is both sides) (CRUK, 2019).

Stage 3 is known as locally advanced prostate cancer (Macmillan, 2019).

c. Stage T3 is a condition where the tumour has come out of the prostate capsule and may have spread to the seminal vesicles (Macmillan, 2019). Stage T3 consists of stage T3a (cancer has broken through the capsule of the prostate gland) and T3b (cancer has spread into the tubes that carry semen (seminal vesicles) (**Figure 1.15**) (CRUK, 2019).

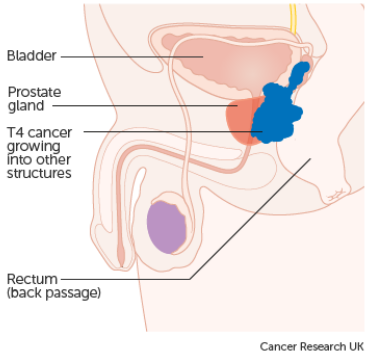


Source: CRUK (2019)

Figure 1.15. Stage 1 to 3 of tumour prostate cancer

Stage 4 is known as advanced (metastatic) prostate cancer (Macmillan, 2019).

a. Stage T4 is a condition in which cancer has spread to nearby body parts such as rectum (back passage), bladder or pelvic wall (**Figure 1.16**) (CRUK, 2019).



Source: CRUK

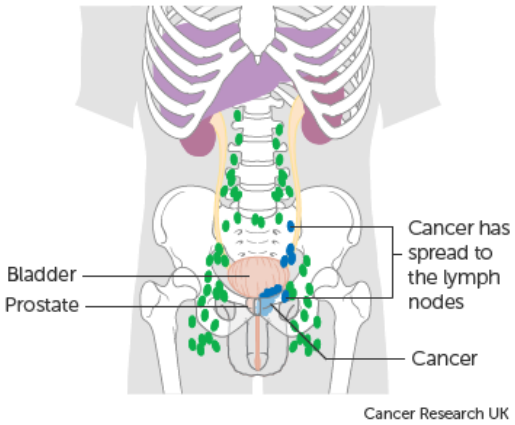
Figure 1.16. Stage 4 of tumour prostate cancer

1.8.5.1.2. Node (N)

The node describes whether cancer has spread in lymph nodes which are classified as (CRUK, 2019):

a. N0 is a condition in which cancer cells do not spread to nearby lymph nodes.

b. N1 is a condition where cancer cells have spread to lymph nodes around it (**Figure 1.17**)



Source: CRUK

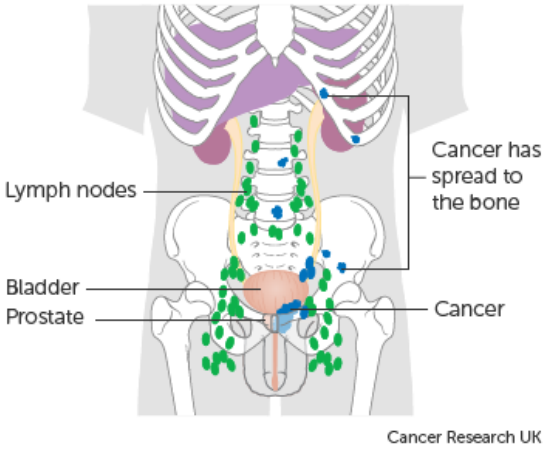
Figure 1.17. Nodes spread in prostate cancer

1.8.5.1.3. Metastasis (M)

Metastasis describes whether cancer has spread to other parts of the body classified as (CRUK, 2019):

a. M0 is a condition in which cancer cells do not spread to other parts of the body.

b. M1 is a condition in which cancer cells have spread to other parts of the body, consisting of M1a (cancer has spread to lymph nodes outside the pelvis), M1b (cancer has spread to bone cells) and M1c (cancer has spread to other parts of the body) (**Figure 1.18**).



Source: CRUK

Figure 1.18. Metastasis in prostate cancer

1.8.5.2. Grade

Grading in prostate cancer is used to describe the degree of differentiation of the tumour cells which is an indicator of their aggressiveness. Here are the grading categories in prostate cancer (Macmillan, 2019):

1.8.5.2.1. Gleason score

Gleason score gives a picture of the pattern of cancer cells in the prostate on a scale of 1 (very similar to normal prostate cells) to 5 (very different from normal prostate cells). Grades 1 and 2 are no longer used in clinical practice. Each tumour is assigned two grades, the first refers to the grade of the dominant area of tumour and the second to the less common pattern. The two grades are then added together to give a range from 6 to 10. The following is the grading used:

a. Gleason score 6 is a condition where cancer cells grow slowly and are less likely to spread.
b. Gleason score 7 is a condition in which cancer cells show intermediate growth
c. Gleason score 8 to 10 is a condition where cancer cells grow fast and spread (high grade)

The grading scheme in prostate cancer has been recently revised to the grade group system, namely:

a. grade 1 group (Gleason score 6) is the lowest grade and cancer is not likely to spread
b. grade 2 group (Gleason score 3 + 4 = 7)
c. grade 3 group (Gleason score 4 + 3 = 7)
d. grade 4 group (Gleason score 8)
e. grade 5 group (Gleason scores 9 and 10).

1.9. Androgen deprivation therapy (ADT) for prostate cancer

Androgen deprivation therapy (ADT) is mainly used for symptomatic metastatic prostate cancer therapy. This therapy is widely used in men with biochemical recurrence (i.e. a PSA relapse) after prostatectomy or radiation therapy, locally advanced disease, lymph node metastases, and asymptomatic metastatic disease (Sountoulides and Rountos, 2013). This therapy refers to interventions that deactivate androgen receptor signalling in target cells either through reduced testosterone production or inhibition of androgen receptors (Connolly et al., 2012).

1.9.1. Indication for use of ADT

ADT is used to treat clinically localized and locally advanced prostate cancer. According to Connolly (2012), patients in the T1 and T2 tumour categories were the groups referred to in the clinically localized definition, although T3a patient category has also included as clinically localized disease by some references. More detailed indications for the use of ADT were clinically localized patients with T2b/c disease, Gleason score 7 or PSA levels 10-20 ng/ml which are considered to have a moderate risk of disease recurrence and those with clinically localized T3a tumours, Gleason score 8-10 or PSA level> 20 ng/ml which was considered a high risk of disease recurrence (Connolly et al., 2012). Whereas locally advanced

prostate cancer patients according to this review were patients with category T3b/4 who were considered very high risk (Connolly et al., 2012).

1.9.2. ADT Type

According to Connolly et al (2012), ADT therapy is done through several methods. The first method can be done with surgery. The castration surgery with bilateral orchiectomy has been known since the 1940s and is a method known to rapidly reduce testosterone levels, but its use has been greatly reduced because it is an irreversible method and has the potential to cause physiological distress (Connolly et al., 2012). The second method is the most commonly used method that is medical castration. This method generally increases the production of endogenous luteinizing hormone (LH) and follicle-stimulating hormone (FSH) and requires combination therapy to produce the maximum effect (Connolly et al., 2012). Whereas the third method is the use of anti-androgens which bind to androgen receptors to competitively inhibit testosterone and dihydrotestosterone (DHT) attachment.

1.9.3. Side effects of ADT

ADT has some common side effects such as sexual disorders which include decreased libido and erectile dysfunction; changes in body composition which include gynecomastia, weight gain, reduce muscle mass and muscle tone, and increased subcutaneous and abdominal fat; cognitive impairment (memory loss); and metabolic disorders consisting of hyperglycaemia, impaired fat profile, decreased insulin sensitivity, and osteoporosis (Sountoulides and Rountos, 2013). Side effects can also be divided into short and long term as revealed by Allan et al (2014) in the following table:

Table 1.3. The side effect of ADT by time

Short time	Long time
Reduce the quality of life including mood and cognition	Osteoporosis
Hot flushes	Type 2 diabetes mellitus
Sexual dysfunction (loss libido and erectile dysfunction	Cardiovascular disease
Increased fat mass and loss of skeletal muscle	
Increased total, LDL, HDL cholesterol and TG levels	
Hyperinsulinemia	

Source: Allan et al (2014)

The decreased libido and erectile dysfunction experienced by patients resulted from the combination of decreased testosterone and other factors (Higano, 2003, Sountoulides and Rountos, 2013). The erectile dysfunction is a result of a decrease in tissue response to vasodilators which results in decreased blood 'inflow' and decreased tissue compliance which causes an increase in 'outflow' where all these processes will result in an inability to obtain an adequate erection (Allan et al., 2014).

Hot flashes were often found in prostate cancer patients with ADT. Hot flashes were characterised with warm conditions in the face, neck, upper chest and back that last from seconds to hours in duration. This condition frequently caused discomfort and disrupted daily activity (Higano, 2003). Hot flashes can occur due to inappropriate stimulation of body temperature regulators in the hypothalamus which causes vasodilation of peripheral vessels (Sountoulides and Rountos, 2013).

ADT administration also resulted in decreased bone mineral density (Higano, 2003). The administration of ADT resulted in a 3-5% decrease in bone mineral density with each year of use, with prostate cancer patients on ADT overall having a 6-17% lower bone mineral density than those not taking ADT (Sountoulides and Rountos, 2013). Another review reported that the rate of bone loss was five to ten times higher with ADT treatment (Allan et al., 2014).

ADT also increased the risk of fractures six times higher annually (Sountoulides and Rountos, 2013) and was associated with 21-45% increased clinical fracture risk (Smith, 2015). Furthermore, in the early stages of ADT administration, patients also reported experiencing the flare phenomenon although that was unusual (Pollen et al., 1984). The flare is a state of a surge of serum testosterone that arises due to LHRH receptor stimulation in the early weeks of treatment that may reflect the healing of bone lesions. Although, the effect of this phenomenon was one of concern because it has been associated with spinal cord compression and fractures, but only in <1% of patients (Sountoulides and Rountos, 2013).

Anaemia that was normochromic normocytic anaemia (i.e. anaemia in which the red blood cells are of average size and contain normal amounts of haemoglobin) was also found in the prostate cancer patients treated with ADT (Higano, 2003). In a review article by Soutoulindes and Rountous (2013), researchers suspect a role for androgens in the hematopoietic system through erythropoietin stimulation, increasing bone marrow activity and iron incorporation into the red cells, with these pathways indirectly inhibited by ADT. It was estimated that ADT administration associated with a >10% reduction in haemoglobin levels, resulting in symptomatic anaemia cases in approximately 10% of prostate cancer patients (Sountoulides and Rountos, 2013). The use of ADT was associated with a three-fold increase in the risk of anaemia in men with this therapy when compared to not using it (23.5 vs 5.9 per 100 person-years) (Hicks et al., 2017).

While another side effect of ADT was the emergence of mental and emotional disorders. According to Higano (2003), prostate cancer patients with ADT experience substantially more mood swings, emotions, depressive symptoms or anxiety that result in decreased quality of life. Based on a retrospective study the percentage of depression and cognitive impairment was found to be higher in prostate cancer patients compared to people without prostate cancer (31.3% vs. 23.7%, $p < 0.001$) (Allan et al., 2014). On the other hand, ADT also results in a decrease in memory and attention which causes a decrease in self-esteem

in patients which also impacts on quality of life (Sountoulides and Rountos, 2013). Patients with ADT have decreased scores related to immediate attention span, working memory and visual-spatial function or have decreased score for at least one cognitive domain (Allan et al., 2014)

ADT administration can be associated with lipid profile changes. Baseline data in patients with ADT have shown an increase in total and LDL cholesterol over a period of ≥ 12 months (Basaria et al., 2006). While other studies also mentioned an increase in HDL in addition to an increase in total and LDL cholesterol (Smith et al., 2002). The effects of various ADTs have also been reported by a review (Allan et al., 2014).

Changes in body composition that occur during the use of ADT in prostate cancer patients have been reported in several studies (Haseen et al., 2010a, Smith et al., 2002). A review conducted by Haseen (2010) reported varied changes with an average reduction of 2.8% of muscle mass and a 7% increase in body fat mass from the studies analysed. Another review conducted by Allan et al (2014) also underlined the adverse effects of ADT on changes in body composition.

The possible mechanism between the administration of ADT and changes in body composition is based on the relationship between androgens and obesity. Obese men are reported as having decreased testosterone and gonadotropins, while Luteinizing Hormone (LH) and Follicle-stimulating Hormone (FSH) were normal or slightly reduced (Pasquali, 2006). Administration of ADT will disrupt the balance of secretion, transport, and metabolism or the action of these hormones. Disturbances in LH and FSH are reported which will indirectly result in an increase in waist to hip ratio and total adiposity. Meanwhile, testosterone, whose role is still being debated in prostate cancer, is also associated with the presence of the abdominal obesity phenotype in men. According to Pasquali (2006), obesity itself is also said to affect sex-hormone-binding globulin (SHBG) through the insulin resistance mechanism. In addition,

when BMI increases, LH will progressively decrease which will worsen adiposity. High leptin levels in obesity are also said to be an important contributor to lowering testosterone levels. Based on these reviews, it can be understood that the cycle of mechanisms can exacerbate one another, with ADT playing a role in triggering it

Metabolic disorders and cardiovascular morbidity due to suppression of the hormone testosterone have also been reported in ADT patients. ADT administration was associated with insulin resistance (Allan et al., 2014), obesity, elevated levels of triglycerides and abdominal fat and HDL, all of which are markers of the metabolic syndrome (Sountoulides and Rountos, 2013). In addition, Sountoulindes and Rountos (2013) also found that ADT was thought to be associated with some evidence of cardiovascular morbidities, such as earlier myocardial infarction events and an increased risk of dangerous vascular toxicity. A study in 2017 reported that ADT was associated with a higher risk of heart failure (adjusted HR 1.81, 95% CI 1.40–2.32) in men without pre-existing CVD. While this study also reported an association between ADT and increased arrhythmia risk (adjusted HR 1.44, 95% CI 1.02–2.01) among patients with pre-existing cardiovascular disease (Haque et al., 2017).

This thesis is structured to review the relationship between obesity and prostate cancer which has not been fully explained. The overall objective of this project is to study the role of adipokines (leptin and adiponectin) and lipid profiles as possible contributors to the interactions between obesity and prostate cancer. To answer these main objectives, the second chapter presents a systematic review and meta-analysis of leptin and adiponectin in relation to prostate cancer risk, aggressiveness, and progression. This systematic review and meta-analysis were conducted to provide a comprehensive review of the association between adipokines, namely leptin and adiponectin, with risk, aggressiveness and progression of prostate cancer. To make a comprehensive review, the review involved not only studying the serum levels of each adipokine but also in terms of DNA (single nucleotide polymorphisms,

SNPs) and receptor expression. The unique result of this chapter is the mapping of research conducted to date, in which it reveals the findings of published studies in this area, as well as identifying which areas are still lacking in our knowledge of the association of obesity with prostate cancer risk, aggressiveness and progression. Systematic review and meta-analysis can also show the direction of the existing relationships between obesity and prostate cancer and how these relationships were investigated by each study. These results can then be used to formulate suggestions regarding future studies that are needed.

Furthermore, in chapter three, an existing Randomized Controlled Trial (RCT) to test the efficacy of a 6-month dietary and physical activity intervention on the dietary intake and lipid profiles of prostate cancer patients receiving ADT is discussed. The post-hoc analysis conducted on this RCT evaluated the efficacy of a six-months dietary and physical activity intervention on these secondary outcomes. These results will describe the impact of the intervention on dietary behaviour, the lipid profile and the Q-Risk score (an algorithm for predicting cardiovascular disease) of patients recruited to this RCT, determining the efficacy of this dietary and physical activity intervention and associated weight loss on the cardiovascular health and lifestyle behaviours of prostate cancer patients treated with ADT, and also exploring the different levels of adherence to the lifestyle guidelines and outcomes responses. The results of this chapter are focused on discovering whether the intervention exerted any effects on lipid profiles, and how these results can then be used to give additional knowledge in treating prostate cancer.

In chapter four, this thesis examines the results of survival analysis testing the association between adipokines, lipid profile, insulin, and all-cancer and prostate cancer mortality in the PRIME cohort. This analysis was carried out to see whether various metabolic factors associated with obesity had an influence on male mortality related to prostate cancer. It was hoped that the results of this cohort analysis would be reactive to and provide answers

to the gaps found from the results of systematic review and meta-analysis in the earlier chapter. In the end, the combination of the results of the three chapters will provide a more complete explanation of the relationship between obesity, adipokines, lipids and prostate cancer.

2. A Systematic Review and Meta-analysis of Leptin and Adiponectin in relation to Prostate Cancer Risk, Aggressiveness and Progression.

2.1. Introduction

Prostate cancer is currently the second most commonly diagnosed cancer among men worldwide (Bray et al., 2018), and the highest incidence rates are found in developed countries (Siegel et al., 2019, Center et al., 2012). While differences in prostate specific antigen (PSA) screening rates do contribute to this, geographic variation in incidence rates, differences in lifestyle factors and non-communicable disease risk factors, including dietary patterns, physical activity, and obesity may also play a role. Obesity has been identified as a potentially modifiable risk factor for both advanced and lethal prostate cancer (WCRF, 2018). Obesity, affecting 13% or 650 million adults worldwide in 2016 (WHO, 2019b), has been associated with increased incidence of aggressive prostate cancer, higher risk of biochemical recurrence after treatment, and increased prostate cancer-specific mortality (Allott and Hursting, 2015, Dickerman et al., 2017, Freedland et al., 2019, Candelaria et al., 2017, Freedland and Aronson, 2004, Siegel et al., 2019).

Alterations in adipokines such as leptin and adiponectin have been suggested as a potential mechanism linking obesity and prostate cancer (Di Sebastiano et al., 2018). Leptin and adiponectin have a substantial role in cell homeostasis (Ikeda et al., 2015). Higher leptin serum and receptor expression in obesity is also closely related to the processes of inflammation, cell differentiation, apoptosis, angiogenesis, and supports the development of metastatic cells (Candelaria et al., 2017, Guo et al., 2012). Several epidemiological studies have examined both leptin and adiponectin as a potential mechanism linking obesity and prostate cancer, with mixed findings (Kang et al., 2018, Lai et al., 2014, Medina et al., 2014, Rider et al., 2015).

A review of the polymorphisms of leptin, adiponectin and their receptors by Hu et al (2016) states that the role of leptin, adiponectin and receptors varies in prostate cancer; based on a meta-analysis the researchers found heterogeneity in the direction of association observed. According to researchers some genetic variants of the receptors (e.g. LEP and ADIPOQ) might be related to increased risk and some others (e.g. LEPR and ADIPOR1) might be related to reduced risk (Hu et al., 2016b). Another review focusing on serum leptin and adiponectin conducted by Angel et al (2019) stated that there was no relationship between leptin and incidence of total (RR 0.93 95% CI 0.75-1.16, p = 0.52) or advanced prostate cancer (RR 0.90 95% CI 0.74-1.10, p = 0.30). This review also reported that there might a weak inverse association between higher levels of adiponectin and risk of advanced prostate cancer (RR 0.81 95% CI 0.61-1.08, p = 0.15), however, there were not enough studies to analyse the association between adiponectin and prostate cancer incidence (Angel et al., 2019).

There does, therefore, appear to be some inconsistency in the literature regarding the adipokines and their relationship with prostate cancer, and the observations may depend on how the adipokines are measured, and differ according to cancer stage. This review builds on the data synthesis conducted in previous systematic reviews, but Hu et al (2016) focused only on genetic variants in leptin and adiponectin and their receptors in prostate cancer and the search is now over four years old. Angel et al (2019) is more recent, but it only focused on serum levels of adiponectin and leptin. This review aimed to comprehensively investigate the relationship of leptin and adiponectin through exploring serum levels, receptor expression and genetic polymorphisms in relation to prostate cancer risk, aggressiveness, and progression. The results of this review were expected to add evidence helping explain the relationship, which may be complex, between adipokines, obesity, and clinically relevant prostate cancer.

2.2. Methods

2.2.1. Data sources and search strategy

A systematic search strategy was developed in conjunction with a Medical librarian from the School of Medicine, Dentistry and Biomedical Sciences, Queen's University Belfast to identify studies eligible for inclusion in this review. Three electronic databases, MEDLINE, EMBASE and Web of Science, were searched for relevant articles published from database inception until March 2019. The search strategy contained a combination of several keywords and Medical Subject Headings (MESH) for prostate cancer ("carcinoma prostate" OR "malignant prostate" OR "prostatic adenocarcinoma") AND the adipokines leptin ("LEP" OR "LEPR" OR "OB gene") AND adiponectin ("ADIPOQ" OR "ADPN"OR "Adiponectin precursor"). The search strategy was limited to human, but no language or geographical restrictions were applied. A copy of the full search strategy in Medline, EMBASE and Web of Science is provided in appendix 1.

2.2.2. Eligibility criteria

The principal reviewer (F.A.N) independently screened all articles, while other reviewers (R.O.N and E.H.A) acted as second and third independent reviewers at the full-text stage. Any disagreements between reviewers were resolved via discussion. Initially, article titles were reviewed, and duplicates and review articles were excluded. The following predetermined inclusion criteria were subsequently applied:

a. observational designs (cohort, case-control, or cross-sectional studies) with a non-cancer population as a control group except for studies examining tumour aggressiveness, where some case-only studies comparing adipokine levels in aggressive vs. non-aggressive tumours were included,
b. prostate cancer cases with a histologically confirmed diagnosis,

c. studies providing either a measurement of serum adipokine levels, tissue expression of adipokines and/or genetic polymorphisms in leptin and/or adiponectin genes or their receptors.

Therefore, intervention studies, studies in which patients were treated with the drug and/or hormone therapies, cell line studies, and studies using benign prostate hyperplasia as a control group were excluded. Review of the reference lists of all articles was carried out to minimize the possibility of missing articles. The detail of this process can be seen in **Figure 2.1**.

Eligible studies were included in a narrative review, but accompanying meta-analyses were conducted where possible. Studies that reported effect estimates in the form of a hazard ratio (HR), odds ratio (OR), or relative risk ratio (RR) (and their corresponding 95% confidence intervals), or that provided enough information to calculate these effect estimates, were included in a series of meta-analyses. Studies included in the meta-analyses were grouped according to the type of adipokine (i.e. leptin or adiponectin), biological measurement (i.e. serum level, receptor expression or DNA), their outcomes (i.e. prostate cancer risk, tumour aggressiveness or progression) and according to the type of study design (i.e. (nested) case-control vs. cross-sectional).

2.2.3. Data extraction

The extracted data included information about the study's identity, exposure(s), covariates, outcome(s), and summary of findings. The study identity consisted of the author names, the publishing journal, publication year, geographic location, the overall aim/objective of the study, the study design, the number of cases (and controls, if relevant), and whether the research was part of a larger study. All information on the type of adipokine studied, whether leptin, adiponectin, or a combination of both, and information about how this exposure was assessed, whether by measuring serum levels, tissue expression of these

adipokines and/or their receptors, and/or genetic polymorphisms were also extracted. Also extracted was information about exposure classification for serum measurements (i.e. quartiles, quantiles or continuous) and outcome classification (i.e. risk defined as OR/RR/HR; aggressiveness defined as grade or Gleason score; or progression defined as, for example, earlier versus later stage). Information regarding the timing of blood sample collection relative to prostate cancer diagnosis, as well as the type of adipokine receptor and polymorphisms that were studied were also identified. The information regarding model covariates included in each study was also extracted. The final information extracted was the OR/RR/HR with 95% CI or equivalent and p-value to assess the relationship between adipokines and prostate cancer.

The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines were used to report the selection and reporting of articles for this systematic review and meta-analysis. As not all articles could be included in a meta-analysis, the narrative review portion involved the creation of tables containing the data extracted, as reported above, and the description of the balance of evidence according to adipokine type, how the adipokine was measured, the different stages of prostate cancer, and the study design used.

All studies included in the meta-analysis stage were analysed using their OR or RR values. There were no specific restrictions regarding adjusted variables used in the analysis, but the most complex or fully adjusted model was used where possible and the estimates had to have been adjusted for age and BMI ideally, or at least age to be included. This was based on the consideration of the limited number of studies. Random effect models were used to calculate summary risk estimates and 95% CIs from the studies included (DerSimonian and Laird, 1986). Meta-analyses were presented in forest plots, while the possibility of publication bias was explored with a funnel plot using a fixed-effect model and Begg's test (Begg and Mazumdar, 1994). The entire analysis process was carried out using the Review Manager 5

software (The Nordic Cochrane Centre TCC. Review Manager (RevMan) Version 5.3. 2014.). Inconsistencies among the studies involved were measured using the I^2 statistic, in which a value of 0-25% indicated low heterogeneity, a value of 26-50% indicated medium and more than 50% indicated substantial heterogeneity (Higgins and Thompson, 2002). Furthermore, a sensitivity analysis was carried out by removing one study at a time from the meta-analysis to determine which studies contributed greatly to the high I^2 (heterogeneity) value and whether their removal altered the results of the meta-analysis. The quality of the studies included in the meta-analyses was assessed using the Newcastle-Ottawa Scale (NOS) (Wells et al., 2019). The scoring process was based on three main things, namely on how the population selection was done, the comparability of the study and the explanation of the exposure classification. Although there are still no standard provisions regarding the NOS score limit to distinguish a high- or low-quality study, however, recently published study has reported that a study with average NOS value ≥ 7 is considered as a high-quality study (Islam et al., 2016).

2.3. Results

2.3.1. Search summary

A total of 3,447 articles were generated from searches in the three databases, with the addition of one article from reference checking. After excluding duplicate articles, as well as articles related to cell line and animal studies, 631 articles remained. Inclusion and exclusion criteria were then applied to the remaining abstracts, with 171 articles being retained to undergo a full-text examination. Finally, 42 articles were agreed by all reviewers as being eligible for the review. The detailed process of selecting articles is presented in the flow chart in **Figure 2.1**.

A total of 17 leptin studies reported an association between leptin and prostate cancer risk, which included 13 serum studies, three DNA studies and one receptor expression study. A total of 16 leptin studies reported an association between leptin and prostate cancer

aggressiveness, which consisted of 14 serum studies and two DNA studies. No studies explored the relationship between leptin and prostate cancer progression. A total of 14 adiponectin studies tested the association between adiponectin and prostate cancer risk which consisted of 8 studies in serum, 5 studies in DNA and one study which reported receptor expression (this study also reported serum levels, hence the disparity in overall numbers). The association between adiponectin and prostate cancer aggressiveness was reported by 17 studies with 15 measuring adiponectin in serum and two receptor expression (one study reporting both serum and receptor expression, hence the disparity in total numbers). Only two studies reported the association between adiponectin and prostate cancer progression, consisting of one DNA study and one receptor expression study.

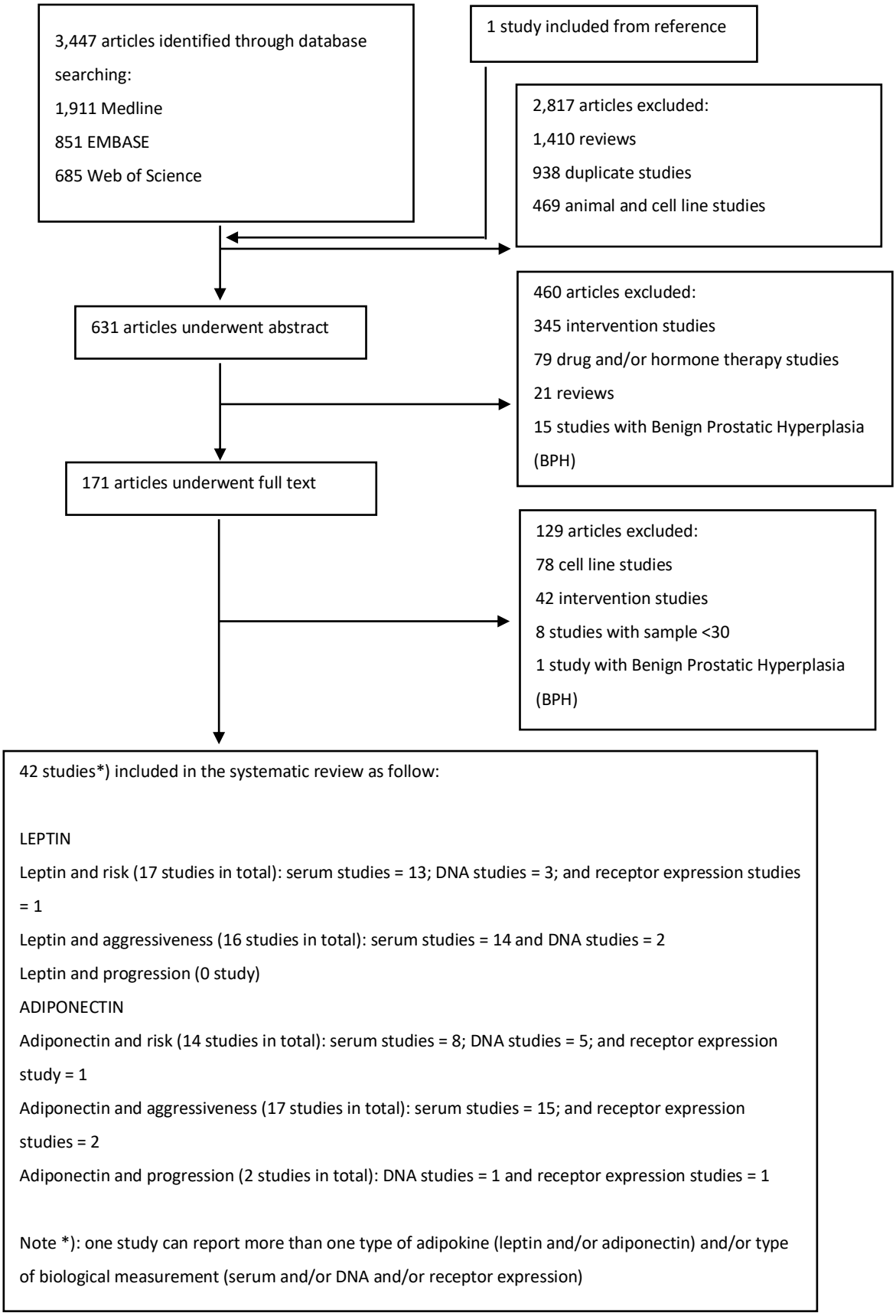


Figure 2.1. The PRISMA flowchart depicting the screening and article selection process

2.3.2. Narrative review of included studies

All the studies considered suitable for inclusion in the systematic review were first summarised narratively.

2.3.2.1. Leptin and prostate cancer risk

Seventeen studies discussed the relationship between leptin with prostate cancer risk. Six were nested case-control serum studies (Lai et al., 2014, Li et al., 2010, Stattin et al., 2003, Stattin et al., 2001, Stocks et al., 2007, Touvier et al., 2013), six were case-control serum studies (Arisan et al., 2009, Gade-Andavolu et al., 2006, Hsing et al., 2001, Lagiou et al., 1998, Saglam et al., 2003, Zhang et al., 2018), one was a cross-sectional serum study (Baillargeon et al., 2006), one a nested case-control DNA study (Moore et al., 2009), two case-control DNA studies (Kote-Jarai et al., 2003, Ribeiro et al., 2004) and one a case-control receptor study (Gade-Andavolu et al., 2006). The details of these studies are included in **Table 2.1** and **2.2**.

Of the six nested case-control serum studies which explored the association between leptin and prostate cancer risk, only one reported a significant relationship between leptin and prostate cancer risk. Stocks et al (2007) showed decreasing trend in prostate cancer risk associated with higher serum leptin (OR 0.55 95% CI 0.36-0.84, p = 0.006) though this association was only observed in patients <59 years of age at diagnosis. In addition, the researchers showed that for every one-unit increase in serum leptin, prostate cancer risk decreased (OR 0.93 95% CI 0.89-0.97, p = 0.002). In contrast, three nested case-control serum studies did not support a statistically significant relationship between leptin and prostate cancer risk. A study with long follow-up (> 17 years) published in 2003 by Stattin et al. was unable to detect an association between high serum leptin and prostate cancer risk, whether using unadjusted or adjusted models (OR 0.9 95% CI 0.6-1.6; OR 0.9 95 % CI 0.6-1.6, respectively). Similar results were also demonstrated by Li et al (2009) in a study in which

serum leptin was not associated with overall risk of prostate cancer (OR 1.06 95% CI 0.65-1.72, p = 0.8). Touvier et al (2013) also reported no significant association between high serum leptin and prostate cancer risk (OR 0.69 95% CI 0.27-1.75, p = 0.9). Two other nested case-control serum studies reported somewhat mixed results. Lai et al (2014) reported no overall association between serum leptin and prostate cancer risk (OR 0.85 95% CI 0.65-1.12, p = 0.14) although the researchers suggested an inverse relationship might exist when adjustments were made. Stattin et al (2001), reported that moderate, but not high levels of serum leptin were associated with an increased risk of prostate cancer (Q3 vs. Q1 RR 2.6 95% CI 1.4-4.8) and in those who had greater than the median follow-up (>3.9-year follow-up), researchers reported that this risk persisted (Q2&3 vs. Q1 RR 2.7 95% CI 1.2-6.4).

A total of six case-control serum studies also reported an inconsistent relationship between leptin and prostate cancer risk. Four case-control serum studies reported a statistically significant association between leptin and prostate cancer risk. Saglam et al (2003) reported a lower mean serum leptin level in men with organ-confined compared with those with advanced cancer (ng/mL) (19.01 ± 2.72 vs. 36.47 ± 12.73, p <0.001). Similarly, serum leptin levels were higher in those with a high Gleason score compared with those with lower Gleason score (33.15 ± 3.36 vs 19.52 ± 2.02, p = 0.003) which may explain the differences in prostate cancer risk. Furthermore, Arisan et al (2009) reported a statistically significant relationship between higher serum leptin and total serum PSA, biopsy or prostatectomy Gleason score, and age in prostate cancer patients (p <0.015). Zhang et al (2018) also showed that higher serum leptin was significantly positively correlated with PSA levels (r = 0.335, p <0.001). In previous studies conducted by Gade-Andavolu (2006), serum leptin was significantly higher in cases compared with controls (mean ± SE; 14.7 ± 1.38 vs. 7.88 ± 1.08, p <0.0001), indicating a possible association with prostate cancer risk. In contrast, one case-control serum study found no association between serum leptin and prostate cancer risk; the study by Lagiou et al (1998) reported that leptin levels were not significantly associated with

prostate cancer risk (p = 0.53), analysis of increased leptin levels (per 4 ng/mL) in the case group also did not show potential association (OR 0.70 95% CI 0.31 -1.55, p = 0.38). The remaining case-control serum study (16.7%) by Hsing et al (2001), reported mixed results. For example, men in the highest tertile of leptin had an approximately twofold risk of prostate cancer compared with men in the lowest tertile (OR 1.78 95% CI 1.07-2.95, p = 0.02), but the risk was attenuated when models were adjusted for age, education, BMI and waist-hip ratio (OR 1.10 95% CI 0.59-2.07, p = 0.66).

There was one cross-sectional study of serum leptin and prostate cancer risk (Baillargeon et al., 2006) and it showed that leptin was not significantly associated with prostate cancer risk (highest vs. lowest tertile) (OR 0.77 95% CI 0.28-1.37, p trend = 0.57).

A nested case-control genetic study by Moore et al (2009) reported no relationship between all variants of leptin receptor (LEPR) with prostate cancer risk. They did, however, show an association between genetic variation in the leptin gene (LEP) 14858 A> G locus (OR heterozygotes 0.76 95% CI 0.62-0.93; OR homozygotes 0.79 95% CI 0.60-1.04) and 13288 G> A (OR homozygotes 1.29 95% CI 0.99-1.67) and risk of prostate cancer.

However, two case-control DNA studies examined whether leptin was significantly associated with prostate cancer risk, and one demonstrated an association and one did not. Kote-Jarai et al (2003) reported no statistically significant association between OBR 109Arg genotype (OR homozygous 1.36 95% CI 0.65-2.85, p = 0.41) or 223Arg alleles (OR homozygous 0.82 95% CI 0.58-1.26, p = 0.39) and prostate cancer risk. However, Ribeiro et al (2004) reported that overrepresentation of single A-allele LEP in prostate cancer patients compared with control was significantly associated with a higher risk of prostate cancer in A carriers (OR 1.60 95% CI 1.13-2.28, p = 0.008) while the AA (OR heterozygous 2.93 95% CI 1.27-6.75, p = 0.003) and AG (OR homozygous 2.11 95% CI 1.20-3.71) genotypes of LEP carry a significantly higher risk of prostate cancer.

A case-control receptor expression study by Gade-Andavolu (2006) reported that there was a significant increase in the frequency of long alleles for LEP ($p < 0.008$) and LEPR ($p < 0.006$) gene polymorphisms in prostate cancer patients ($p < 0.02$) compared with the controls.

Therefore, in summary, if all methods of assessment of leptin are considered, while the majority of case-control studies support an association between leptin and prostate cancer risk, this is less consistently supported by nested case-control studies, which would be considered a methodologically stronger study design, and is not supported by the single, and weaker, cross-sectional study (**Table 2.1**). If the type of measurement is considered, then, similarly, the evidence base for the association can be described as mixed for both serum and DNA, whereas for receptor expression there is only one study published to date.

Table 2.1. Summary association for leptin and prostate cancer risk

No	Author (Year)	Study Design	Biological measurement	Association	
				Type	Direction
1	Stattin (2001)	Nested case-control	Serum	Mixed	not linear
2	Stattin (2003)	Nested case-control	Serum	Not associated	n/a
3	Stock (2007)	Nested case-control	Serum	Associated	-
4	Li (2010)	Nested case-control	Serum	Not associated	n/a
5	Touvier (2013)	Nested case-control	Serum	Not associated	n/a
6	Lai (2014)	Nested case-control	Serum	Mixed	n/a; potentially -
7	Lagiou (1998)	Case-control	Serum	Not associated	n/a
8	Hsing (2001)	Case-control	Serum	Mixed	potentially +
9	Saglam (2003)	Case-control	Serum	Associated	+
10	Gade-Andavolu (2006)	Case-control	Serum	Associated	+
11	Arisan (2009)	Case-control	Serum	Associated	+
12	Zhang (2018)	Case-control	Serum	Associated	+
13	Baillargeon (2006)	Cross-sectional	Serum	Not associated	n/a
14	Moore (2009)	Nested case-control	DNA	Mixed	potentially +
15	Kote-Jarai (2003)	Case-control	DNA	Not associated	n/a
16	Ribeiro (2004)	Case control	DNA	Associated	+
17	Gade-Andavolu (2006)	Case-control	Receptor expression	Associated	+

Note: (+): positive, higher leptin-increased risk or lower leptin-decreased risk, (-): negative, higher leptin-decreased risk or lower leptin-increased risk, (potentially): mixed results, but suggested direction given, n/a: not applicable; no significant association detected

Table 2.2. The list of leptin and prostate cancer risk studies reviewed base on type of outcome, type of biological measurement and type of study design.

No	Author, (Year)	Country, (participants)	Type of outcome	Type of biological measurement	Type of Study Design	Exposure	Covariates	Summary
Leptin and prostate cancer (risk; serum; nested case control)								
1	Stattin et al, (2001)	Sweden, (149 PCA, 298 controls) [a]	Risk	Serum	Nested case-control	Levels of leptin (Quantiles: $Q_{4\text{-}5}$ >5.5 vs. Q_1 ≤2.5); blood donated before prostate cancer diagnosis (median of 3.9 years prior to diagnosis)	Univariate: unadjusted; Multivariate: *Model 1* - adjusted for BMI, insulin, cholesterol, fasting and post load glucose, diastolic and systolic BP, smoking, snuffing, IGF-I, IGFBPs 1-2, testosterone, and SHBG.	Relative risk of prostate cancer was associated with an intermediate range of plasma *leptin* Univariate: (RR $_{unadjusted}$ Q2 2.1 95%CI 1.1-4.1); Q3 2.6 95%CI 1.4-4.8) Multivariate: (RR $Q_{2\text{-}3}$ 2.3 95% CI 1.2-4.2); In the group with a follow-up time more than median (>3.9 yrs.), the increased risk for intermediately elevated levels of leptin was still significant (RR $Q_{2\text{-}3}$ 2.7 95% CI, 1.2– 6.4). Risk was not significantly increased at higher levels of plasma leptin.
2	Stattin et al, (2003)	Norway, (200 PCA, 397 controls)	Risk	Serum	Nested Case-control	Leptin serum (Quartiles: Q_4-no cut-off); follow-up time 17 years' time between blood collection and diagnosis	Unadjusted; *Model 1* - Adjusted for serum levels of testosterone, estradiol, and SHBG; *Model 2* - subgroup analysis in two group to follow-up time (17 yrs. time between blood collection and diagnosis).	There was no associated between *leptin* and PCA risk (OR $_{unadjusted}$ 0.9 95%CI 0.6-1.6); (OR $_{adjusted}$ 0.9 95%CI 0.6-1.6); (OR 0.7 95%CI 0.4-1.4)
3	Stocks et al, (2007), Risk	Sweden, (392 PCA, 392 controls) [c]	Risk	Serum	Nested Case-control	Leptin serum (Quartiles Q_4 >6.9 vs. Q_1 <3.0; Continuous: per unit increase); leptin measured pre diagnosis (median 6.2 years prior diagnosis)	Unadjusted	*Leptin* was associated with significant decreases in risk of PCA (Q4 vs Q1 OR 0.55 95%CI 0.36-0.84, p_{trend} = 0.006); *Leptin* (per one unit increased) was significantly associated with a decreased risk of PCA (OR 0.93 95%CI 0.89-0.97, p = 0.002).
4	Li et al, (2010)	USA, (654 PCA, 644 controls) [d]	Risk	Serum	Nested case-control	Level of leptin plasma (Quintile: Q_5 median 13.4 µg/L vs. Q_1 median 2.4 µg/L).	*Model 1* - adjusted for age and smoking status at base line; *Model 2* - adjusted for age, BMI, C-peptide, stage, grade; *Model 3* - (-)	Leptin was not associated with overall PCA risk (OR 1.06 95% CI 0.65-1.72, p = 0.8).
5	Touvier et al, (2012)	France, (512 PCA, 1,024 controls) [e]	Risk	Serum	Nested Case-control	Leptin (Quartiles: Q_4 6.6 vs. Q_1 ref).	All Model - adjusted for age, BMI, height, SU.VI.MAX intervention group, alcohol intake, physical activity, smoking status, educational level, and baseline PSA level	There was no association between PCA and *leptin* (OR 0.69 95%CI 0.27-1.75, p trend = 0.9).

Studies as part of a larger Study: [a] Monitoring of Trend and Determinant in Cardiovascular Disease (WHO MONICA)-the Vasterbotten Intervention Program (VIP); [b] San Antonio Center for Biomarkers of Risk of Prostate Cancer Cohort Study (SABOR); [c] the Vasterbotten Intervention Project (VIP); the Northern Sweden Health and Disease Cohort; [d] Physicians' Health Study; [e] the Supplementation en Vitamines et Mineraux Antioxydants (SU.VI.MAX); [f] Health Professional Follow-up Study; [g] The Alpha-Tocopherol, Beta-carotene (ATBC) Cancer Prevention Study; [h] the Nashville Men's Health Study (NHS); [i] the Prostate Testing for Cancer and Treatment (ProtecT)

Table 2.2. The list of leptin and prostate cancer risk studies reviewed base on type of outcome, type of biological measurement and type of study design (continue).

No	Author, (Year)	Country, (participants)	Type of outcome	Type of biological measurement	Type of Study Design	Exposure	Covariates	Summary
6	Lai et al, (2014)	USA, (1,314 cases, 1,314 controls) [f]	Risk	Serum	Nested case-control	Leptin serum (Quartiles: Q_4 24.5 ng/mL vs. Q_1 11.41 ng/mL; advanced (≥T3b or N1 or M1 or lethal); also stratified by categorises of disease aggressiveness compared to non-cancer controls.	*Model 1* - adjusted for age, PSA test before blood draw, and year, time of day, and season of blood draw, BMI, history of diabetes, height, family history of prostate cancer, vasectomy, vigorous physical activity, smoking in the past 10 years, intakes of total energy, alcohol, lycopene, red meat, fish, calcium, alpha-linolenic acid, fructose, used of a vitamin E, or selenium supplement; *Model 2*- adjusted for age, PSA test before blood draw, BMI, history of diabetes, height, family history of prostate cancer, vasectomy, vigorous physical activity, smoking in the past 10 years, intakes of total energy, alcohol, lycopene, red meat, fish, calcium, alpha-linolenic acid, fructose, use of a vitamin E, or selenium supplement.	Leptin was not associated with PCA risk (OR 0.85 95%CI 0.65-1.12). Authors suggest may be associations when adjustments made.
Leptin and prostate cancer (risk; serum; case-control)								
7	Lagiou et al, (1998)	USA, (43 PCA, 48 controls)	Risk	Serum	Case-control	Levels of leptin serum (Continuous: per 4 ng/ml)	*Model 1* - adjusted for age, height, year of schooling, BMI, estradiol, testosterone, DHT, DHEAS, SHBG, and insulin-like growth factor I (IGF-I).	Levels of *leptin* (ng/mL) after BMI adjustment was not significantly show relationship with prostate cancer risk (p = 0.53). Level of *leptin* increment (per 4 ng/mL) was not significantly show correlation with prostate cancer cases (cancer vs. control) (OR 0.70 95%CI 0.31-1.55, p = 0.38).
8	Hsing et al, (2001)	China, (128 PCA, 306 controls)	Risk	Serum	Case-control	Levels of leptin serum (Tertiles: T3 >4.04 ng/ml vs. T1 <2.30 ng/ml)	*Model 1* - adjusted for age; *Model 2* - adjusted for age, education, BMI, WHR.	In adjustment of age, the highest tertile men of *leptin* had approximately twofold risk of PCA (OR 1.78 95%CI 1.07-2.95), p = 0.02, however, higher levels of *leptin* did not associate with an increased risk of PCA after adjustment of age, education, BMI, and waist-to-hip ratio (OR 1.10 95% CI 0.59-2.07), p = 0.66.
9	Saglam et al, (2003)	Turkey, (21 PCA, 50 controls)	Risk	Serum	Case-control	Leptin serum (Mean: 33.15±6.36 vs. 19.52±2.02); stratified by disease spread and differentiation degree	*Model* 1 - confined vs advanced PCA; *Model* 2 - GS 8-10 (poorly differentiated) vs GS 2-3 (well differentiated).	Mean *leptin* (ng/mL) of organ confined group is lower than in advanced disease (19.01 ± 2.72 vs 36.47 ± 12.73, p < 0.001); Mean *leptin* (ng/mL) of GS 8-10/poorly differentiated group is significantly highest compare GS 2-4/well differentiated (33.15 ± 3.36 vs 19.52 ± 2.02, p = 0.003)

Studies as part of a larger Study: [a] Monitoring of Trend and Determinant in Cardiovascular Disease (WHO MONICA)-the Vasterbotten Intervention Program (VIP); [b] San Antonio Center for Biomarkers of Risk of Prostate Cancer Cohort Study (SABOR); [c] the Vasterbotten Intervention Project (VIP); the Northern Sweden Health and Disease Cohort; [d] Physicians' Health Study; [e] the Supplementation en Vitamines et Mineraux Antioxydants (SU.VI.MAX); [f] Health Professional Follow-up Study; [g] The Alpha-Tocopherol, Beta-carotene (ATBC) Cancer Prevention Study; [h] the Nashville Men's Health Study (NHS); [i] the Prostate Testing for Cancer and Treatment (ProtecT)

Table 2.2. The list of leptin and prostate cancer risk studies reviewed base on type of outcome, type of biological measurement and type of study design (continue).

No	Author, (Year)	Country, (participants)	Type of outcome	Type of biological measurement	Type of Study Design	Exposure	Covariates	Summary
10	Gade-Andavolu et al, (2006)	USA, (69 PCA, 137 controls)	Risk	Serum	Case-control	Leptin serum (case >14.1 ng/ml vs. control ≤7 ng/ml)	(-)	A significantly higher serum leptin levels in cases vs. controls (14.7 ± 1.38 vs 7.88 ± 1.08), $p < 0.0001$
11	Arisan et al, (2009)	Turkey, (50 PCA, 50 controls)	Risk	Serum	Case-control	Levels of leptin (Continuous: ng/ml)	(-)	There were statistically significant associations between higher serum *leptin* and serum total PSA, biopsy or prostatectomy GS and age (all $p < 0.015$).
12	Zhang et al, (2018)	China, (92 PCA, 92 controls)	Risk	Serum	Case-control	Levels of leptin (cut-off: 2.40µg/mL)	(-)	Higher serum *leptin* correlated positively with PSA ($r = 0.335$, $p < 0.001$). *Leptin* correlated with BMI ($r = 0.269$, $p < 0.001$).
Leptin and prostate cancer (risk; serum; cross-sectional)								
13	Baillargeon et al, (2006)	USA, (125 PCA, 125 controls) [b]	Risk	Serum	Cross-sectional	Serum leptin (BMI: <25, 25-29.9, ≥30; prospectively measured adipokines (mean time of 1.43 years prior diagnosis)	*Model 1* - matching age adjusted race/ethnicity; *Model 2* - adjusted for age and race/ethnicity; *Model 3* - adjusted for age and race/ethnicity.	Leptin was not statistically significant associated with PCA risk (highest vs. lowest tertile) (OR 0.77 95%CI 0.28-1.37, $p_{trend} = 0.57$).
Leptin and prostate cancer (risk; DNA; nested case control)								
14	Moore et al, (2009)	USA, (1,053 cases, 1,053 controls) [g]	Risk	DNA	Nested Case-control	LEPR polymorphism (no cut-off)	All model - adjusted on age at randomised and treatment group	Polymorphisms in *LEPR* genes was not associated with PCA risk. In *LEP*, which was the -14858 A>G locus (OR $_{heterozygotes}$ 0.76 95%CI CI 0.62-0.93 and OR $_{homozygotes}$ 0.79 95%CI 0.60-1.04) and 13288 G>A AA genotype (OR 1.29 95%CI 0.99-1.67), was associated with a suggestive increased risk of PCA.
Leptin and prostate cancer (risk; DNA; case control)								
15	Kote -Jarai et al, (2003)	UK, (271PCA, 277 controls)	Risk	DNA	Case-control	Leptin receptor polymorphisms in PCA risk (no cut-off)	(-)	There was no statistically significant association between *OBR 109Arg* genotype (OR $_{homozygous}$ 1.36 95%CI 0.65-2.85), $p = 0.41$ or *223Arg* allele (OR $_{homozygous}$ 0.82 95%CI 0.58-1.26), $p = 0.39$ and prostate cancer risk.
16	Riberio et al, (2004)	Portugal, (150 PCA, 118 controls)	Risk	DNA	Case-control	Over expression of leptin (A-allele)-Leptin -2548 G/A genotypes (no cut-off)	(-)	Overrepresentation of *LEP* single A-allele in PCA patients comparing with control is significantly associated with higher risk of PCA in A carriers (OR 1.60 95%CI 1.13-2.28, $p = 0.008$) while the AA (OR $_{heterozygous}$ 2.93 95%CI 1.27-6.75, $p = 0.003$) and AG OR $_{homozygous}$ 2.11 95%CI 1.20-3.71) genotypes of LEP represent significantly higher risk of PCA.

Studies as part of a larger Study: [a] Monitoring of Trend and Determinant in Cardiovascular Disease (WHO MONICA)-the Vasterbotten Intervention Program (VIP); [b] San Antonio Center for Biomarkers of Risk of Prostate Cancer Cohort Study (SABOR); [c] the Vasterbotten Intervention Project (VIP); the Northern Sweden Health and Disease Cohort; [d] Physicians' Health Study; [e] the Supplementation en Vitamines et Mineraux Antioxydants (SU.VI.MAX); [f] Health Professional Follow-up Study; [g] The Alpha-Tocopherol, Beta-carotene (ATBC) Cancer Prevention Study; [h] the Nashville Men's Health Study (NHS); [i] the Prostate Testing for Cancer and Treatment (ProtecT)

Table 2.2. The list of leptin and prostate cancer risk studies reviewed base on type of outcome, type of biological measurement and type of study design (continue).

No	Author, (Year)	Country, (participants)	Type of outcome	Type of biological measurement	Type of Study Design	Exposure	Covariates	Summary
Leptin and prostate cancer (risk; receptor expression; case control)								
17	Gade-Andavolu et al, (2006)	USA, (69 PCA, 137 controls)	Risk	DNA	Case-control	Leptin gene and receptor allele	(-)	There was a significant increase frequency of long allele in PCA subject ($p < 0.02$). Patients with PCA varied significantly from control with majority carrying short allele for *LEP* (≤ 0.008) and long allele for *LEPR* ($p \leq 0.006$) gene polymorphisms.

Studies as part of a larger Study: [a] Monitoring of Trend and Determinant in Cardiovascular Disease (WHO MONICA)-the Vasterbotten Intervention Program (VIP); [b] San Antonio Center for Biomarkers of Risk of Prostate Cancer Cohort Study (SABOR); [c] the Vasterbotten Intervention Project (VIP); the Northern Sweden Health and Disease Cohort; [d] Physicians' Health Study; [e] the Supplementation en Vitamines et Mineraux Antioxydants (SU.VI.MAX); [f] Health Professional Follow-up Study; [g] The Alpha-Tocopherol, Beta-carotene (ATBC) Cancer Prevention Study; [h] the Nashville Men's Health Study (NHS); [i] the Prostate Testing for Cancer and Treatment (ProtecT)

2.3.2.2. Leptin and prostate cancer aggressiveness

There were sixteen studies reporting the association between leptin and prostate cancer aggressiveness; these consisted of one cohort study, with measurement in serum (Zhang et al., 2014), three nested case-control serum studies (Lai et al., 2014, Li et al., 2010, Stocks et al., 2007), three case-control serum studies (Arisan et al., 2009, Fowke et al., 2013, Lopez Fontana et al., 2011), seven cross-sectional serum studies (Baillargeon et al., 2006, Burton et al., 2013, Chang et al., 2001, Di Sebastiano et al., 2017, Kang et al., 2018, Sieminska et al., 2018, Tewari et al., 2013) one cohort DNA study (Lin et al., 2011) and one case control DNA study (Ribeiro et al., 2004) (**Table 2.3** and **2.4**).

A cohort serum study by Zhang et al (2014) reported an association between leptin and aggressiveness of prostate cancer; higher levels of leptin were detected in the high-risk group compared with those in the medium- and low-risk groups (31.67 ± 6.12 vs 11.28 ± 4.77, p = 0.012).

Three nested case-control serum studies have reported the results between leptin and prostate cancer aggressiveness. According to Li et al (2010), leptin was not associated with high grade (RR 1.29 95% CI 0.44-3.80, p = 0.34) or lethal prostate cancer (RR 0.94 95% CI 0.25-3.51, p = 0.81). Lai et al (2014) also presented findings that there was no association between leptin serum and advanced or lethal prostate cancer (OR 0.74 95% CI 0.41-1.36, p = 0.34) or with a high grade (Gleason > 7) of prostate cancer (OR 0.84 95% CI 0.57-1.23, p = 0.28). In contrast, one nested case-control serum study by Stocks et al (2007) reported no association between leptin and aggressive prostate cancer in men > 59 years (OR 0.90 95% CI 0.59-1.35, p = 0.55). However, the authors suggested that leptin might be associated with non-aggressive prostate cancer in younger patients (OR 0.16 95% CI 0.06-0.44, p <0.001) (Stocks et al., 2007).

Three case-control leptin serum studies reported the association between leptin and prostate cancer aggressiveness, with two out of three (66.7%) demonstrating a statistically significant association. A study conducted by Arisan et al (2009) showed that serum leptin levels were significantly associated with higher stage and grade prostate cancer ($p = 0.027$ and 0.038, respectively). Lopez-Fontana et al (2011) also suggested that higher leptin levels might be related to Gleason scores-related aggressiveness (12.1 ± 3.01 ng / mL, $p < 0.001$). Fowke et al (2013) was the only case-control study that showed no association between leptin and prostate cancer aggressiveness overall. However, the authors reported that higher leptin levels were associated with high-grade prostate cancer only among men without prostate enlargement (OR 3.00 95% CI 1.16-7.73, $p = 0.02$) and no association was shown overall within the cases group (OR 0.56 95% CI 0.26-1.21, $p = 0.14$).

A total of seven cross-sectional studies explored the association between serum leptin and prostate cancer aggressiveness. Four cross-sectional serum studies reported a statistically significant association between leptin and prostate cancer aggressiveness. A study by Chang et al (2001) reported that higher leptin levels were associated with higher volumes of prostate cancer (OR adjusted 2.35 95% CI 1.01-5.44). Tewari et al (2013) also reported that higher leptin levels were associated with both high-grade and high-stage prostate cancer (OR 1.31 95% CI 1.10-1.56, $p < 0.0001$ and OR 1.01 95% CI 1.00-1.02, $p = 0.03$, respectively). Subsequent studies by Di Sebastiano et al (2017) also revealed that patients with a higher Gleason score ($\geq 4 + 3$) had higher leptin levels compared with those with low Gleason score ($p = 0.013$) (15.6 ± 3.3 ng/ml vs. 8.1 ± 8.1 ng/ml, $p < 0.05$). Sieminska et al (2018) reported that leptin was significantly correlated with the Gleason score of prostate cancer patients ($R = 0.20$, $p < 0.05$) and was significantly higher in men with advanced cancer compared with those in the control group (mean ± SD, median) (13.34 ± 11.20, 9.69 vs. 7.73 ± 7.01, 5.65; $p < 0.05$). The remaining two cross-sectional studies reported varied results. Baillargeon et al (2006) reported that leptin was not associated with high-grade disease (highest vs lowest tertile) (OR 1.20 95% CI 0.48-

3.01, p trend = 0.85). Burton et al (2013) reported that leptin was not associated with prostate cancer stage. Kang et al (2018), also reported mixed results; leptin was associated with an increased risk of advanced prostate cancer (OR univariate 1.13 95% CI 0.92-1.39, p = 0.534) though this was only statistically significant when the analysis was restricted to obese patients (BMI ≥ 25 kg/m^2) (OR multivariate 1.15 95% CI 1.01-1.32, p = 0.045).

A single leptin DNA cohort study by Lin et al (2011) showed that the presence of LEPR polymorphism (rs1137100) was associated with lower prostate cancer-specific mortality (HR 0.29 95% CI 0.14-0.60, p = 0.0001 and HR 0.82 95% CI 0.67 -1.00, p = 0.027, respectively). Similarly, a case-control DNA study conducted by Ribeiro et al (2004) also supported the relationship between leptin and prostate cancer aggressiveness. This study showed that prostate cancer patients with the presence of single A-allele for the LEP gene had an increased risk of advanced cancer (1.91 95% CI 1.24-2.95, p = 0.003), while homozygotes (AA) had a more than 4-fold increased risk (OR 4.67 95% CI 1.69-12.88). Those with AG LEP genotype also had an increased risk of advanced cancer (OR 2.58 95% CI 1.19-5.58).

Therefore, in summary, cohort studies, and the majority of cross-sectional studies and case-control studies support an association between leptin (measured in a range of ways) and prostate cancer aggressiveness, but this is less convincing within nested case-control studies (Table 2.3). If the type of measurement is considered, then, similarly, the evidence base for the association can be described as mixed for serum, while there are no studies exploring receptors, and, for DNA, only two studies have been published, but both support an association between leptin and prostate cancer risk.

Table 2.3. Summary association for leptin and prostate cancer aggressiveness

No	Author (Year)	Study Design	Biological measurement	Association	
				Type	Direction
1	Zhang (2014)	Cohort	Serum	Associated	+
2	Stock (2007)	Nested case-control	Serum	Mixed	potentially +
3	Li (2010)	Nested case-control	Serum	Not associated	n/a
4	Lai (2014)	Nested case-control	Serum	Not associated	n/a
5	Arisan (2009)	Case-control	Serum	Associated	+
6	Lopez-Fontana (2011)	Case-control	Serum	Associated	+
7	Fowke (2013)	Case-control	Serum	Not associated	n/a
8	Chang (2001)	Cross-sectional	Serum	Associated	+
9	Baillargeon (2006)	Cross-sectional	Serum	Not associated	n/a
10	Tewari (2013)	Cross-sectional	Serum	Associated	+
11	Burton (2013)	Cross-sectional	Serum	Mixed	potentially +
12	Di Sebastiano (2017)	Cross-sectional	Serum	Associated	+
13	Sieminska (2018)	Cross-sectional	Serum	Associated	+
14	Kang (2018)	Cross-sectional	Serum	Mixed	+
15	Lin (2011)	Cohort	DNA	Associated	+
16	Ribeiro (2004)	Case-control	DNA	Associated	+

Note: (+): positive, higher leptin-increased risk or lower leptin-decreased risk, (-): negative, higher leptin-decreased risk or lower leptin-increased risk, (potentially): mixed results, but suggested direction given, n/a: not applicable; no significant association detected

Table 2.4. The list of leptin and aggressiveness prostate cancer studies reviewed base on type of outcome, type of biological measurement and type of study design

No	Author (Year)	Country, (participants)	Type of outcome	Type of biological measurement	Type of Study Design	Exposure	Covariates	Summary
Leptin and prostate cancer (aggressiveness; serum; cohort)								
1	Zhang et al, (2014)	China, (184 PCA)	Aggressiveness	Serum	Cohort	Leptin serum (high 31.67±6.12 vs. low 11.28±4.77); stratified by clinical and pathologic factors	(-)	LEPR polymorphism (rs1137100) might be associated with prostate cancer-specific mortality (HR 0.29 95% CI 0.14-0.60, p = 0.0001 and HR 0.82 95% CI 0.67 -1.00, p = 0.027).
Leptin and prostate cancer (aggressiveness; serum; nested case-control)								
2	Stocks et al, (2007)	Sweden, (392 PCA, 392 controls) [c]	Aggressiveness	Serum	Nested Case-control	Leptin serum (Quartiles Q_4 >6.9 vs. Q_1 <3.0; Continuous: per unit increase); leptin measured pre diagnosis (median 6.2 years prior diagnosis)	Unadjusted	*Higher leptin* was not associated with aggressiveness in old men (>59 years) (OR 0.90 95% CI 0.59-1.35, p = 0.55) and only significantly associated with non-aggressive PCA in younger men (<59 years) (OR 0.16 95% CI 0.06-0.44, p < 0.001).
3	Li et al, (2010)	USA, (654 PCA, 644 controls) [d]	Aggressiveness	Serum	Nested case-control	Level of leptin plasma (Quintile: Q5 median 13.4 µg/L vs. Q1 median 2.4 µg/L)	*Model 1* - adjusted for age and smoking status at base line; *Model 2* - adjusted for age, BMI, C-peptide, stage, grade; *Model 3* - (-)	Leptin was not associated with high grade (RR 1.29 95% CI 0.44-3.80, p = 0.34) or lethal (RR 0.94 95% CI 0.25-3.51, p = 0.81) prostate cancer.
4	Lai et al, (2014)	USA, (1,314 cases, 1,314 controls) [f]	Aggressiveness	Serum	Nested case-control	Leptin serum (Quartiles: Q_4 24.5 ng/mL vs. Q_1 11.41 ng/mL; advanced (≥T3b or N1 or M1 or lethal); also stratified by categorises of disease aggressiveness compared to non-cancer controls	*Model 1* - adjusted for age, PSA test before blood draw, and year, time of day, and season of blood draw, BMI, history of diabetes, height, family history of prostate cancer, vasectomy, vigorous physical activity, smoking in the past 10 years, intakes of total energy, alcohol, lycopene, red meat, fish, calcium, alpha-linolenic acid, fructose, used of a vitamin E, or selenium supplement; *Model 2*- adjusted for age, PSA test before blood draw, BMI, history of diabetes, height, family history of prostate cancer, vasectomy, vigorous physical activity, smoking in the past 10 years, intakes of total energy, alcohol, lycopene, red meat, fish, calcium, alpha-linolenic acid, fructose, use of a vitamin E, or selenium supplement	Leptin was not associated with risk of advanced (OR 0.74 95% CI 0.41-1.36, p = 0.34) or lethal disease (OR 0.84 95% CI 0.57-1.23, p = 0.28).

Studies as part of a larger Study: [a] Monitoring of Trend and Determinant in Cardiovascular Disease (WHO MONICA)-the Vasterbotten Intervention Program (VIP); [b] San Antonio Center for Biomarkers of Risk of Prostate Cancer Cohort Study (SABOR); [c] the Vasterbotten Intervention Project (VIP); the Northern Sweden Health and Disease Cohort; [d] Physicians' Health Study; [e] the Supplementation en Vitamines et Mineraux Antioxydants (SU.VI.MAX); [f] Health Professional Follow-up Study; [g] The Alpha-Tocopherol, Beta-carotene (ATBC) Cancer Prevention Study; [h] the Nashville Men's Health Study (NHS); [i] the Prostate Testing for Cancer and Treatment (ProtecT)

Table 2.4. The list of leptin and aggressiveness prostate cancer studies reviewed base on type of outcome, type of biological measurement and type of study design (continue).

No	Author (Year)	Country, (participants)	Type of outcome	Type of biological measurement	Type of Study Design	Exposure	Covariates	Summary
Leptin and prostate cancer (aggressiveness; serum; case-control)								
5	Arisan et al, (2009)	Turkey, (50 PCA, 50 controls)	Aggressiveness	Serum	Case-control	Levels of leptin (Continuous: ng/ml)	(-)	*Higher leptin* was positively associated with high-stage and high-grade PCA (p = 0.027 and 0.038).
6	Lopez-Fontana et al, (2011)	Argentina, (35 PCA, 35 controls)	Aggressiveness	Serum	Case-control	Levels of Leptin (GS: high 12.1±3.01 ng/ml, intermediate 3.83±0.61 ng/ml, low 2.06±0.41 ng/ml)	(-)	*Higher leptin* level were higher in subjects with high GS (12.1 ± 3.01 ng/mL vs. intermediate and low (3.38 ± 0.61 ng/mL and 2.60 ± 0.41 ng/mL, respectively) (p < 0.001).
7	Fowke et al, (2013)	USA, (95 low grade PCA, 98 high grade PCA, 137 controls) [h]	Aggressiveness	Serum	Case-control	Level of leptin serum (BMI: <30 vs. ≥30; WC in cm: <104.1 vs. ≥ 104.1; WHR: <1.01 vs. ≥1.01; Height in cm: <175.3 vs. ≥175.3)	All Model - adjusted for age, alpha-blocker use, treatment for diabetes, number of cores collected at biopsy, and prostate volume	A higher *leptin* levels were significantly associated with *high grade* PCA among men without prostate enlargement (OR 3.00 95%CI 1.16-7.73, p = 0.02) and was not found among men on cases group (OR 0.56 95%CI 0.26- 1.21, p = 0.14)
Leptin and prostate cancer (aggressiveness; serum; cross-sectional)								
8	Chang et al, (2001)	USA, (48 low volume tumour, 151 high volume tumour)	Aggressiveness	Serum	Cross-sectional	Plasma leptin (low- vs. high-volume leptin-testosterone)	Unadjusted; Adjusted for BMI and plasma testosterone	Higher *leptin* levels were positively associated with higher volume disease ($OR_{unadjusted}$ 2.41 95%CI 1.16-5.01); ($OR_{adjusted}$ 2.35 95%CI 1.01-5.44)
9	Baillargeon et al, (2006)	USA, (125 PCA, 125 controls) [b]	Aggressiveness	Serum	Cross-sectional	Serum leptin (BMI: <25, 25-29.9, ≥30; high vs. low grade; prospectively measured adipokines (mean time of 1.43 years before diagnosis)	*Model 1* - matching age adjusted race/ethnicity; *Model 2* - adjusted for age and race/ethnicity; *Model 3* - adjusted for age and race/ethnicity	Leptin was not associated with high *grade* disease (highest vs lowest tertile) (OR 1.20 95%CI 0.48-3.01, p_{trend} = 0.85)
10	Tewari et al, (2013)	India, (95 PCA)	Aggressiveness	Serum	Cross-sectional	Levels leptin - stratified on grade (low and high), stage (III and IV)	Unadjusted	*Leptin* levels were higher in high grade (OR 1.31 95%CI 1.10-1.56, p < 0.0001) and higher in high stage prostate cancer (OR 1.01 95%CI 1.00-1.02, p = 0.03).
11	Burton et al, (2013)	UK, (331 locally advanced PCA, 413 localized PCA) [i]	Aggressiveness	Serum	Cross-sectional	Leptin serum (Q_4 7.3-54.4 ng/ml vs. Q_1 0.3-2.8 ng/ml); stratified on stage (locally advanced & localised) and grade (GS ≥7 vs ≤6); 'controls' are men with localized PC) blood taken (a mean of 9 weeks prior diagnosis)	*Model 1* - adjusted on age at recruitment assay plate; *Model 2* - adjusted on age at recruitment, assay plate, recruitment centre	Leptin was not associated with stage of prostate cancer; however, it might be related with overweight and obesity-related advanced disease (OR 0.50 95%CI 0.32-0.78, p = 0.009).

Studies as part of a larger Study: a Monitoring of Trend and Determinant in Cardiovascular Disease (WHO MONICA)-the Vasterbotten Intervention Program (VIP); b San Antonio Center for Biomarkers of Risk of Prostate Cancer Cohort Study (SABOR); c the Vasterbotten Intervention Project (VIP); the Northern Sweden Health and Disease Cohort; d Physicians' Health Study; e the Supplementation en Vitamines et Mineraux Antioxydants (SU.VI.MAX); f Health Professional Follow-up Study; g The Alpha-Tocopherol, Beta-carotene (ATBC) Cancer Prevention Study; h the Nashville Men's Health Study (NHS); i the Prostate Testing for Cancer and Treatment (ProtecT)

Table 2.4. The list of leptin and aggressiveness prostate cancer studies reviewed base on type of outcome, type of biological measurement and type of study design (continue).

No	Author (Year)	Country, (participants)	Type of outcome	Type of biological measurement	Type of Study Design	Exposure	Covariates	Summary
12	Di Sebastiano et al, (2017)	Canada, (36 high risk PCA, 15 PCA)	Aggressiveness	Serum	Cross-sectional	Leptin serum (GS: 3+3, 3+4, ≥4+3)	(-)	Gleason ≥4 + 3 patients had higher *leptin* levels compared with Gleason 3 + 4 patients (p = 0.013) (15.6 ± 3.3 ng/ml vs. 8.1 ± 8.1 ng/ml, p < 0.05)
13	Sieminska et al, (2018)	Poland, (74 PCA, Gleason score ≤6 n=24; Gleason score 7 n=28; Gleason score ≥8 n=22)	Aggressiveness	Serum	Cross-sectional	Leptin serum (GS: poorly differentiated ≥8 vs. well differentiated ≤6)	(-)	*Leptin* was correlated with GS in PCA men (R = 0.20, p < 0.05) and was significantly higher in advanced group when compared with control (mean ± SD, median) (13.34 ± 11.20, 9.69 vs. 7.73 ± 7.01, 5.65; p < 0.05)
14	Kang et al, (2018)	Korea, (25 non-obese PCA, 37 obese PCA)	Aggressiveness	Serum	Cross-sectional	Leptin serum (BMI: obese ≥25 vs. normal <25)	*Model 1 and 2* - univariate; *Model 3* - multivariate	there were no evidence regarding *leptin* (OR $_{univariate}$ 1.13 95%CI 0.92-1.39, p = 0.534) in predicting advance tumour stage In all PCA patients; *leptin* was only significantly predicting advanced pathological stage (OR $_{multivariate}$ 1.15 95%CI 1.01-1.32, p = 0.045) in PCA obese patients (BMI ≥ 25 kg/m^2),
Leptin and prostate cancer aggressiveness (aggressiveness; DNA; cohort)								
15	Lin et al (2011)	USA, (1,309 PCA)	Aggressiveness	DNA	Cohort	SNPs variant related prostate cancer mortality (no cut off)	(-)	The presence of LEPR SNP (rs1137100) was associated with prostate cancer-specific mortality in two cohort studies (HR 0.29 95% CI 0.14-0.60, p = 0.0001 and HR 0.82 95% CI 0.67-1.00, p = 0.027).
Leptin and prostate cancer (aggressiveness; DNA; case-control)								
16	Ribeiro et al, (2004)	Portugal, (150 PCA, 118 controls)	Aggressiveness	DNA	Case-control	Over expression of leptin (A-allele)-Leptin -2548 G/A genotypes (no cut-off)	(-)	The presence of Single A-allele in PCA patients associated with advanced PCA (1.91 95%CI 1.24-2.95, p = 0.003) while The AA (OR 4.67 95%CI 1.69-12.88) and AG (OR 2.58 95%CI 1.19-5.58) genotypes of *LEP* represent significantly higher risk of advanced PCA.

Studies as part of a larger Study: a Monitoring of Trend and Determinant in Cardiovascular Disease (WHO MONICA)-the Vasterbotten Intervention Program (VIP); b San Antonio Center for Biomarkers of Risk of Prostate Cancer Cohort Study (SABOR); c the Vasterbotten Intervention Project (VIP); the Northern Sweden Health and Disease Cohort; d Physicians' Health Study; e the Supplementation en Vitamines et Mineraux Antioxydants (SU.VI.MAX); f Health Professional Follow-up Study; g The Alpha-Tocopherol, Beta-carotene (ATBC) Cancer Prevention Study; h the Nashville Men's Health Study (NHS); i the Prostate Testing for Cancer and Treatment (ProtecT)

2.3.2.3. Leptin and prostate cancer progression

There were no studies found within this systematic review that explored the association between leptin and the progression of prostate cancer.

2.3.2.4. Adiponectin and prostate cancer risk

There were fourteen studies reporting the association between adiponectin and prostate cancer risk; consisting of three nested case-control studies measuring adiponectin in serum (Li et al., 2010, Medina et al., 2014, Touvier et al., 2013), three case-control serum studies (Michalakis et al., 2015, Michalakis et al., 2007, Zhang et al., 2018), two cross-sectional serum studies (Baillargeon et al., 2006, Ikeda et al., 2015), two nested case-control DNA studies (Dhillon et al., 2011, Moore et al., 2009), three case-control DNA studies (Beebe-Dimmer et al., 2010, Gu et al., 2014, Kaklamani et al., 2011) and one case-control receptor expression study (Michalakis et al., 2007) (**Table 2.5** and **2.6**).

Three nested case-control studies of serum adiponectin levels have been conducted. Li et al (2010) showed no association between serum and risk of total prostate cancer (RR 0.73 95% CI 0.46-1.14, p = 0.38). Touvier et al (2013) also reported no association between serum adiponectin and prostate cancer risk (OR 1.34 95% CI 0.68-2.61, p trend = 0.3). The final nested case-control serum study, by Medina et al (2014), reported that the risk of prostate cancer was associated with high molecular weight (HMW) of adiponectin (p = 0.04), but the pattern seemed to depend on obesity status. For example, an increased percentage of HWM adiponectin tended to be associated with an increased prostate cancer risk in normal and overweight subjects (OR 1.24 95% CI 0.41-3.75), but a decreased risk in obese subjects (OR 0.62 95% CI 0.32-1.18).

Three case-control serum adiponectin studies have been conducted and all reported a statistically significant association with prostate cancer risk. Michalakis (2007) stated that

adiponectin levels were inversely associated with prostate cancer risk (OR 0.29 95% CI 0.10-0.82, p = 0.03). Another case-control study by Michalakis et al (2015) reported a strong inverse association between adiponectin and prostate cancer risk; prostate cancer patients had lower plasma adiponectin levels compared with BPH and healthy subjects (median, min-max; ng / mL) (7.6, 1.6-25.1 vs. 8.8. 0.9-29.3 and 9.7, 1.1-43.2; p = 0.025). Michalakis et al (2015) also reported that adiponectin levels were inversely associated with prostate cancer risk (OR univariate 0.931 95% CI 0.888-0.977, p = 0.004). Adiponectin's association with prostate cancer remained statistically significant after adjustment for HOMA-IR (a measure of insulin resistance) and QUICKI (a measure of insulin sensitivity) and in multivariate analysis (OR adjusted 0.916 95% CI 0.867-0.698, p = 0.002 or OR adjusted 0.915 95% CI 0.851-0.983, p <0.001, respectively). Finally a recent study by Zhang (2018) also showed that higher adiponectin levels were associated with PSA (r = 0.282, p <0.001, but were not associated with grade of prostate cancer (X^2 = 0.047, p = 0.964), and this study was therefore classified as having mixed findings.

Two cross-sectional serum studies have been conducted. Baillargeon et al (2006) found that adiponectin was not statistically significant associated with prostate cancer risk (OR 0.87 95%CI 0.46-1.65, p_{trend} = 0.24). In contrast, Ikeda et al (2015) reported a significant positive correlation being observed between adiponectin level and PSA levels (r = 0.054, p =0.0061).

Two nested case-control adiponectin DNA studies have been conducted. Moore et al (2009) showed no association between ADIPOQ genes polymorphisms (rs182052, rs822393, rs2241766, rs1736674, all p> 0.05) and prostate cancer risk. In contrast, a DNA related study conducted by Dhillon et al (2011) demonstrated varying association between four ADIPOQ polymorphisms present and prostate cancer risk (rs266729 (OR CG 1.14 95% CI 0.97-1.36, p = 0.049), rs182052 (OR AG 1.03 95% CI 0.87-1.22, p = 0.04), rs822391 (OR CT 0.81 95% CI 0.68-

0.96, p = 0.02), and rs2082940 (OR CT 0.81 95% CI 0.66-0.99, p 0.006)). Researchers also suggested that the ADIPOR1/2 receptor variant was not associated with prostate cancer risk in this DNA study.

Three case-control studies measuring adiponectin polymorphisms demonstrated contrasting results between adiponectin and prostate cancer risk. According to Beebe-Dimmer et al (2010), there was no relationship between adiponectin signalling status and prostate cancer risk where analysis of the two single nucleotide polymorphisms (SNPs), rs1501299 and rs2241766 showed no difference between cases and controls (OR 0.99 95% CI 0.57-1.73). In contrast, a genetic analysis conducted by Kaklamani et al (2011) reported that the areas under ROC curves (AUCs) of epistatic (dihybrid cross/interaction of gene that can influence the phenotype) models (OR 0.73 95% CI 0.70-0.77) were higher compared with the non-epistatic models (OR 0.65 95% CI 0.62-0.69) that might indicate a role for adiponectin in the prediction of prostate cancer risk. Gu et al (2014) also reaffirmed the relationship between ADIPOQ gene and prostate cancer risk where the present of ADIPOQ rs3774262 variant AA genotype was associated with a decreased prostate cancer risk (OR adjusted: 0.66 95% CI 0.48–0.92, p = 0.01).

Finally, a case-control adiponectin receptor expression study by Michalakis (2007) reported that expression of the AdipoR1 was more likely to be associated with prostate cancer risk (29%) compared with the AdipoR2 (21%).

Therefore, in summary, when considering all ways of assessing adiponectin status, while the majority of case-control studies support an association between adiponectin and prostate cancer risk, this is less consistently supported by nested case-control studies, which would be considered methodologically stronger, and is supported by one, and rejected by another one, weaker cross-sectional studies (**Table 2.5**). When sub-divided by method of

assessing adiponectin status, the evidence base is also inconsistent, except for receptor expression, where there is only a single study.

Table 2.5. Summary association for adiponectin and prostate cancer risk

No	Author (Year)	Study Design	Biological measurement	Association	
				Type	Direction
1	Li (2010)	Nested case-control	Serum	Not associated	n/a
2	Touvier (2013)	Nested case-control	Serum	Not associated	n/a
3	Medina (2014)	Nested case-control	Serum	Mixed	mixed
4	Michalakis (2007)	Case-control	Serum	Associated	-
5	Michalakis (2015)	Case-control	Serum	Associated	-
6	Zhang (2018)	Case-control	Serum	Mixed	potentially +
7	Baillargeon (2006)	Cross-sectional	Serum	Not associated	n/a
8	Ikeda (2015)	Cross-sectional	Serum	Associated	+
9	Moore (2009)	Nested case-control	DNA	Not associated	n/a
10	Dhillon (2011)	Nested case-control	DNA	Mixed	potentially +
11	Beebe-Dimmer (2010)	Case-control	DNA	Not associated	n/a
12	Kaklamani (2011)	Case-control	DNA	Associated	+
13	Gu (2014)	Case-control	DNA	Associated	+
14	Michalakis (2007)	Case-control	Receptor expression	Associated	+

Note: (+): positive, higher adiponectin-increased risk or lower adiponectin-decreased risk, (-): negative, higher adiponectin-decreased risk or lower adiponectin-increased risk, (potentially): mixed results, but suggested direction given, n/a: not applicable; no significant association detected

Table 2.6. The list of adiponectin and prostate cancer risk studies reviewed base on type of outcome, type of biological measurement and type of study design

No	Author, (Year)	Country, (participants)	Type of outcomes	Type of study Design	Type of biological measurement	Exposure	Covariates	Summary
Adiponectin and prostate cancer (risk; serum; nested case-control)								
1	Li et al (2010)	USA, (654 PCA, 644 controls) [d]	Risk	Nested case-control	Serum	Level of Adiponectin plasma (Quintile: Q_5 median 13.3 mg/L vs Q_1 median 2.7 mg/L)	*Model 1* - adjusted for age and smoking status at base line; *Model 2* - adjusted for age, BMI, C-peptide, stage, grade; *Model 3* - (-)	Adiponectin might not be associated with all risk of prostate cancer (RR 0.73 95% CI 0.46-1.14, p = 0.38).
2	Touvier et al (2012)	France, (512 PCA, 1,024 controls) [e]	Risk	Nested Case-control	Serum	Adiponectin (Quartiles: Q_4 9.2 vs. Q_1 ref.)	All Model - adjusted for age, BMI, height, SU.VI.MAX intervention group, alcohol intake, physical activity, smoking status, educational level, and baseline PSA level	There was no association between PCA and *adiponectin* (OR 1.34 95%CI 0.68-2.61, p trend = 0.3)
3	Medina et al (2014)	USA, (228 PCA, 239 controls) [b]	Risk	Nested case-control	Serum	Adiponectin serum (BMI: Obese ≥30)	(-)	The risk of prostate cancer was associated with high molecular weight (HMW) of adiponectin wherein normal and overweight subjects, the incline risk was in line with an increase of HMW percentage (OR 1.24 95%CI 0.41-3.75), while in obese subjects, the declined risk was in line with an increase of HMW percentage (OR 0.62 95% CI 0.32-1.18).

Studies as part of a larger Study: [b] San Antonio Center for Biomarkers of Risk of Prostate Cancer Cohort Study (SABOR); [d] Physicians' Health Study; [e] the Supplementation en Vitamines et Mineraux Antioxydants (SU.VI.MAX); [g] The Alpha-Tocopherol, Beta-carotene (ATBC) Cancer Prevention Study; [i] the Prostate Testing for Cancer and Treatment (ProtecT); [j] Flint Men's Health Study (FMHS); [k] The Nashville Men's Health Study (NHS); [l] Cancer Prevention Study II Nutrition Cohort; [m] Physicians' Health Study (PHS), Health Professionals Follow-up Study (HPFS)

Table 2.6. The list of adiponectin and prostate cancer risk studies reviewed base on type of outcome, type of biological measurement and type of study design (continue)

No	Author, (Year)	Country, (participants)	Type of outcomes	Type of study Design	Type of biological measurement	Exposure	Covariates	Summary
Adiponectin and prostate cancer (risk; serum; case-control)								
4	Michalakis et al (2007)	Greece, (75 PCA, 150 healthy controls)	Risk	Case-control	Serum	Serum adiponectin (cut-off: 8.7 µg/mL)	*Model 1* - adjusted by age, BMI, smoking status, alcohol use, insulin level, testosterone; *Model 2&3* - matched case non-tumour tissue n [%] PCA vs normal	*Adiponectin* was significantly inversely associated with PCA risk (OR 0.29 95%CI 0.10-0.82, p = 0.03)
5	Michalakis et al (2015)	Greece, (75 PCA, 150 controls)	Risk	Case-control	Serum	Serum adiponectin (Continuous: median 8.7 ng/mL)	*Model 1* - univariate; *Model 2* - adjusted for HOMA-IR and QUICKI; *Model 3* - adjusted for age (significant), BMI, smoking, cholesterol (not significant)	PCA patients had significantly lower plasma adiponectin levels compared with BPH and control (median, min-max; ng / mL) (7.6, 1.6-25.1 vs. 8.8. 0.9-29.3 and 9.7, 1.1-43.2; p = 0.025). *Adiponectin* levels had significant effect on identifying PCA ($OR_{univariate}$ 0.931 95%CI 0.888-0.977, p = 0.004); The effects of *adiponectin* levels remained statistically significant after adjusted HOMA-IR and QUICKI ($OR_{adjusted}$ 0.916 95%CI 0.867-0.698, p = 0.002); after adjusted multivariate ($OR_{adjusted}$ 0.915 95%CI 0.851-0.983, p < 0.001).
6	Zhang et al (2018)	China, (92 PCA, 92 controls)	Risk	Case-control	Serum	Levels adiponectin (cut-off: 8.28 µg/mL)	(-)	*Higher adiponectin* levels were associated with PSA (r = 0.282, p < 0.001, but were not associated with grade (X^2 = 0.047, p = 0.964).

Studies as part of a larger Study: [b] San Antonio Center for Biomarkers of Risk of Prostate Cancer Cohort Study (SABOR); [d] Physicians' Health Study; [e] the Supplementation en Vitamines et Mineraux Antioxydants (SU.VI.MAX); [g] The Alpha-Tocopherol, Beta-carotene (ATBC) Cancer Prevention Study; [i] the Prostate Testing for Cancer and Treatment (ProtecT); [j] Flint Men's Health Study (FMHS); [k] The Nashville Men's Health Study (NHS); [l] Cancer Prevention Study II Nutrition Cohort; [m] Physicians' Health Study (PHS), Health Professionals Follow-up Study (HPFS)

Table 2.6. The list of adiponectin and prostate cancer risk studies reviewed base on type of outcome, type of biological measurement and type of study design (continue)

No	Author, (Year)	Country, (participants)	Type of outcomes	Type of study Design	Type of biological measurement	Exposure	Covariates	Summary
Adiponectin and prostate cancer (risk; serum; cross-sectional)								
7	Baillargeon et al (2006)	USA, (125 PCA, 125 controls) [b]	Risk	Cross-sectional	Serum	Serum adiponectin (BMI: <25, 25-29.9, ≥30)	*Model 1* - matching age adjusted race/ethnicity; *Model 2* - adjusted for age and race/ethnicity; *Model 3* - adjusted for age and race/ethnicity	Adiponectin was not statistically significant associated with PCA risk (OR 0.87 95%CI 0.46-1.65, p_{trend} = 0.24)
8	Ikeda et al (2015)	Japan, (24 PCA, 2,817 controls)	Risk	Cross-sectional	Serum	Adiponectin serum (cut-off: 6.7 µg/mL)	(-)	A significant positive correlation was observed between *adiponectin* level and PSA levels (r = 0.054, p =0.0061)
Adiponectin and prostate cancer (risk; DNA; nested case-control)								
9	Moore et al (2009)	USA, (1,053 cases, 1,053 controls) [g]	Risk	Nested Case-control	DNA	ADIPOQ polymorphism (no cut-off)	All model - adjusted on age at randomised and treatment group	*ADIPOQ* genes polymorphisms (rs182052, rs822393, rs2241766, rs1736674, all p > 0.05) might not associated with PCA risk.
10	Dhillon et al (2011)	USA, (1,286 PCA, 1,267 controls) [d]	Risk	Nested Case-control	DNA	Adiponectin gene variation (no cut-off)	*All Model* - adjusted for age at randomisation, cigarette smoking status, and time between blood draw and event date	Four *ADIPOQ* polymorphisms rs266729 (OR_{CG} 1.14 95%CI 0.97-1.36, p = 0.049), rs182052 (OR_{AG} 1.03 95%CI 0.87-1.22, p = 0.04), rs822391 (OR_{CT} 0.81 95%CI 0.68-0.96, p = 0.02), and rs2082940 (OR_{CT} 0.81 95%CI 0.66-0.99, p 0.006) present were significantly associated with PCA risk.

Studies as part of a larger Study: [b] San Antonio Center for Biomarkers of Risk of Prostate Cancer Cohort Study (SABOR); [d] Physicians' Health Study; [e] the Supplementation en Vitamines et Mineraux Antioxydants (SU.VI.MAX); [g] The Alpha-Tocopherol, Beta-carotene (ATBC) Cancer Prevention Study; [i] the Prostate Testing for Cancer and Treatment (ProtecT); [j] Flint Men's Health Study (FMHS); [k] The Nashville Men's Health Study (NHS); [l] Cancer Prevention Study II Nutrition Cohort; [m] Physicians' Health Study (PHS), Health Professionals Follow-up Study (HPFS)

Table 2.6. The list of adiponectin and prostate cancer risk studies reviewed base on type of outcome, type of biological measurement and type of study design (continue)

No	Author, (Year)	Country, (participants)	Type of outcomes	Type of study Design	Type of biological measurement	Exposure	Covariates	Summary
Adiponectin and prostate cancer (risk; DNA; nested case-control)								
11	Beebe-Dimmer et al (2010)	USA, (131 PCA, 344 controls) [j]	Risk	Case-control	DNA	ADIPOQ and ADIPOR1 genetic variation in PCA-obese (no cut-off)	(-)	There was no association between *Adiponectin* signalling status and prostate cancer risk where analysis on two SNPs which were rs1501299 and rs2241766 suggested no different between case and control (OR 0.99 95%CI 0.57-1.73).
12	Kaklamani et al (2011)	USA, (465 cases, 441 controls)	Risk	Case-control	DNA	Adiponectin gene variation (no cut-off)	(-)	The areas under ROC curves (AUCs) of epistatic models (OR 0.73 95%CI 0.70-0.77) was higher than nonepistatic models (OR 0.65 95%CI 0.62-0.69) that might indicate a powerful predictors role of adiponectin to detecting PCA risk.
13	Gu et al (2014)	China, (917 cases, 1036 controls)	Risk	Case-control	DNA	Adiponectin nucleotide polymorphisms (no cut-off)	*Model* - adjusted for age, smoking status, and BMI	The present of ADIPOQ rs3774262 variant AA genotype was associated with both decreased PCA risk (OR adjusted: 0.66 95%CI 0.48–0.92, p = 0.01).

Studies as part of a larger Study: [b] San Antonio Center for Biomarkers of Risk of Prostate Cancer Cohort Study (SABOR); [d] Physicians' Health Study; [e] the Supplementation en Vitamines et Mineraux Antioxydants (SU.VI.MAX); [g] The Alpha-Tocopherol, Beta-carotene (ATBC) Cancer Prevention Study; [i] the Prostate Testing for Cancer and Treatment (ProtecT); [j] Flint Men's Health Study (FMHS); [k] The Nashville Men's Health Study (NHS); [l] Cancer Prevention Study II Nutrition Cohort; [m] Physicians' Health Study (PHS), Health Professionals Follow-up Study (HPFS)

Table 2.6. The list of adiponectin and prostate cancer risk studies reviewed base on type of outcome, type of biological measurement and type of study design (continue)

No	Author, (Year)	Country, (participants)	Type of outcomes	Type of study Design	Type of biological measurement	Exposure	Covariates	Summary
Adiponectin and prostate cancer (risk; receptor expression; nested case-control)								
14	Michalakis et al (2007)	Greece, (75 PCA, 150 healthy controls)	Risk	Case-control	Receptor expression	(-)	*Model 1* - adjusted by age, BMI, smoking status, alcohol use, insulin level, testosterone; *Model 2&3* - matched case non-tumour tissue n [%] PCA vs normal	*Strong* expression of *AdipoR1* was associated with strong adipokines receptor in immunohistochemistry analysis than AdipoR2 (29% vs 21%).

Studies as part of a larger Study: [b] San Antonio Center for Biomarkers of Risk of Prostate Cancer Cohort Study (SABOR); [d] Physicians' Health Study; [e] the Supplementation en Vitamines et Mineraux Antioxydants (SU.VI.MAX); [g] The Alpha-Tocopherol, Beta-carotene (ATBC) Cancer Prevention Study; [i] the Prostate Testing for Cancer and Treatment (ProtecT); [j] Flint Men's Health Study (FMHS); [k] The Nashville Men's Health Study (NHS); [l] Cancer Prevention Study II Nutrition Cohort; [m] Physicians' Health Study (PHS), Health Professionals Follow-up Study (HPFS)

2.3.2.5. Adiponectin and prostate cancer aggressiveness

There were seventeen studies reporting the association of adiponectin with prostate cancer aggressiveness, which consisted of two nested case-control serum studies (Li et al., 2010, Stevens et al., 2014), five case-control serum studies (Arisan et al., 2009, Fowke et al., 2013, Freedland et al., 2005, Goktas et al., 2005, Lopez Fontana et al., 2011), eight cross-sectional serum studies (Baillargeon et al., 2006, Burton et al., 2013, Di Sebastiano et al., 2017, Housa et al., 2008, Kang et al., 2018, Sieminska et al., 2018, Tewari et al., 2013) and two cross-sectional receptor expression studies (Housa et al., 2008, Tan et al., 2015) (**Table 2.7** and **2.8**).

The two nested case-control studies reported inconsistent results. One nested case-control study, by Stevens et al (2014), showed that adiponectin was not associated with prostate cancer aggressiveness (OR 1.11 95% CI 0.64-1.93 p trend = 0.59). In contrast, the other nested case-control serum study by Li et al (2010) reported mixed results. For example higher adiponectin was not associated with high-grade prostate cancer (Gleason score ≥8) (RR 0.23 95% CI 0.06-0.83, p trend = 0.08) or lethal cancer (RR 0.61 95% CI 0.12-2.99, p trend = 0.44) (Li et al., 2010). However, the higher prediagnostic concentration of adiponectin was associated with lower prostate cancer-specific mortality (HR 0.35 95% CI 0.14-0.89, p trend = 0.03) and lower likelihood of progression to fatal prostate cancer, mainly among men who were overweight or obese (BMI ≥25 kg / m2) (HR 0.10 95% CI 0.01-0.78, p trend = 0.02).

Five case-control serum studies reported inconsistent results between adiponectin and prostate cancer aggressiveness. Goktas et al (2005) showed that adiponectin levels in prostate cancer patients was significantly lower than controls (5.3 ± 1.6 vs 16.2 ± 4.1, $p < 0.001$) but higher in the organ-confined group compared with controls (6.0 ± 1.7 vs 4.7 ± 1.2, $p = 0.012$). Adiponectin was also statistically significantly correlated with PSA, biopsy Gleason score, and Gleason score ($r = -0.478$, $p = 0.008$; $r = -0.621$, $p = 0.001$; $r = -0.642$, $p < 0.001$) (Goktas et al., 2005). Arisan et al (2009) also reported that advanced prostate cancer subjects

had higher adiponectin levels than the organ-confined patients (p = 0.044). In the advanced prostate cancer group adiponectin levels were even lower than in control (p = 0.0021) and BPH groups (p = 0.0023) (Arisan et al., 2009). Researchers also showed that the leptin-to-adiponectin ratio was higher in the advanced prostate cancer group than in the organ-confined group (p = 0.028) and this ratio was found to be 3.9 times higher in high-grade patients. In addition, Arisan et al (2009) also showed that the leptin-to-adiponectin ratio was higher in prostate cancer patients compared with the control and BPH group ($p < 0.05$). Other case-control serum studies reported no evidence of an association between adiponectin and prostate cancer aggressiveness. According to Lopez-Fontana et al (2011), adiponectin levels were not associated with tumour aggressiveness (p = 0.131). Another study by Fowke et al (2013) also confirmed this, stating that a lower adiponectin level was not statistically significantly associated with high-grade prostatic intraepithelial neoplasia (HGPIN) or prostate cancer (OR 0.63 95% CI 0.23-1.68, p = 0.33 or OR 1.32 95 % CI 0.60-2.49, p = 0.49, respectively). A study by Freedland (2005) had mixed findings, describing that adiponectin was positively associated with high stage prostate cancer in the normal weight group (BMI <25 kg/m2) (OR 1.14 95% CI 1.02-1.29, p = 0.03) but not related to high-grade prostate cancer (OR 1.05 95 % CI 0.94-1.18, p = 0.38). Conversely, adiponectin was not found to be associated with high-grade (OR 0.94 95% CI 0.87-1.01, p = 0.09) or high stage prostate cancer (OR 0.97 95% CI 0.91-1.04, p = 0.43) in the overweight group (BMI ≥ 25 kg/m2) (Freedland et al., 2005).

There were eight cross-sectional studies which explored the association between serum adiponectin and prostate cancer aggressiveness. In univariate analysis, Sher et al (2008) showed that lower adiponectin levels were associated with increased odds of pathologic Gleason scores ≥7 (OR 2.04 95% CI 1.16-3.58, p = 0.014). Tewari (2013) also showed that lower adiponectin levels were associated with high grade (OR 0.86 95% CI 0.80-0.92, p <0.0001) and high stage (OR 0.94 95% CI 0.88-0.99, p = 0.02) of prostate cancer. Burton (2013) also reported that adiponectin was inversely associated with prostate cancer stage particularly in

overweight and obese men (OR 0.62 95% CI 0.42-0.90, p = 0.006), but was not associated with grade (0.90 95 % CI 0.63-1.28, p = 1.00). Di Sebastiano et al (2017) states that subjects with Gleason ≥4 + 3 tended to have lower adiponectin compared with other groups, but this was not statistically significant when compared with control (p = 0.069). Another study by Housa (2008) analysing serum noted that higher adiponectin levels were found in locally advanced relative to organ-confined cancer (p <0.005), correlated with the sub stage of disease (rho = 0.35, p <0.02) and PSA levels (rho = 0.40, p <0.01). In contrast, three cross-sectional studies did not show an association with prostate cancer aggressiveness. Sieminska et al (2018) did not show an association between adiponectin and aggressiveness with no different between adiponectin levels in advanced prostate cancer compared with controls (mean ± SD, median; ug / mL) (18.29 ± 6.28, 17.0 vs. 17.53 ± 8.35, 16). Furthermore, Kang et al (2018) showed no evidence of an association between adiponectin and tumour stage (OR univariate 0.97 95% CI 0.88-1.06, p = 0.534), as did Baillargeon et al (2006) (OR 1.93 95% CI 0.74-5.10, p trend 0.85).

Two cross-sectional receptor expression studies reported contrasting results. A study exploring adiponectin receptors by Tan (2015) reported that adiponectin expression was down regulated in prostate cancer cases (p <0.01). Researchers also reported that decreased adiponectin expression was significantly associated with a high Gleason score (p <0.001). However, no significant association was identified between adiponectin expression levels and preoperative PSA levels (p = 0.552) or higher pathological tumour stage (pT) (p = 0.351) (Tan et al., 2015). In contrast Housa et al (2008) reported no association between adipokine receptors and prostate cancer aggressiveness (although their data were not shown).

Therefore, in summary, case-control studies and nested case-control studies and cross-sectional studies all report a mixed association between adiponectin and prostate cancer aggressiveness (**Table 2.7**), and this inconsistent pattern was maintained even if the method of assessment (mostly conducted in serum) is considered.

Table 2.7. Summary association for adiponectin and prostate cancer aggressiveness

No	Author (Year)	Study Design	Biological measurement	Association	
				Type	Direction
1	Li (2010)	Nested case-control	Serum	Mixed	potentially +
2	Stevens (2014)	Nested case-control	Serum	Not associated	n/a
3	Goktas (2005)	Case-control	Serum	Associated	-
4	Freedland (2005)	Case-control	Serum	Mixed	mixed
5	Arisan (2009)	Case-control	Serum	Associated	+
6	Lopez-Fontana (2011)	Case-control	Serum	Not associated	n/a
7	Fowke (2013)	Case-control	serum	Not associated	n/a
8	Baillargeon (2006)	Cross-sectional	Serum	Not associated	n/a
9	Sher (2008)	Cross-sectional	Serum	Associated	-
10	Housa (2008)	Cross-sectional	Serum	Associated	+
11	Tewari (2013)	Cross-sectional	Serum	Associated	-
12	Burton (2013)	Cross-sectional	Serum	Mixed	potentially -
13	Di Sebastiano (2017)	Cross-sectional	Serum	Mixed	potentially -
14	Sieminska (2018)	Cross-sectional	Serum	Not associated	n/a
15	Kang (2018)	Cross-sectional	Serum	Not associated	n/a
16	Housa (2008)	Cross-sectional	Receptor expression	Not associated	n/a
17	Tan (2015)	Cross-sectional	Receptor expression	Mixed	mixed

Note: (+): positive, higher adiponectin-increased risk or lower adiponectin-decreased risk, (-): negative, higher adiponectin-decreased risk or lower adiponectin-increased risk, (potentially): mixed results, but suggested direction given, n/a: not applicable; no significant association detected

Table 2.8. The list of adiponectin and prostate cancer aggressiveness studies reviewed base on type of outcome, type of biological measurement and type of study design

No	Author (Year)	Country, (participants)	Type of outcomes	Type of study Design	Type of biological measurement	Exposure	Covariates	Summary
Adiponectin and prostate cancer (aggressiveness; serum; nested case-control)								
1	Li et al (2010)	USA, (654 PCA, 644 controls) [d]	Aggressiveness	Nested case-control	Serum	Level of Adiponectin plasma (Quintile: Q_5 median 13.3 mg/L vs Q_1 median 2.7 mg/L)	*Model 1* - adjusted for age and smoking status at base line; *Model 2* - adjusted for age, BMI, C-peptide, stage, grade; *Model 3* - (-)	Higher Adiponectin was not associated with high-grade prostate cancer (Gleason score ≥8) (RR 0.23 95%CI 0.06-0.83, p_{trend} = 0.08) and lethal cancer (RR 0.61 95%CI 0.12-2.99, p_{trend} = 0.44). However, prediagnostic higher concentration of *adiponectin* might be related with prostate cancer-specific mortality (HR 0.35 95%CI 0.14-0.89, p_{trend} = 0.03). While higher prediagnostic *adiponectin* concentration might also be related with progression to fatal prostate cancer after diagnosis mainly among men who were overweight or obese (BMI ≥25 kg/m2) (HR 0.10 95% CI 0.01-0.78, p_{trend} = 0.02).
2	Stevens et al (2014)	USA, (272 PCA, 272 controls) [l]	Aggressiveness	Nested Case-control	Serum	Adiponectin plasma (stratified on pair: GS ≥ 7 (4+3) or T3-T4) (Quartiles: Q4 ≥ 11.109 vs Q1 < 6.178 ng/ml); comparing cancer cases (with aggressive disease) with non-cancer controls	Adjusted for family history of prostate cancer, BMI, physical activity in metabolic equivalents (METs), total calcium intake, energy intake	The *adiponectin* was not associated with prostate cancer all aggressiveness risk (OR 1.11 95%CI 0.64-1.93 p_{trend} = 0.59)

Studies as part of a larger Study: [b] San Antonio Center for Biomarkers of Risk of Prostate Cancer Cohort Study (SABOR); [d] Physicians' Health Study; [e] the Supplementation en Vitamines et Mineraux Antioxydants (SU.VI.MAX); [g] The Alpha-Tocopherol, Beta-carotene (ATBC) Cancer Prevention Study; [i] the Prostate Testing for Cancer and Treatment (ProtecT); [j] Flint Men's Health Study (FMHS); [k] The Nashville Men's Health Study (NHS); [l] Cancer Prevention Study II Nutrition Cohort; [m] Physicians' Health Study (PHS), Health Professionals Follow-up Study (HPFS)

Table 2.8. The list of adiponectin and prostate cancer aggressiveness studies reviewed base on type of outcome, type of biological measurement and type of study design (continue)

No	Author (Year)	Country, (participants)	Type of outcomes	Type of study Design	Type of biological measurement	Exposure	Covariates	Summary
Adiponectin and prostate cancer (aggressiveness; serum; case-control)								
3	Goktas et al (2005)	Turkey, (30 PCA, 36 controls)	Aggressiveness	Case-control	Serum	Adiponectin serum in µg/mL (PCA 5.3±1.6 vs. control 6.0±1.7; advanced 4.7±1.2 vs. organ confined 6.0±1.7)	*Model 1* - PCA vs control; *Model 2* - confined vs advanced PCA	Levels of *adiponectin* PCA group was significantly lower compare with control group (5.3 ± 1.6 vs 16.2 ± 4.1, p < 0.001); Levels of *adiponectin* organ confined group was also significantly lower compare with control group (6.0 ± 1.7 vs 4.7 ± 1.2, p = 0.012). Furthermore, levels of *adiponectin* were correlated significantly with PSA, biopsy GS, and GS (r = -0.478, p = 0.008; r = -0.621, p = 0.001; r = -0.642, p < 0.001).
4	Freedland et al (2005)	USA, (158 pT2, 78 pT3a or greater)	Aggressiveness	Case-control	Serum	Adiponectin serum (BMI : < 25 and ≥ 25); stage (≥ pT3); grade (GS ≥ 7)	*All Model* - adjusted for age and BMI	In BMI < 25, *adiponectin* was positively associated with high stage PCA (OR 1.14 95%CI 1.02-1.29, p = 0.03) but no association with high grade PCA (OR 1.05 95%CI 0.94-1.18, p = 0.38); In BMI ≥ 25, *adiponectin* was not associated with high-*grade* (OR 0.94 95%CI 0.87-1.01, p = 0.09) or high *stage* PCA (OR 0.97 95%CI 0.91-1.04, p = 0.43).

Studies as part of a larger Study: [b] San Antonio Center for Biomarkers of Risk of Prostate Cancer Cohort Study (SABOR); [d] Physicians' Health Study; [e] the Supplementation en Vitamines et Mineraux Antioxydants (SU.VI.MAX); [g] The Alpha-Tocopherol, Beta-carotene (ATBC) Cancer Prevention Study; [i] the Prostate Testing for Cancer and Treatment (ProtecT); [j] Flint Men's Health Study (FMHS); [k] The Nashville Men's Health Study (NHS); [l] Cancer Prevention Study II Nutrition Cohort; [m] Physicians' Health Study (PHS), Health Professionals Follow-up Study (HPFS)

Table 2.8. The list of adiponectin and prostate cancer aggressiveness studies reviewed base on type of outcome, type of biological measurement and type of study design (continue)

No	Author (Year)	Country, (participants)	Type of outcomes	Type of study Design	Type of biological measurement	Exposure	Covariates	Summary
5	Arisan et al (2009)	Turkey, (50 PCA, 50 controls)	Aggressiveness	Case-control	Serum	Levels of adiponectin (Continuous: ng/ml)	(-)	Advanced PCA patients had higher *adiponectin* levels than organ-confined one (p = 0.044). While the decline of adiponectin levels was greater than other groups (p = 0.0021 and p = 0.0023) In addition, the *leptin-to-adiponectin ratio* was higher in advanced PCA than organ-confined one (p = 0.028) and this ratio was found to be 3.90 time higher in high-grade subject. All grade PCA *leptin-to-adiponectin ratio* was higher compare with control and BPH group (p < 0.05).
6	Lopez-Fontana et al (2011)	Argentina, (35 PCA, 35 controls)	Aggressiveness	Case-control	Serum	Levels of Adiponectin (no cut-off)	(-)	*Adiponectin* levels showed no statistical differences regarding the presence and aggressiveness of the tumour (p = 0.131).
7	Fowke et al (2013)	USA, (95 low grade PCA, 98 high grade PCA, 137 controls) [k]	Aggressiveness	Case-control	Serum	Level of leptin serum (BMI: <30 vs. ≥30; WC in cm: <104.1 vs. ≥ 104.1; WHR: <1.01 vs. ≥1.01; Height in cm: <175.3 vs. ≥175.3)	All Model - adjusted for age, alpha-blocker use, treatment for diabetes, number of cores collected at biopsy, and prostate volume	A higher *adiponectin* levels were not significantly associated with *high grade* PCA among control and case (OR 0.63 95%CI 0.23-1.68, p = 0.33) and (OR 1.32 95%CI 060-2.49, p = 0.49).

Studies as part of a larger Study: [b] San Antonio Center for Biomarkers of Risk of Prostate Cancer Cohort Study (SABOR); [d] Physicians' Health Study; [e] the Supplementation en Vitamines et Mineraux Antioxydants (SU.VI.MAX); [g] The Alpha-Tocopherol, Beta-carotene (ATBC) Cancer Prevention Study; [i] the Prostate Testing for Cancer and Treatment (ProtecT); [j] Flint Men's Health Study (FMHS); [k] The Nashville Men's Health Study (NHS); [l] Cancer Prevention Study II Nutrition Cohort; [m] Physicians' Health Study (PHS), Health Professionals Follow-up Study (HPFS)

Table 2.8. The list of adiponectin and prostate cancer aggressiveness studies reviewed base on type of outcome, type of biological measurement and type of study design (continue)

No	Author (Year)	Country, (participants)	Type of outcomes	Type of study Design	Type of biological measurement	Exposure	Covariates	Summary
Adiponectin and prostate cancer (aggressiveness; serum; cross-sectional)								
8	Baillargeon et al (2006)	USA, (125 PCA, 125 controls) [b]	Aggressiveness	Cross-sectional	Serum	Serum adiponectin (BMI: <25, 25-29.9, ≥30; high vs. low grade; prospectively measured adipokines (mean time of 1.43 years prior diagnosis)	*Model 1* - matching age adjusted race/ethnicity; *Model 2* - adjusted for age and race/ethnicity; *Model 3* - adjusted for age and race/ethnicity	Adiponectin was not related with high *grade* disease (highest vs lowest tertile) (OR 1.93 95%CI 0.74-5.10, p_{trend} 0.85).
9	Sher et al (2008)	USA, (505 PCA-Biopsy GS at diagnosis, 179 PCA-GS at RP)	Aggressiveness	Cross-sectional	Serum	Adiponectin serum at radical prostatectomy (≥7 vs <6) (univariate)	*Model* - adjusted for BMI	In univariate analysis, lower *adiponectin* levels associated with increased odds of RP pathologic GS ≥7 (OR 2.04 95%CI 1.16-3.58, p = 0.014)
10	Housa et al (2008)	Czech Republic, (43 PCA)	Aggressiveness	Cross-sectional	Serum,	Serum adiponectin stratified on pT2 and pT3	(-)	A significantly higher *adiponectin* levels in locally advanced relative to organ-confined cancer were found (p < 0.005). After grades stratification, *adiponectin* positively correlated with the sub stage of disease (rho = 0.35, p < 0.02) and correlated PSA levels (rho = 0.40, p < 0.01). In organ-confined cancer a p_{trend} toward inverse relationship between *adiponectin* levels and BMI (rho = -0.40, p_{trend} = 0.07).

Studies as part of a larger Study: [b] San Antonio Center for Biomarkers of Risk of Prostate Cancer Cohort Study (SABOR); [d] Physicians' Health Study; [e] the Supplementation en Vitamines et Mineraux Antioxydants (SU.VI.MAX); [g] The Alpha-Tocopherol, Beta-carotene (ATBC) Cancer Prevention Study; [i] the Prostate Testing for Cancer and Treatment (ProtecT); [j] Flint Men's Health Study (FMHS); [k] The Nashville Men's Health Study (NHS); [l] Cancer Prevention Study II Nutrition Cohort; [m] Physicians' Health Study (PHS), Health Professionals Follow-up Study (HPFS)

Table 2.8. The list of adiponectin and prostate cancer aggressiveness studies reviewed base on type of outcome, type of biological measurement and type of study design (continue)

No	Author (Year)	Country, (participants)	Type of outcomes	Type of study Design	Type of biological measurement	Exposure	Covariates	Summary
11	Tewari et al (2013)	India, (95 PCA)	Aggressiveness	Cross-sectional	Serum	Levels adiponectin (Grade (low and high); Stage (III and IV))	Unadjusted	*Lower Adiponectin* levels on grade (OR 0.86 95%CI 0.80-0.92, p < 0.0001); lower *Adiponectin* levels on stage (OR 0.94 95%CI 0.88-0.99, p = 0.02).
12	Burton et al (2013)	UK, (331 locally advanced PCA, 413 localized PCA) [i]	Aggressiveness	Cross-sectional	Serum	Adiponectin serum (Q_4 9.7-37.2 ng/ml vs. Q_1 0.9-4.5 ng/ml); stratified on stage (locally advanced & localised) and grade (GS ≥7 vs ≤6); 'controls' are men with localized PC) blood taken (a mean of 9 weeks prior diagnosis)	*Model 1* - adjusted on age at recruitment assay plate; *Model 2* - adjusted on age at recruitment, assay plate, recruitment centre	*Adiponectin* was inversely associated with prostate cancer *stage* in overweight and obese men (OR 0.62 95%CI 0.42-0.90, p = 0.006); whereas on *grade* (OR 0.90 95%CI 0.63- 1.28, p = 1.00). No evidence of relationship between *leptin* or l*eptin-to-adiponectin ratio* in prostate cancer stage.
13	Di Sebastiano et al (2017)	Canada, (36 high risk PCA, 15 PCA)	Aggressiveness	Cross-sectional	Serum	Adiponectin serum (GS: 3+3, 3+4, ≥4+3)	(-)	Patients with Gleason ≥4 + 3 tended had lower *adiponectin* compared with other groups, but the difference was not significant (p = 0.069). Gleason ≥4 + 3 patients had significantly highest *leptin-to-adiponectin ratio* compare to other groups (p = 0.013). *Leptin-to-adiponectin ratio* was statistically effect Gleason score prediction (r^2 = 0.398, p = 0.027) together with age and PSA.

Studies as part of a larger Study: [b] San Antonio Center for Biomarkers of Risk of Prostate Cancer Cohort Study (SABOR); [d] Physicians' Health Study; [e] the Supplementation en Vitamines et Mineraux Antioxydants (SU.VI.MAX); [g] The Alpha-Tocopherol, Beta-carotene (ATBC) Cancer Prevention Study; [i] the Prostate Testing for Cancer and Treatment (ProtecT); [j] Flint Men's Health Study (FMHS); [k] The Nashville Men's Health Study (NHS); [l] Cancer Prevention Study II Nutrition Cohort; [m] Physicians' Health Study (PHS), Health Professionals Follow-up Study (HPFS)

Table 2.8. The list of adiponectin and prostate cancer aggressiveness studies reviewed base on type of outcome, type of biological measurement and type of study design.

No	Author (Year)	Country, (participants)	Type of outcomes	Type of study Design	Type of biological measurement	Exposure	Covariates	Summary
14	Sieminska et al (2018)	Poland, (74 PCA, Gleason score ≤6 n=24; Gleason score 7 n=28; Gleason score ≥8 n=22)	Aggressiveness	Cross-sectional	Serum	Adiponectin serum (GS: poorly differentiated ≥8 vs. well differentiated ≤6)	(-)	Adiponectin serum was not different in advanced PCA when compared with control (mean ± SD, median; ug/mL) (18.29 ± 6.28, 17.0 vs. 17.53 ± 8.35, 16).
15	Kang et al (2018)	Korea, (25 non-obese PCA, 37 obese PCA)	Aggressiveness	Cross-sectional	Serum	Adiponectin serum (BMI: obese ≥25 vs. normal <25)	*Model 1 and 2* - univariate; *Model 3* - multivariate	In all PCA patients, there were no evidence regarding *adiponectin* (OR $_{univariate}$ 0.97 95%CI 0.88-1.06, p = 0.534) in predicting advance tumour stage.
Adiponectin and prostate cancer (aggressiveness; receptor expression; cross-sectional)								
16	Housa et al (2008)	Czech Republic, (43 PCA)	Aggressiveness	Cross-sectional	Receptor expression	(-)	(-)	No association between adipokines receptor and PCA aggressiveness (but data not shown)
17	Tan et al (2015)	China, (96 PCA)	Aggressiveness	Cross-sectional	Receptor expression	Adiponectin genetic expression (% power of expression)	(-)	*Adiponectin* expression was significantly down-regulated in PCA cases compared with BPH ($p < 0.01$); Decreased *adiponectin* expression was significantly associated with high GS ($p < 0.001$); No significant association was identified between *adiponectin* expression levels and preoperative PSA levels (p = 0.552) or higher pathological tumour stage (pT) (p = 0.351).

Studies as part of a larger Study: [b] San Antonio Center for Biomarkers of Risk of Prostate Cancer Cohort Study (SABOR); [d] Physicians' Health Study; [e] the Supplementation en Vitamines et Mineraux Antioxydants (SU.VI.MAX); [g] The Alpha-Tocopherol, Beta-carotene (ATBC) Cancer Prevention Study; [i] the Prostate Testing for Cancer and Treatment (ProtecT); [j] Flint Men's Health Study (FMHS); [k] The Nashville Men's Health Study (NHS); [l] Cancer Prevention Study II Nutrition Cohort; [m] Physicians' Health Study (PHS), Health Professionals Follow-up Study (HPFS)

2.3.2.6. Adiponectin and prostate cancer progression

Two studies reported the association of adiponectin with prostate cancer progression; these consisted of one cohort study (Rider et al., 2015) and one cross-sectional study (Gu et al., 2014) (**Table 2.9** and **2.10**).

One receptor expression study of prostate cancer progression by Rider et al (2015) reported that the increased risk of lethal prostate cancer for the upper quartiles of AdipoR 2 expression was significant only when controlling for BMI (HR 1.7 95% CI 1.1-2.6, p = 0.01). The association between AdipoR 2 expression and lethal prostate cancer risk might be stronger in overweight men compared with healthy weight men (HR 2.28 95% CI 1.18-4.37 vs. HR 1.17 95% CI 0.60-2.28, p interaction = 0.16) although it was not statistically significant (Rider et al., 2015). The association between adiponectin DNA and prostate cancer progression was reported by Gu et al (2015) through a cross-sectional study, which stated that ADIPOQ rs182052 variant allele was associated with both increased risk of biochemical recurrence (HR 2.44 95% CI 1.57-3.79, p = 0. 000006) and decreased adiponectin levels in subjects with prostate cancer (β = -0.048, p = 0.004).

Therefore, in summary, the two studies which have been conducted both report an association between adiponectin and prostate cancer progression. The result from the cross-sectional study (DNA) is fully supported by the cohort study (receptor), which could be considered as the strongest research methodology (Table 9), but the overall number of studies is small.

Table 2.9. Summary association for adiponectin and prostate cancer progression

No	Author (Year)	Study Design	Biological measurement	Association	
				Type	Direction
1	Rider (2015)	Cohort	Receptor expression	Mixed	Potentially +
2	Gu (2015)	Cross-sectional	DNA	Associated	+

Note: (+): positive, higher adiponectin-increased risk or lower adiponectin-decreased risk, (-): negative, higher adiponectin-decreased risk or lower adiponectin-increased risk, (potentially): mixed results, but suggested direction given, n/a: not applicable; no significant association detected

Table 2.10. The list of adiponectin and prostate cancer progression studies reviewed base on type of outcome, type of biological measurement and type of study design

No	Author, Journal, (Year)	Country, (participants)	Type of outcomes	Type of study Design	Type of biological measurement	Exposure	Covariates	Summary
Adiponectin and prostate cancer (progression; receptor expression; cohort)								
1	Rider et al (2015)	USA, (866 PCA) [m]	Progression	Cohort	Receptor expression	AdipoR2 expression (no cut-off)	*Model 1* - dichotomous median from model 1-3; *Model 2* - adjusted for age at diagnosis, GS, year of diagnosis, cohort, BMI at baseline, ki67 expression	Estimated lethal PCA for the upper quartiles of *AdipoR2* expression was significant only in controlling BMI group (HR 1.7 95%CI 1.1-2.6, p = 0.01); AdipoR2 expression was stronger in overweight men (HR 2.28 95%CI 1.18-4.37) vs healthy weight men (HR 1.17 95%CI 0.60-2.28) although it was not statistically significant ($p_{interaction}$ = 0.16).
Adiponectin and prostate cancer (progression; DNA; nested case-control)								
2	Gu et al (2015)	China, (728 PCA)	Progression	Cross-sectional	DNA	ADIPO rs182052 variant allele (no cut-off); biochemical recurrence & decrease adiponectin levels	Model - adjusted for age, PSA at diagnosis, GS, pathologic stage and lymph node involvement	*ADIPOQ* rs182052 variant allele was associated with both increased risk of biochemical recurrence (HR 2.44 95%CI 1.57-3.79, p = 0. 000006) and decreased adiponectin level (β = -0.048, p = 0.004).

Studies as part of a larger Study: [b] San Antonio Center for Biomarkers of Risk of Prostate Cancer Cohort Study (SABOR); [d] Physicians' Health Study; [e] the Supplementation en Vitamines et Mineraux Antioxydants (SU.VI.MAX); [g] The Alpha-Tocopherol, Beta-carotene (ATBC) Cancer Prevention Study; [i] the Prostate Testing for Cancer and Treatment (ProtecT); [j] Flint Men's Health Study (FMHS); [k] The Nashville Men's Health Study (NHS); [l] Cancer Prevention Study II Nutrition Cohort; [m] Physicians' Health Study (PHS), Health Professionals Follow-up Study (HPFS)

2.3.3. Quantitative meta-analysis of included studies

In the meta-analysis stage, involved studies had to meet the following requirements: a) studies must be the same in terms of biological measurement and outcomes, b) studies must have the OR or RR and p-value and c) studies must have a control group and a case group. Studies that did not fulfil required prerequisites could not be included within the meta-analysis. However, due to the large degree of heterogeneity among studies in this review, a definitive meta-analysis was difficult to conduct. In the end, the pooled analysis only included serum studies related to risk and aggressiveness in both leptin and adiponectin. Analysis of prostate cancer progression was not possible, due to the lack of available studies. In the end, there were only nine out of 20 studies measuring serum leptin and five out of 18 studies measuring serum adiponectin that could be included in the meta-analysis.

The studies included in the meta-analysis were all serum studies and were a combination of nested case-control, case-control, and cross-sectional studies. ORs or RRs and their corresponding 95% confidence intervals were pooled using results from the unadjusted (or age-adjusted) models, and from the maximally adjusted regression models.

All studies involved in the meta-analysis were assessed with the Newcastle-Ottawa Scale (NOS). The NOS scores for studies considered within the review ranged from 5 to 9, with 11 studies being considered to have a high score (7-9) and the 5 other studies were considered to have a low score (5-6). The average value obtained from all studies included within the meta-analysis was 7.2. Details of NOS scoring are presented in **Table 2.11** and **2.12** below.

Table 2.11. NOS scoring for case-control and nested case-control studies

Newcastle-Ottawa Scale Analysis for Case-control & Nested Case-control										
Author	Years	Selection				Comparability	Exposure			Total Quality Scores
		The case definition is adequate	Representativeness of cases	Selection of control	Definition of control	Case and control with comparability based on the design or analysis	Ascertainment of exposure	Ascertainment of exposure using the same method for cases and controls	Ascertainment of exposure with non-response rate for both groups	
Lagiou	1998	*	*	*	-	*	*	*	-	6
Stattin	2001	*	*	*	*	*	*	*	-	7
Hsing	2001	*	*	*	*	*	**	*	-	8
Stattin	2003	*	*	*	-	*	**	*	-	7
Baillargeon	2006	*	*	*	*	*	**	*	-	8
Gade-Andavolu	2006	-	-	*	*	*	*	*	-	5
Stocks	2007	*	*	*	*	**	**	*	-	9
Michalakis	2007	*	*	-	*	*	*	*	-	6
Li	2010	*	*	*	*	**	**	*	-	9
Touvier	2012	*	*	*	*	*	-	*	-	6
Fowke	2013	*	*	*	*	**	*	*	-	8
Lai	2014	*	*	*	*	**	**	*	-	9
Stevens	2014	*	*	*	*	*	*	*	-	7

Table 2.12. NOS scoring for cross-sectional studies

Newcastle-Ottawa Scale Analysis for Cross-sectional									
Author	Years	Selection				Comparability	Exposure		Total Quality Scores
		Representativeness of sample	Sample size	Non-respondents	Ascertainment of exposure (risk factor)	The subject in different outcome group are comparable, based on study design or analysis	Assessment of the outcome	Statistical Test	
Freedland	2005	*	*	*	**	*	**	*	8
Sher	2008	*	-	-	**	*	-	*	5
Burton	2013	*	*	*	**	*	**	*	9

2.3.3.1. Serum leptin and prostate cancer risk

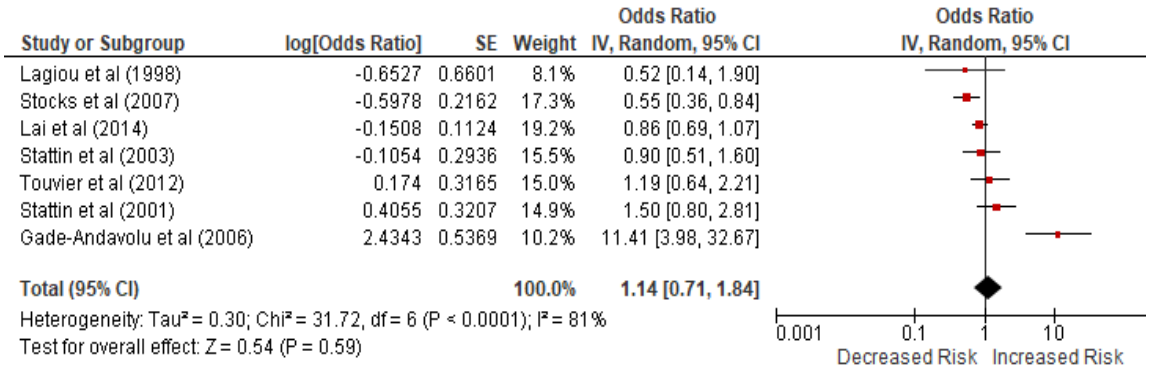
Meta-analysis of the association between serum leptin and prostate cancer risk was performed separately for unadjusted and for multivariable-adjusted results. The meta-analysis of the association between serum leptin and prostate cancer risk using unadjusted data involved five nested case-control studies and two case-control studies from the total seven selected studies. The analysis result showed no significant relationship between serum leptin and prostate cancer risk (OR 1.14 95% CI 0.71-1.84, p = 0.59) with substantial heterogeneity between studies (I^2 = 81%) (**Figure 2.2**A).

The pooled analysis of the multivariable-adjusted results, including five nested case-control studies, one case-control study and one cross-sectional study of the seven selected studies. The meta-analysis showed no association between serum leptin and prostate cancer risk (OR 0.95 95% CI 0.79-1.15, p = 0.60) but there was no heterogeneity between the included studies (I^2 = 0%) (**Figure 2.2**B).

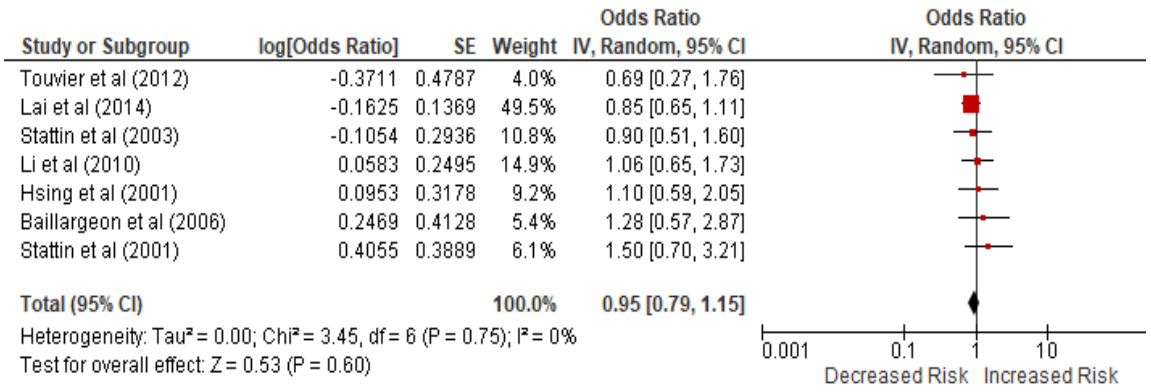
2.3.3.2. Serum leptin and prostate cancer aggressiveness

Meta-analysis of the association between serum leptin and prostate cancer aggressiveness was performed separately for (nested) case control and for cross-sectional studies. The first meta-analysis of the association between serum leptin and prostate cancer aggressiveness using multivariable-adjusted data included three studies [two nested case-control studies (66.6 %) and one case-control study (33.3 %)] and showed no significant association (OR 0.94 95% CI 0.69-1.28, p = 0.71), and no heterogeneity between included studies (I^2 = 0%) (**Figure 2.2**C).

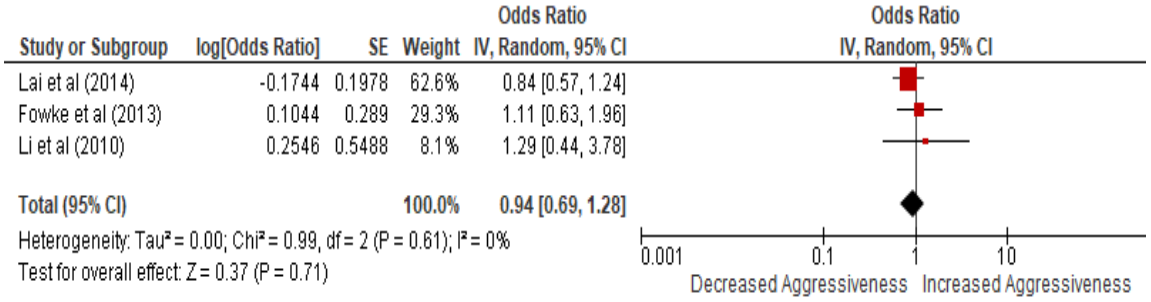
The second multivariable adjusted meta-analysis included two cross-sectional studies showing no association between serum leptin and prostate cancer aggressiveness (OR 1.09 95% CI 0.74-1.60, p = 0.60) and no heterogeneity between included studies (I2 = 0%) as shown in **Figure 2.2**D. Furthermore, when the meta-analysis used only higher-quality studies for analysis, there was no change in the observed results (data not shown).



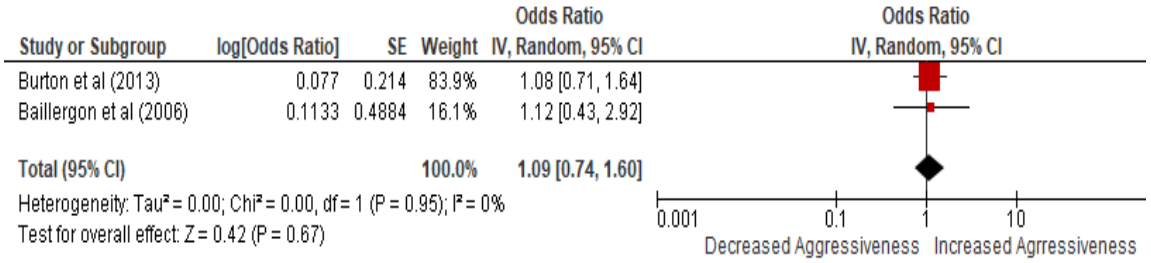
A: unadjusted (some adjusted only for age) estimates for associations between serum leptin and overall prostate cancer risk from (nested) case-control studies



B: multivariable-adjusted estimates for associations between serum leptin and overall prostate cancer risk from (nested) case-control studies



C: multivariable-adjusted estimates for associations between serum leptin and prostate cancer aggressiveness defined by grade from (nested) case-control studies



D: multivariable-adjusted estimates for associations between serum leptin and prostate cancer aggressiveness defined by grade from cross-sectional studies

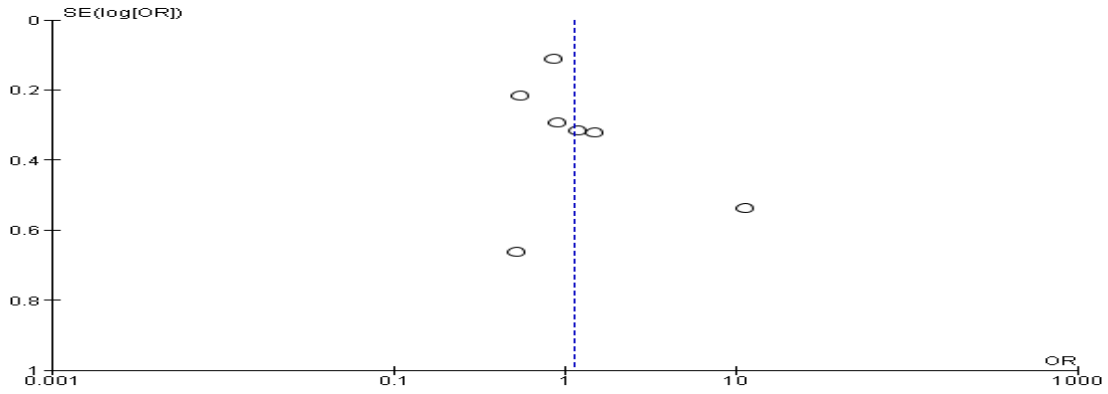
Note: Stattin (2001) and Li (2010) studies reported RR, other studies reported OR.

Figure 2.2. Forest plot showing the results from the leptin meta-analyses

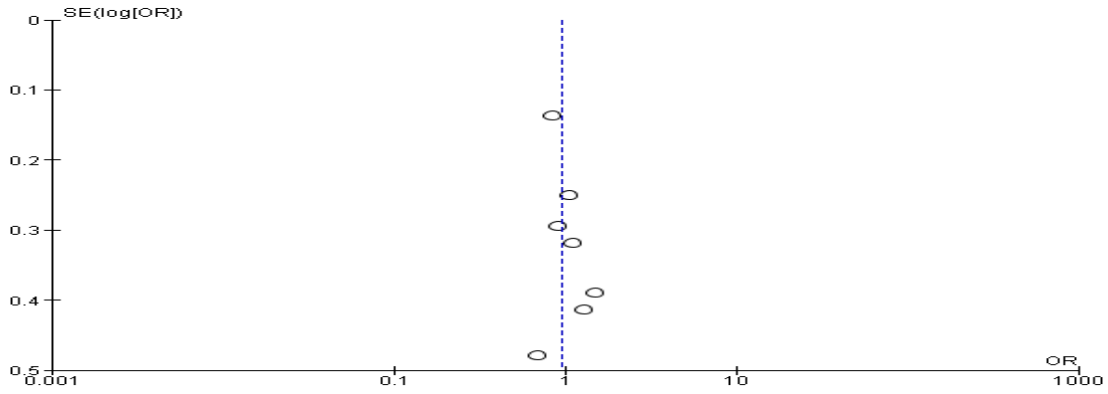
2.3.3.3. Funnel plot for serum leptin and prostate cancer

Funnel plots should generally be used to visualise whether there is likely to be publication bias. Funnel plots could be produced, but, as numbers of studies were small,

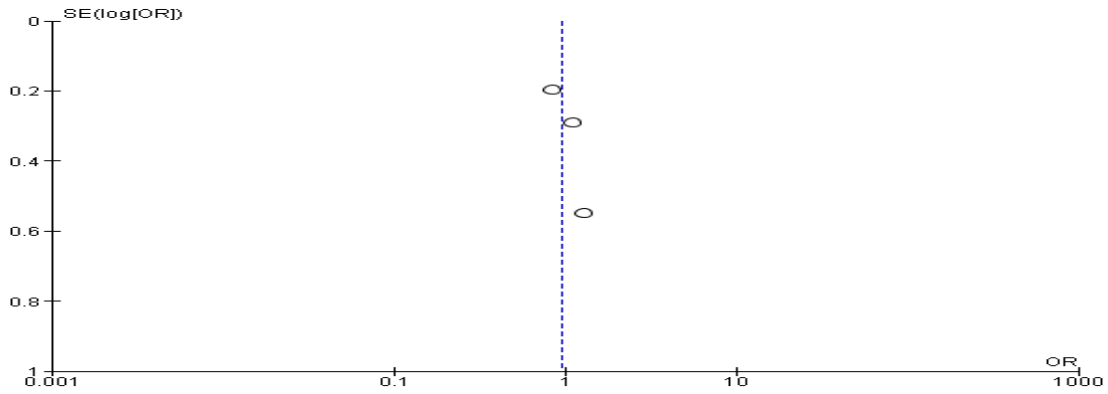
drawing conclusions on the likelihood of publication bias is challenging. The result of Funnel plots is shown in **Figure 2.3**.



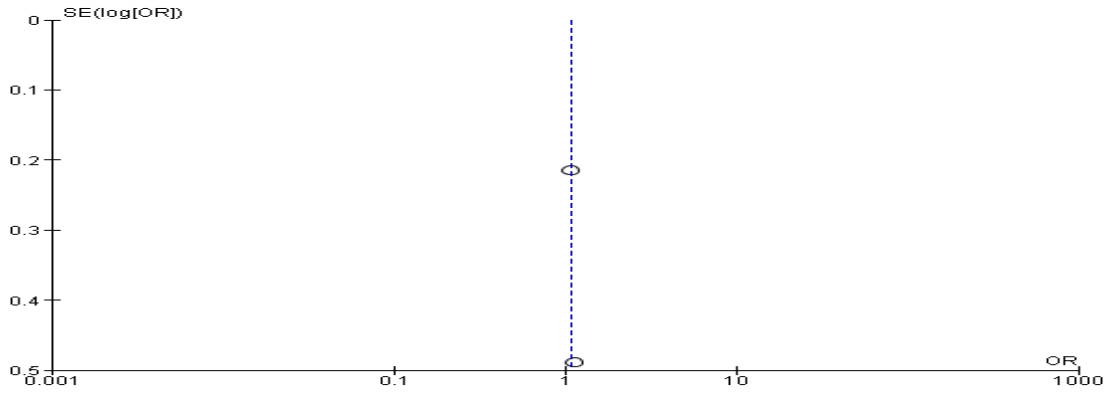
A: unadjusted (some adjusted only for age) estimates for associations between serum leptin and overall prostate cancer risk from (nested) case-control studies



B: multivariable-adjusted estimates for associations between serum leptin and overall prostate cancer risk from (nested) case-control studies



C: multivariable-adjusted estimates for associations between serum leptin and prostate cancer aggressiveness defined by grade from (nested) case-control studies



D: multivariable-adjusted estimates for associations between serum leptin and prostate cancer aggressiveness defined by grade from cross-sectional studies

Figure 2.3. Funnel plot from the leptin studies meta-analyses

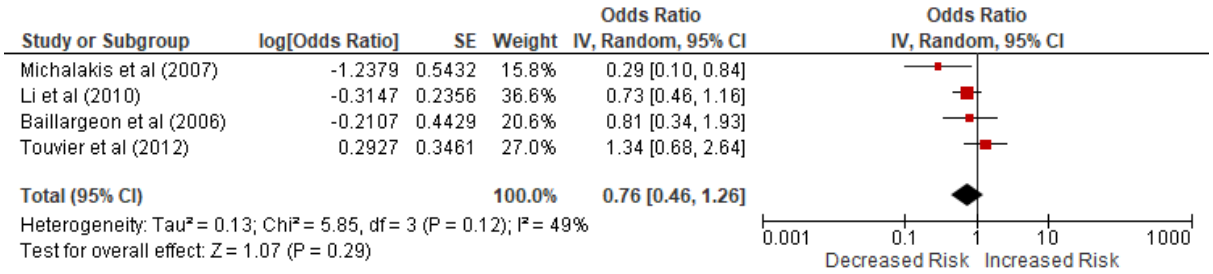
2.3.3.4. Serum adiponectin and prostate cancer risk

Using multivariate-adjusted data from four studies (two nested case-control studies and two case-control studies), no association was shown between serum adiponectin and prostate cancer risk (OR 0.76 95% CI 0.46-1.26, p = 0.29). There was moderate heterogeneity between included studies (I^2 = 49%) (**Figure 2.4A**).

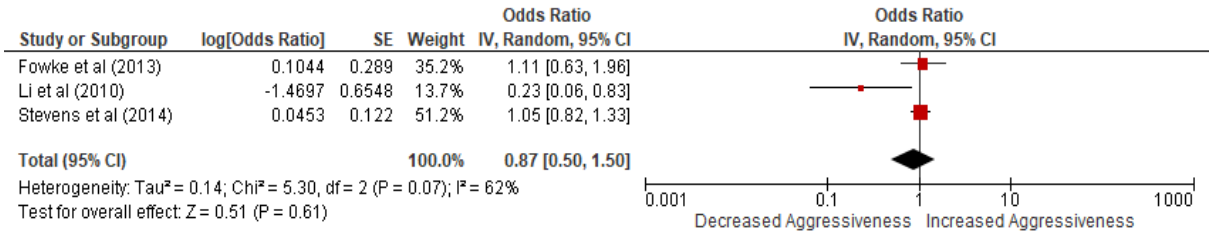
2.3.3.5. Serum adiponectin and prostate cancer aggressiveness

Using multivariate-adjusted data in seven studies, two nested case-control (28.5%), one case-control study (14.2%) and four cross-sectional studies (57.1%), no association was shown between serum adiponectin and prostate cancer grade, either in the combined nested case-control and case-control studies or in the cross-sectional studies (OR 0.87 95% CI 0.50-1.50, p = 0.61 and OR 1.15 95% CI 0.69-1.93, p = 0.58, respectively): (Figure 4B, Figure 4C). Furthermore, there was substantial heterogeneity detected between the combined nested case-control and case-control studies (I^2 = 62%) and the cross-sectional studies (I^2 = 56%).

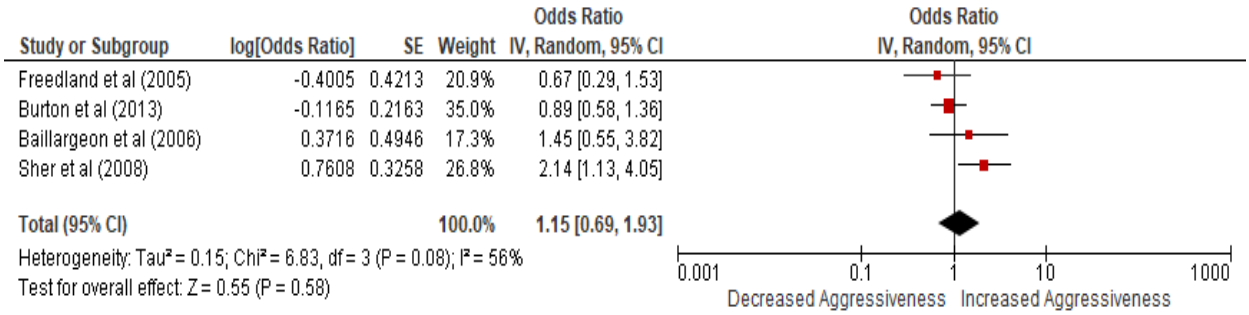
The meta-analysis using multivariable-adjusted data to analyse the association between serum adiponectin and prostate cancer stage included just two cross-sectional studies and showed an inverse association although this was not statistically significant (OR 0.86 95% CI 0.59-1.25, p = 0.40) and there was no heterogeneity between the studies (I^2 = 0%) (Figure 4D). Furthermore, when the meta-analysis used only higher-quality studies for analysis, there was no observed change in results (data not shown).



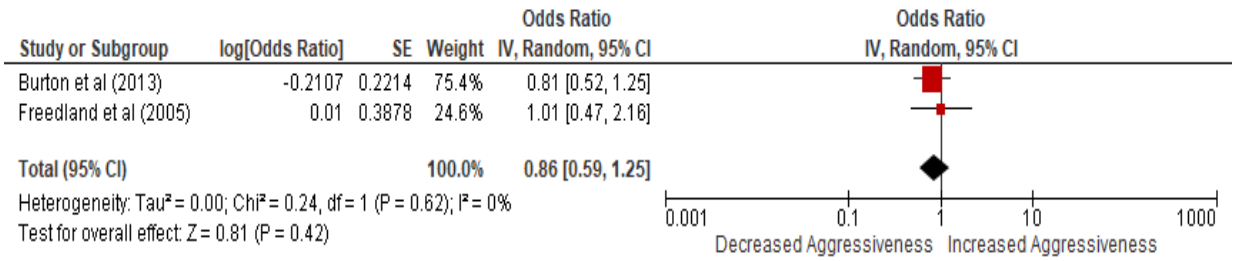
A: multivariable-adjusted estimates for associations between serum adiponectin and overall prostate cancer risk from (nested) case-control studies



B: multivariable-adjusted estimates for associations between serum adiponectin and prostate cancer aggressiveness defined by grade from (nested) case-control studies



C: multivariable-adjusted estimates for associations between serum adiponectin and prostate cancer aggressiveness defined by grade from cross-sectional studies



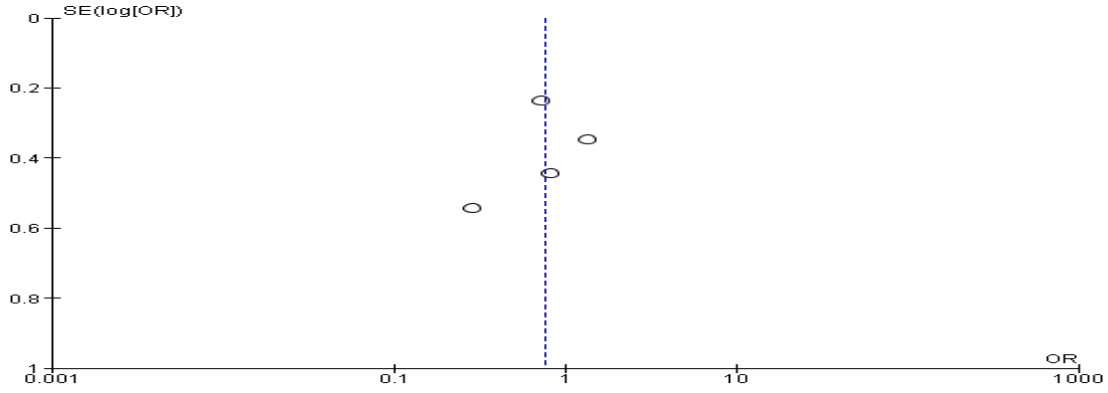
D: multivariable-adjusted estimates for association between serum adiponectin and prostate cancer aggressiveness defined by stage from cross-sectional studies

Li (2010) studies reported RR, other studies reported OR.

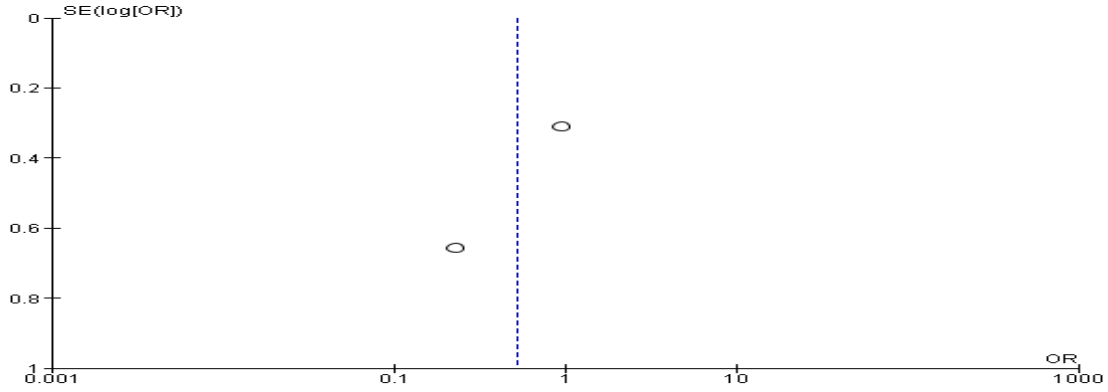
Figure 2.4. Forest plot showing the results from the adiponectin meta-analyses

2.3.3.6. Funnel plot for serum leptin and prostate cancer

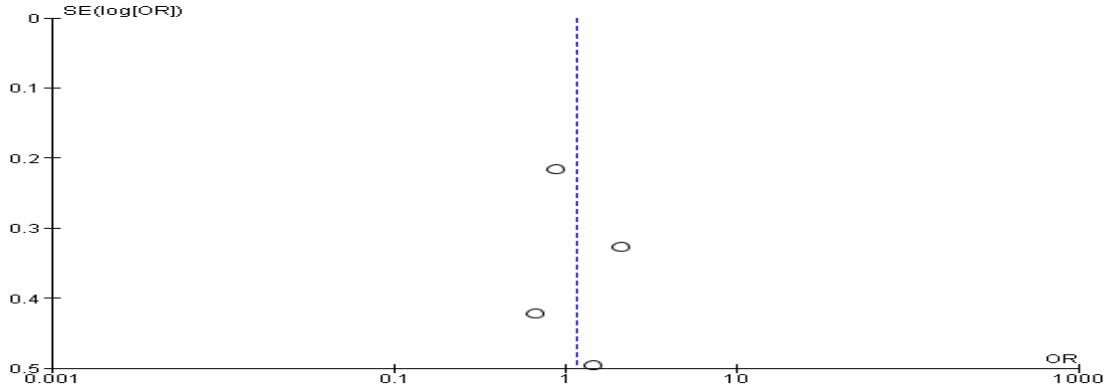
Funnel plots should generally be used to visualise whether there is likely to be publication bias. Funnel plots could be produced, but, as numbers of studies were small, drawing conclusions on the likelihood of publication bias is challenging. The result of Funnel plots is shown in **Figure 2.5**.



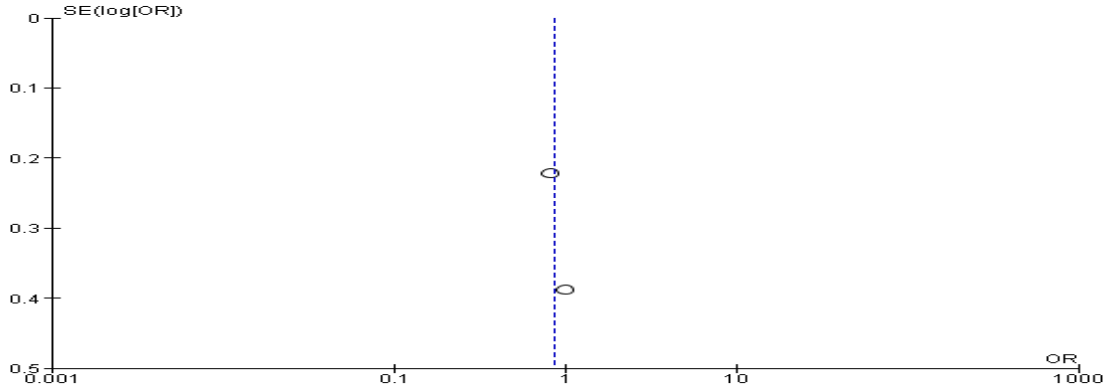
A: multivariable-adjusted estimates for associations between serum adiponectin and overall prostate cancer risk from (nested) case-control studies



B: multivariable-adjusted estimates for associations between serum adiponectin and prostate cancer aggressiveness defined by grade from (nested) case-control studies



C: multivariable-adjusted estimates for associations between serum adiponectin and prostate cancer aggressiveness defined by grade from cross-sectional studies

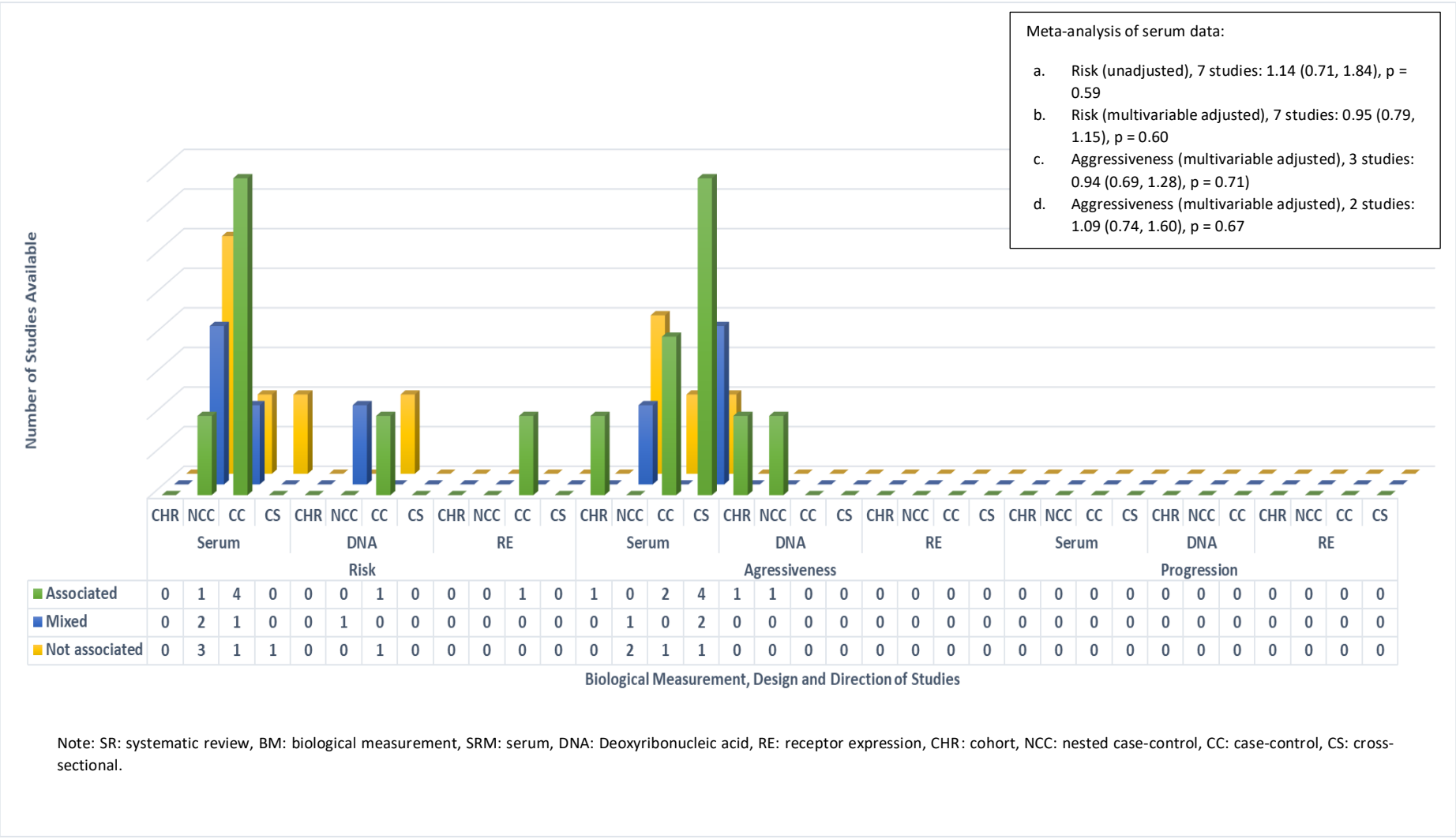


D: multivariable-adjusted estimates for association between serum adiponectin and prostate cancer aggressiveness defined by stage from cross-sectional studies

Figure 2.5. Funnel plot from the adiponectin studies meta-analyses

2.3.4. Summary of narrative systematic review and meta-analysis results

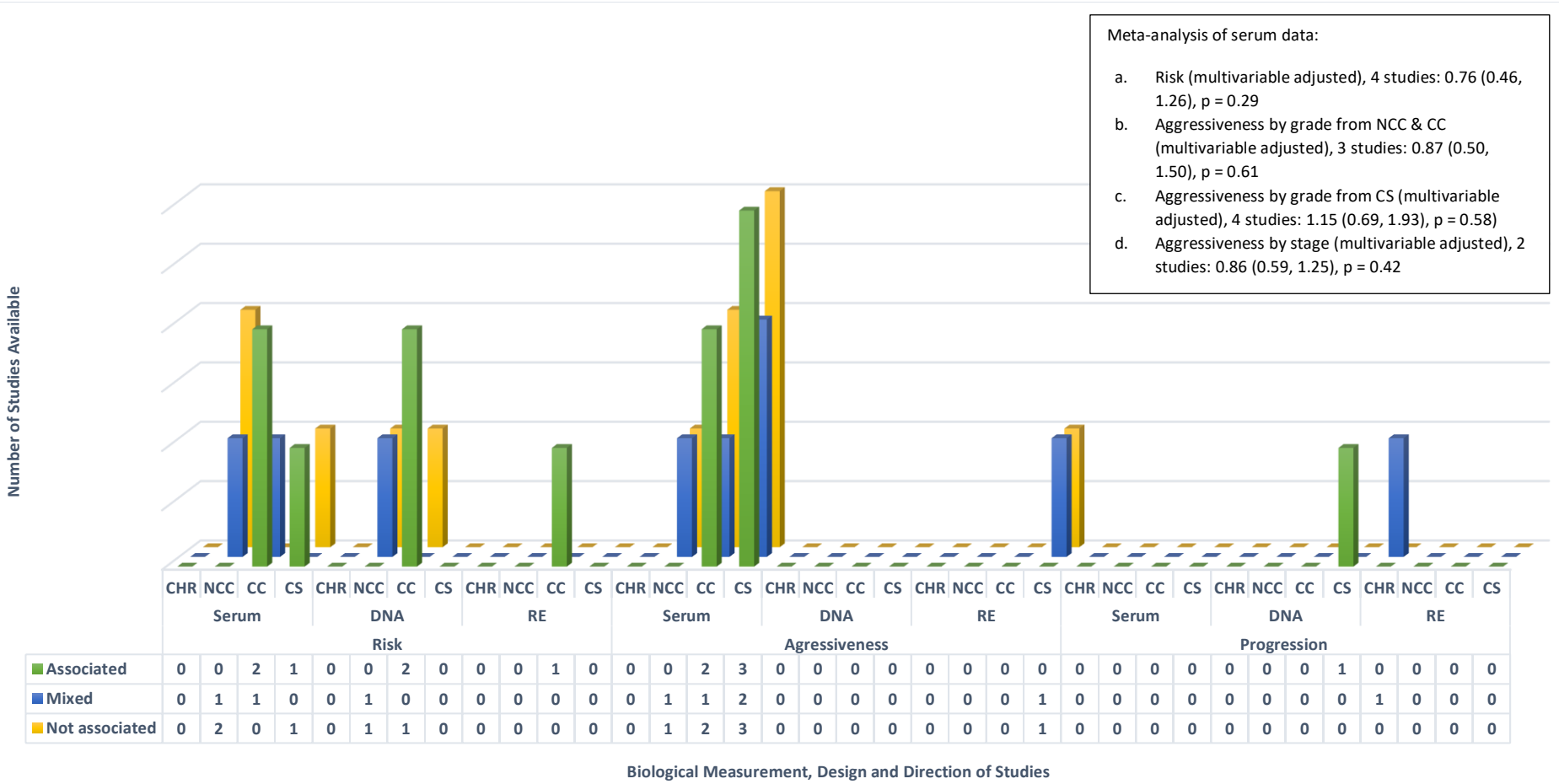
The following Figures try to summarise findings for all available studies (leptin and adiponectin) and their association with prostate cancer outcomes. This study map aims to illustrate the different types of studies, the type of biological measurement and the strength of evidence supporting an association with prostate cancer risk, aggressiveness and progression that have been analysed during this systematic review, but also include the results for the meta-analyses (**Figure 2.6** and **2.7**).



	Risk												Agressiveness												Progression											
	Serum				DNA				RE				Serum				DNA				RE				Serum				DNA				RE			
	CHR	NCC	CC	CS	CHR	NCC	CC	CS	CHR	NCC	CC	CS	CHR	NCC	CC	CS	CHR	NCC	CC	CS	CHR	NCC	CC	CS	CHR	NCC	CC	CS	CHR	NCC	CC	CS	CHR	NCC	CC	CS
Associated	0	1	4	0	0	0	1	0	0	0	1	0	1	0	2	4	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Mixed	0	2	1	0	0	1	0	0	0	0	0	0	0	1	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Not associated	0	3	1	1	0	0	1	0	0	0	0	0	0	2	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Note: SR: systematic review, BM: biological measurement, SRM: serum, DNA: Deoxyribonucleic acid, RE: receptor expression, CHR: cohort, NCC: nested case-control, CC: case-control, CS: cross-sectional.

Figure 2.6. Leptin studies mapping



	Risk								Agressiveness								Progression							
	Serum				DNA				RE				Serum				DNA				RE				Serum				DNA				RE			
	CHR	NCC	CC	CS	CHR	NCC	CC	CS	CHR	NCC	CC	CS	CHR	NCC	CC	CS	CHR	NCC	CC	CS	CHR	NCC	CC	CS	CHR	NCC	CC	CS	CHR	NCC	CC	CS	CHR	NCC	CC	CS
Associated	0	0	2	1	0	0	2	0	0	0	1	0	0	0	2	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0
Mixed	0	1	1	0	0	1	0	0	0	0	0	0	0	1	1	2	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0
Not associated	0	2	0	1	0	1	1	0	0	0	0	0	0	1	2	3	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0

Note: SR: systematic review, BM: biological measurement, SRM: serum, DNA: Deoxyribonucleic acid, RE: receptor expression, CHR: cohort, NCC: nested case-control, CC: case-control, CS: cross-sectional.

Figure 2.7. Adiponectin studies mapping

2.4. Discussion

This systematic review and meta-analysis were conducted with the aim of producing a comprehensive summary and understanding of the evidence for a role for leptin and adiponectin in the association between obesity and prostate cancer. The review strategy used began with a comprehensive search for all possible studies based on keywords, the resulting studies were then judged according to a set of inclusion and exclusion criteria in order to ensure all relevant studies were included. Selected studies were then classified according to whether they explored the relationship between adipokines and prostate cancer risk, aggressiveness, and progression. The search and accompanying analysis also attempted to be comprehensive by including the various ways in which adipokine concentration and activity could be measured, including biological measurements such as in serum, expression of receptors, and via DNA. The analysis explored whether the observed associations differed according to study design, i.e. whether studies were cohort, nested case-control, case-control, or cross-sectional. Where possible, the available studies were included in a meta-analysis, although the number of studies which could be included in this was limited and, therefore, much of the synthesis presented was narrative in nature. In this way, it was intended that this chapter would provide a comprehensive overview of current knowledge regarding adipokine exposure and prostate cancer, and also highlight the gaps in knowledge and make recommendations for future research, but also guide other analyses presented later in this thesis.

2.4.1. Leptin and prostate cancer risk

In summary, the narrative review in this chapter showed that the majority of case-control studies support an association between leptin (usually measured in serum) and prostate cancer risk, this was less consistently supported by nested case-control studies, which would be considered methodologically stronger, and not supported by the limited number of methodologically weaker cross-sectional studies. No analyses have been

conducted in cohort studies. Considering the type of adipokine measurement, the evidence base for association with prostate cancer is really limited to serum, whereas for DNA there were only three studies conducted, and for receptor expression there was only one study published to date. Meanwhile, the meta-analysis showed that serum leptin was not associated with prostate cancer risk, either when considering unadjusted (OR 1.14 95% CI 0.71-1.84, p = 0.59) or multivariable adjusted estimates (OR 0.95 95% CI 0.79-1.15, p = 0.60).

A previous systematic review has also reported the same result; that leptin was not consistently associated with any prostate cancer outcome (Angel et al., 2019), and this was confirmed in meta-analyses for all prostate cancer incidence (RR 0.93 95%CI 0.75-1.16, p = 0.52). Angel et al (2019) also touched on the potential linkage of leptin receptors with the risk of prostate cancer, however, this statement was not supported by their systematic review and meta-analysis since the researchers only explored serum leptin.

The work described in this chapter seemed to suggest an association between leptin and prostate cancer risk, but only in case-control studies, and this was not confirmed in nested case-control studies, or by meta-analysis. No cohort studies have examined the association between serum leptin and prostate cancer risk. Even in the studies which did detect an association between serum leptin and prostate cancer risk, the direction of the association was not consistent, and several of the studies report inconsistent or mixed findings. A limited number of the studies available presented data in a format that allowed pooling and meta-analysis, and therefore the meta-analysis does not reflect all the studies conducted. The studies included in the systematic review and meta-analysis also differed in that the degree of adjustment and the covariates adjusted for were heterogeneous. To illustrate the present heterogeneity between studies, the frequent adjustment covariates found in this chapter were age, BMI, smoking status, alcohol, hormone (insulin and testosterone), stage and grade of prostate cancer. While the occasional covariates were Gleason score, PSA, race/ethnicity,

height, education, cholesterol, energy intake, diabetes mellitus and family history. Covariates that were seldom adjusted for were lymph node, year of diagnosis, treatment, biopsy, physical activity, vitamin and mineral intake, time of blood collection and blood pressure. This heterogeneity in what has been adjusted for may be linked to the high levels of heterogeneity observed in the meta-analysis.

The important thing to note about the relationship between leptin and prostate cancer risk found in this study is the robustness of DNA analysis in detecting risk. A meta-analysis has reported a potentially important role of leptin, adiponectin and their receptors in the aggressiveness and progression of prostate cancer and could be explored as a novel pathway for therapeutic targeting (Hu et al., 2016a). The results of the analysis in a large sample nested case-control study supported by another case-control study revealed that LEP polymorphisms can be associated with PCA risk (Moore et al., 2009). Another study also corroborated by stating that LEP overexpression was associated with the risk of advanced prostate cancer (Ribeiro et al., 2004). While another DNA study disputed this, although it had not directly stated that the leptin genotype could be used to determine someone was not at risk. Examining the role of genetic variation in leptin and adiponectin pathways in relation to total and advanced prostate cancer risk could be potentially explored further in future research, so the result would show a more comprehensive explanation.

2.4.2. Leptin and prostate cancer aggressiveness

The results of the narrative review have shown that cohort studies and the majority of cross-sectional and case-control studies support an association between leptin and prostate cancer aggressiveness, but this was not the case in nested case-control studies, and the lack of consistent association was confirmed by meta-analysis (OR 0.87 95% CI 0.50-1.50, p = 0.61 and OR 1.15 95% CI 0.69-1.93, p = 0.58). While the evidence of association can be described as mixed for serum, no studies have explored leptin receptors, and, for DNA, only

two studies have been published, but both support an association between leptin and prostate cancer risk.

Our findings are similar to the previous meta-analysis of leptin and prostate cancer risk published by Angel et al (2019) who classified prostate cancer aggressiveness based on the stage and grade of the tumour. These researchers stated that there was no association between serum leptin and prostate cancer aggressiveness (RR 0.90 95% CI 0.74-1.10, p = 0.30). The results of the meta-analysis by Angel et al (2019) were therefore in line with this chapter which also show that there was no relationship between leptin and prostate cancer aggressiveness by grade in the two types of study groups, nested case-control/case-control and cross-sectional (OR 0.94 95% CI 0.69-1.28, p = 0.71 and OR 1.09 95% CI 0.74-1.60, p = 0.60).

The studies analysed when examining the relationship between leptin and aggressiveness were mostly derived from cross-sectional studies that are considered weak in terms of study design to prove association. There was a single study with strong reliability (cohort design), which did detect a statistically significant association, but again this number of studies is very limited and too limited to draw firm conclusions. Apart from differences in study designs, the different sized samples of each study also weakened the association of pooled studies.

The analysis also showed that DNA studies identified an association between leptin and the aggressiveness of prostate cancer, but again these studies were so limited in number that it was not strong enough to firmly conclude that there is an association.

In addition, and as above, most of the studies exploring leptin and prostate cancer aggressiveness did not define the covariates used in adjusted analyses, while, on the other hand, there was a single study (Lai et al., 2014) that had a very complex covariate list. There

were also differences in the use of the control group among the case-control studies involved and different sampling methods were used including the variable time interval between serum sampling and prostate cancer diagnosis. Prostate cancer aggressiveness in each individual study was also defined differently such as low- vs. high-volume tumours, low- vs high-grade, locally advanced vs. localized, based on the Gleason score, and several other classifications.

All the aforementioned gaps may be factors that weaken any observed associations and highlight the difficulty of drawing conclusions regarding the association between leptin and prostate cancer aggressiveness in this chapter.

2.4.3. Adiponectin and prostate cancer risk

In summary for risk, when considering all means of assessing adiponectin status, while the majority of case-control studies supported the association between adiponectin and prostate cancer risk, this was less consistently supported by nested case-control studies, which would be considered methodologically stronger, while cross-sectional studies were inconsistent, and no cohort studies had explored this research question. When subdivided by methods of assessing adiponectin status, the evidence base was also inconsistent, except for receptor expression, where there was only one study. The results of the meta-analysis of serum also showed no association between adiponectin and prostate cancer risk (OR 0.76 95% CI 0.46-1.26, p = 0.29).

Angel et al (2019) in their systematic review stated that there were insufficient studies available to measure the association between adiponectin and prostate cancer risk by meta-analysis. Therefore, there was no evidence that can be compared with the results of this chapter.

The results of this chapter showed that six of the 14 studies reported an association between serum adiponectin and prostate cancer aggressiveness whereas the rest did not and were mixed. There was also heterogeneity among available studies, as has previously been found in leptin-related studies. The results of the meta-analysis did not support an association between adiponectin and prostate cancer risk.

This chapter also revealed that there were five DNA-related studies and one related to receptors from case-control or nested case-control studies. For DNA-related studies, these studies suggest that the association between ADIPOQ polymorphisms, which was identified by the type of SNPs, might be useful to explore further as a potential predictor of prostate cancer risk. Likewise, in single study related to adiponectin receptors, it can be seen which type of receptor (AdipoR1) had a stronger expression, suggesting an association between adiponectin and risk, compared with another one (AdipoR2) (Michalakis et al., 2007). These results suggest that DNA and receptors may have a greater ability to predict prostate cancer risk; one potential explanation could be that they may be more reflective of long-term exposure to the adipokine than serum levels which may change more rapidly.

On the other hand, this chapter also showed that most of the adiponectin analyses are generally serum derived. It was important to note that the biological activities are mediated by specific isoform (i.e. HMW type: the most biological effect including proinflammatory effect of serum adiponectin; LMW type: anti-inflammatory effect), as revealed by the results of a study by Medina et al (2014) and supported by a review by Hu et al (2019). This point could serve as a reference that serum adiponectin isoform assessment was also useful in predicting the risk associated with prostate cancer. However, this reference is coming from only one isoform-related study was involved in this chapter, and additional studies examining a potential role for HMW adiponectin in prostate cancer risk are needed.

2.4.4. Adiponectin and prostate cancer aggressiveness

The studies regarding adiponectin and prostate cancer aggressiveness were predominantly from cross-sectional studies (10 of the 17 studies involved). Most of the studies stated no association between adiponectin and prostate cancer aggressiveness (7 of the 17 studies involved). The results of the meta-analysis in this chapter also showed that there was no relationship between adiponectin either with grade (OR 0.87 95% CI 0.50-1.50, p = 0.61 and OR 1.15 95% CI 0.69-1.93, p = 0.58) or stage (0.86 95% CI 0.59-1.25, p = 0.42).

Hu et al (2016) in their review stated that adiponectin levels seemed to be low in prostate cancer patients. Furthermore, according to Angel et al (2019), there was an association between adiponectin and prostate cancer aggressiveness revealed by their narrative review, however, this association was weak and was not supported by the results of their meta-analysis.

This chapter did not find any adiponectin-related DNA studies, however, there were two receptor-related studies available. Furthermore, the results from the adiponectin receptor studies showed inconsistency and cannot allow for conclusions regarding the role of the adiponectin receptor in prostate cancer aggressiveness. Although studies related to DNA and receptors have shown progress and sensitivity for examining the aggressiveness of prostate cancer. However, these studies have challenges including problems of assay specificity and sensitivity, and small study sizes (Sita-Lumsden et al., 2013). This may be the reason why serum studies are still more dominant and chosen because they are simpler and more applicable.

It may also be that the existing data for both leptin and adiponectin could be utilised more effectively to determine the role of adipokines in prostate cancer. The leptin to adiponectin ratio has been mentioned by Arisan et al (2009) as an approach to predict not

only total prostate cancer risk but also to assess the risk of high-grade prostate cancer. The leptin to adiponectin ratio was found to be higher in patients with advanced prostate cancer (ratio > 1), however, this study did not compare the advantages and disadvantages between single measurement of leptin or adiponectin versus leptin to adiponectin ratio. The leptin to adiponectin ratio could be suggested as an option to be explored in future analyses.

2.4.5. Adiponectin and prostate cancer progression

The analysis of the relationship between adiponectin and prostate cancer progression reported in this chapter showed that the number of studies involved was very limited. The two available studies were from a cohort (receptor expression) study and one cross-sectional (DNA) study, while no serum-related studies were found. The associations from the available studies were mixed. Meta-analysis could not be performed because of the limited number of studies.

Neither of the previously published meta-analyses, Angel et al (2016) nor Hu et al (2019), conducted analysis related to adiponectin-related prostate cancer progression, so they cannot be used as a comparison to the results of this chapter.

The note obtained from this chapter was that AdipoR2 receptor expression may be used as a predictor of progression but still requires further verification and replication. While the variation in the ADIPOQ allele was reported not to be associated with prostate cancer progression, however, again, it may necessary to investigate further by studies with stronger designs, as the single study conducted to date was cross-sectional (Gu et al., 2014).

2.4.6. Limitations and strengths

This chapter considered and presented the different methodologies used by each individual study and assessed limitations of the different methods, which is a strength. Some studies did not perform adjustments (unadjusted) in their analyses, while others used

multivariable adjustments, but the co-variates included varied between studies. This chapter suggests that the most important covariate in assessing the association of leptin and adiponectin with risk, aggressiveness and progression of prostate cancer is adiposity (e.g. BMI). Although the results are still inconsistent, BMI might be better if combined with other indicators such as waist circumference, waist to hip ratio and lipid profile while still involving prostate cancer risk factors such as age, race/ethnicity, smoking habits, alcohol consumption and physical activity.

This chapter also suggested that the grade and stage definitions of prostate cancer used to assess aggressiveness and progression by each individual study are also not the same as the different Gleason score classifications (e.g. GS ≥ 7 vs ≤ 6; GS 3 + 3, 3 + 4 ≥ 4 + 3; poorly differentiated ≥ 8 vs well-differentiated ≤ 6). Furthermore, the exposure classification varied between studies (e.g. low vs high level of leptin or adiponectin; ng/ml quartile data; ≥ pT3; ng/ml quintile median data, cut-off 6.7 microgram/ml vs 8.28 microgram/ml, etc). The different definitions regarding grade and stage obtained may make studies and findings less comparable with one another. Establishing and using an agreed standard definition of grade and stage is necessary so that future studies can reduce the heterogeneity of studies and explain the relationship that is identified.

This chapter also showed that there were still few studies with the highest level of reliability (i.e. cohort studies). To create a new cohort is not easy as the natural history of prostate cancer tends to be slow and long and this situation may be enhanced over time, with the difference in male life expectancy that occurs around the world. So, it will be very important to encourage high-reliability studies studying prostate cancer, and maximise use of cohorts already collected, with the assessment of a broad range of health outcomes, including prostate cancer.

In addition, this chapter also observes that research related to the expression of DNA and receptors is very limited in number. The problem of more challenging sample access, sensitivity and specificity of the assay used, and the small sample size (limited to certain groups/ethnicities/races) is a potential cause of the low number of DNA and receptor related studies. Meanwhile, the ease of serum testing may also have contributed to the low use of DNA and receptors in prostate cancer studies. However, DNA and receptor studies are important to continue to obtain a genetic map that will be very useful in guiding more accurate and personalised treatment of prostate cancer in the future.

Furthermore, the use of advanced analysis such as adiponectin molecular weight analysis and leptin to adiponectin ratio is still not widely used. The use of such advanced biomarker (i.e. adiponectin isoform) analysis needs to be a concern for researchers because it may provide added value in detecting an association between these isoforms and prostate cancer through serum testing, especially as serum was the analysis most frequently used by researchers in this chapter.

Although the number of studies included was small, this chapter also found differences in the time span between blood sampling and diagnosis noted in several studies. A single blood sample like this can lead to differences in adipokine levels between studies since the adipokines (leptin and adiponectin) will change over time. In addition, there were not all studies mention about the type of blood sample (fasting or not) that can also cause differences in the results of the analysis. This chapter also shown of different assay methods among the studies involved that might act as another factor that had an effect on the outcome of the study. It is suggested that all of these factors should be taken into account by future studies.

A strength of this chapter is that it has analysed risk, aggressiveness and progression, whereas a previous systematic review did not include progression (Angel et al., 2019, Hu et

al., 2016a). Several studies that were not in the previous review were also used in this chapter (Fowke et al., 2013, Freedland et al., 2005, Hsing et al., 2001, Michalakis et al., 2007), hence showing that the inclusion and exclusion criteria are important and that the field is shifting over time.

Another strength of this chapter is that studies analysed in the meta-analysis were assessed for quality using NOS and analyses were repeated with only high-quality studies so that the results obtained have low levels of possible bias.

2.5. Conclusion

The results suggest through this chapter that there is no association between leptin and adiponectin and prostate cancer risk and aggressiveness. The results of individual studies show inconsistencies regarding existing relationships and associations were not confirmed through meta-analysis. Studies exploring the association between adipokines and prostate cancer other than via measurement in serum are limited, and progression of prostate cancer could only be analysed in relation to adiponectin and the results were inconclusive, while for leptin there were no studies related to prostate cancer progression. Many studies were case-control and few studies have been conducted using more robust study designs; therefore, the role of adipokines in prostate cancer risk, aggressiveness and progression remains to be fully explored.

2.6. Appendix

Key word search.

Prostat* cancer* OR Cancer of the prostate OR Carcinoma of prostate OR Malignant tumo?r* of the prostate OR Malignant prostate OR Malignant prostate neoplasm* OR Prostat* adenoma* OR Prostate neoplasm* OR Prostatic adenocarcinoma*

AND

Leptin OR CD295 Antigen OR CD295 OR DB OR 16 kDA peptide hormone OR Leptin receptor OR LEP OR LEPR OR LEP-R OR LEPD* OR LEPRD OR HuB219 OR OBS OR OB OR OB-R OR Ob gene product OR Ob protein OR Obese gene product OR Obese protein.

OR

Adiponectin OR Adiponectin precursor OR Adipose derived hormone OR ACDC OR ADIPQTL1 OR ADPN OR ADIPQTL1 ADPN OR APM-1 OR APM1 OR GBP28 OR GBP-28 OR CQ1 and collagen domain containing OR apM1 OR apM-1 OR APM1 OR ADIPOQ OR AdipoQ OR ACRP30 OR Acrp30 OR Q15848 OR 30 kDA Adipocyte Complement-related Protein OR Adipose most abundant gene transcript 1 OR Adipose specific collagen-like factor OR Gelatine-binding protein 28*

3. A Randomised Controlled Trial (RCT) to test the efficacy of a six-month dietary and physical activity intervention on the dietary intake and lipid profiles of prostate cancer patients receiving ADT.

3.1. Introduction

Prostate cancer is a type of cancer commonly experienced by men in the UK. At least 35% of new cases of prostate cancer have been experienced by men aged 75 years and over, and, in the last 10 years, there has been an increase in the incidence of prostate cancer by 4% (2015-2017) and with 48,588 new cases throughout the UK in 2017 (CRUK, 2019). This figure is predicted to continue to increase by approximately 12% from 2015 to 2035 or 233 cases per 100,000 men in the UK (CRUK, 2019). Prostate cancer in Northern Ireland is the most commonly diagnosed cancer in men (NICR, 2018).

Obesity has a role in the development and aggressiveness of prostate cancer. A systematic review of 17 cohort studies by Zhang et al (2015) reported that obesity was correlated with a 14% increased risk in disease aggressiveness and a 24% increased mortality from prostate cancer when compared to patients with a healthy weight. Correspondingly, several previous studies have also reported a similar association (Allott et al., 2013, Su et al., 2011, Vidal et al., 2014). This relationship was again reported by the Epidemiological Study of Prostate Cancer (EPICAP) (Lavalette et al., 2018). The role of obesity in the survival rate of prostate cancer patients has also been reported by several epidemiological studies (Demark-Wahnefried et al., 2012, Moller et al., 2015, Vidal et al., 2014). These results were in line with a report by the expert group of World Cancer Research Fund which stated that obesity was a risk factor for metastatic prostate cancer (advanced prostate cancer) (WCRF, 2018).

The hormone therapy for prostate cancer can affect body composition. Specifically, the use of androgen deprivation therapy (ADT) in prostate cancer has been reported to have weight gain-related adverse effects by epidemiological studies (Braunstein et al., 2014, Kim et al., 2011,

Torimoto et al., 2011). A systematic review of longitudinal studies examining the relationship between ADT and the impact on body composition reported a 7.7% increased average body fat percentage (95% CI 4.27-11.15) (p <0.0001), a decreased percentage of average muscle mass -2.82% (95% CI -3.64, - 2.01) (p <0.0001), and an increased body weight percentage of 2.14% (95% CI 1.35-2.94) (p <00001) (Haseen et al., 2010a).

Besides having an impact on body composition, the use of ADT has also been associated with a change in lipid profile which included total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglycerides (TG) in prostate cancer patients. Patients with ADT were reported to have increased total cholesterol (Torimoto et al., 2011). The increased cholesterol levels in prostate cancer patients was associated with the risk of disease aggressiveness (Jamnagerwalla et al., 2018, Kok et al., 2011), although, a conflicting result was obtained by several studies when increased cholesterol was not directly associated with Prostate Specific Antigen (PSA) levels (Allott et al., 2014, Heir et al., 2016, Jamnagerwalla et al., 2018, Oka et al., 2016, Zhao et al., 2017). ADT therapy contributes to an increase in LDL levels (Torimoto et al., 2011). Increased LDL in patients was associated with the risk of aggressiveness (Kok et al., 2011) as well as the development of lethal prostate cancer (Stopsack et al., 2017).

Based on several studies, it was reported that higher HDL levels were associated with low cancer aggressiveness (Kok et al., 2011, Zheng et al., 2019). However, other studies stated that HDL levels are not associated with prostate cancer risk (Allott et al., 2014, Cheng et al., 2019, Jamnagerwalla et al., 2018). Meanwhile, there are inconsistent findings between TG and prostate cancer risk in several observational cohort studies (Allott et al., 2014, Cheng et al., 2019, Kok et al., 2011). However, a recent systematic study reported that an increase in TG levels after radical prostatectomy (RP) might be associated with the risk of biochemical recurrence in patients (OR 1.20 95% CI 1.01-1.42, p = 0.04) (Zheng et al., 2019). In terms of cardiovascular risk, a prospective cohort examined changes in arterial stiffness during treatment with ADT - using a new indicator:

the cardio-ankle vascular index (CAVI) and serum lipid profile changes. Although the cohort suggested no significant change in arterial stiffness throughout the study, the serum lipid levels (HDL, LDL and TC) had increased significantly one month since ADT initiation and these changes were maintained over the 6 month duration (Oka et al., 2016).

The evaluation of diet and physical activity intervention studies by the World Cancer Research Fund expert group reported that such interventions might improve body weight, lipid profile and metabolism, reduce inflammation, prevent bone loss, improve quality of life, reduce cancer-related fatigue and improve physical function in cancer (Demark-Wahnefried et al., 2018). A previous systematic review has also reported that weight loss was correlated with an improved lipid profile (total cholesterol and LDL) in people with overweight and obesity (Poobalan et al., 2004). Several other studies – including a single armed exploratory study in colorectal cancer patients and a randomised controlled trial in prostate cancer patients have also demonstrated that lifestyle modification through diet and physical activity led to weight loss and an improvement in lipid profile (Beeken et al., 2017, Hasegawa et al., 2019, Nobes et al., 2012). Similarly, a Cognitive Behavioural Therapy (CBT) study that promoted weight loss also reported a decreased total cholesterol, LDL and TG and increased HDL when applied to breast cancer patients (Mefferd et al., 2007). Another study reported that there was an advantage obtained when dietary and physical activity intervention was delivered in prostate cancer patients with ADT (Bourke et al., 2011).

In a previously conducted RCT evaluating the efficacy of a diet and physical activity intervention to reduce the body composition-related side effects of ADT, significant changes in body composition were evident in the intervention arm compared to the standard care control arm at endpoint; these results have been published previously (O'Neill et al., 2015). Data on a series of secondary outcomes were also collected, including blood samples to determine lipid profile, dietary data (a 7 day food diary conducted at all three study time points) as well as the

data necessary to calculate a cardiovascular disease risk score for all participants at the beginning and end of the study. This chapter will evaluate the efficacy of a six-month dietary and physical activity intervention on these secondary outcomes. These results will describe the impact of the intervention on dietary behaviour, the lipid profile and the QRisk score of patients recruited to this RCT, also exploring adherence, thus determining the efficacy of this dietary and physical activity intervention and associated weight loss on the cardiovascular health and lifestyle behaviours of prostate cancer patients treated with ADT.

3.2. Hypothesis

It was our hypothesis that the six-month lifestyle intervention would:

a. improve the lipid profile (including, Total Cholesterol, LDL, HDL and TG levels) in men in the treatment group compared to the control group at study endpoint
b. improve the CVD risk scores of men in the treatment group compared to the control group at study endpoint
c. improve the quality of the diet and increase adherence to UK dietary and physical activity guidelines in men in the treatment group compared to the control group at study endpoint

3.3. Methods

The methods used in this study have been published by Haseen (2010) (Haseen et al., 2010c) and were approved by the Office of the Research Ethics Committee of Northern Ireland (ORECNI), the Research Governance Offices of Queen's University Belfast and the Belfast Health and Social Care Trust (BHSCT) (Reference No. 09001 JO-SS). The study was also registered and has an international standard randomised controlled trial number: ISCRTN75282423. The study was conducted between August 2009 and September 2011 (26 months; inclusive) (O'Neill, 2012).

3.3.1. Patient randomisation and allocation concealment

The prostate cancer patients were recruited from the NI Regional Cancer Centre, Belfast City Hospital. The recruited patients were assigned at random, with the help of random

numbers generated by a computer, to either a control or intervention group with a ratio of 1: 1 (O'Neill et al., 2015). In brief, to assign patients to either group, six permutations with a block size of four were prepared. One of six permutations was selected at random from the block and four patients assigned accordingly based on capital letter combination in it ('I' for intervention, 'C' for control) as presented in **Figure 1**. The allocation process was repeated 24 times for all 94 patients (O'Neill, 2012). The patient randomly received a randomised number after verbally consenting to participate. An independent researcher (Dr Marie Cantwell) prepared numbered envelopes from 1-94. After baseline data collection finished, this envelope was opened to know the patient allocation group (O'Neill, 2012).

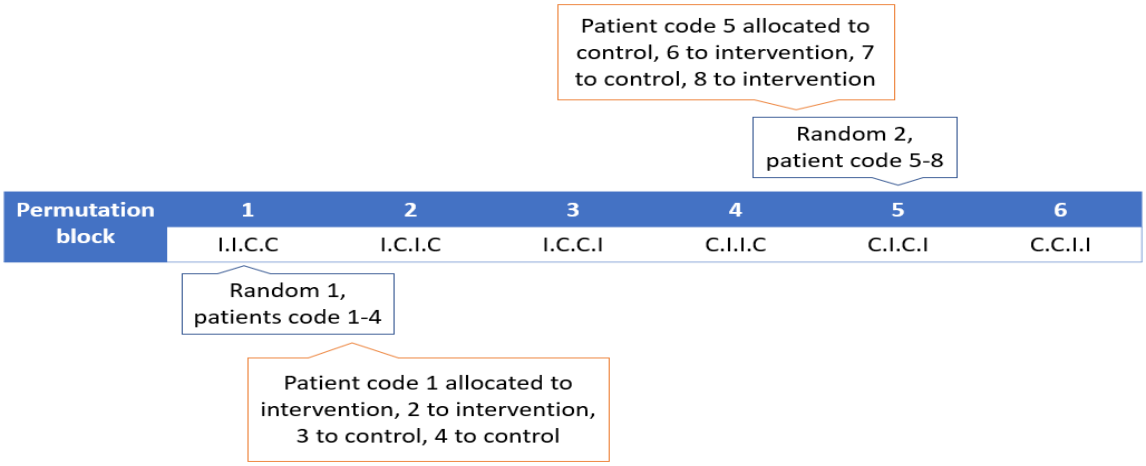


Figure 3.1. Randomised process for patient allocation (reproduced with permission from O'Neill 2012)

3.3.2. Patient eligibility

The eligibility of patients was based on the following inclusion and exclusion criteria (O'Neill et al., 2015). The CONSORT flow diagram (**Figure 3.2**) demonstrates the flow of recruitment and data collection throughout the different phases of the study:

Inclusion

a. Patients with histologically proven adenocarcinoma of the prostate

b. Commencing luteinising hormone-releasing hormone agonist (LHRHa) therapy for at least 6 months

c. Or already treated with LHRHa and planned to continue for at least a further 6 months

Exclusion

a. A co-morbid condition that limit physical activity such as severe cardiac disease, recent myocardial infarction, severe asthma or breathlessness, uncontrolled hypertension (blood pressure >160 /95 mmHg) or severe pain

b. Medical conditions that require a reduced fruit and vegetable diet (e.g. kidney failure)

c. A history of insulin-dependent diabetes; treated with any type of steroid hormone

d. Treated for any other cancer

e. Life expectancy of fewer than 2 years

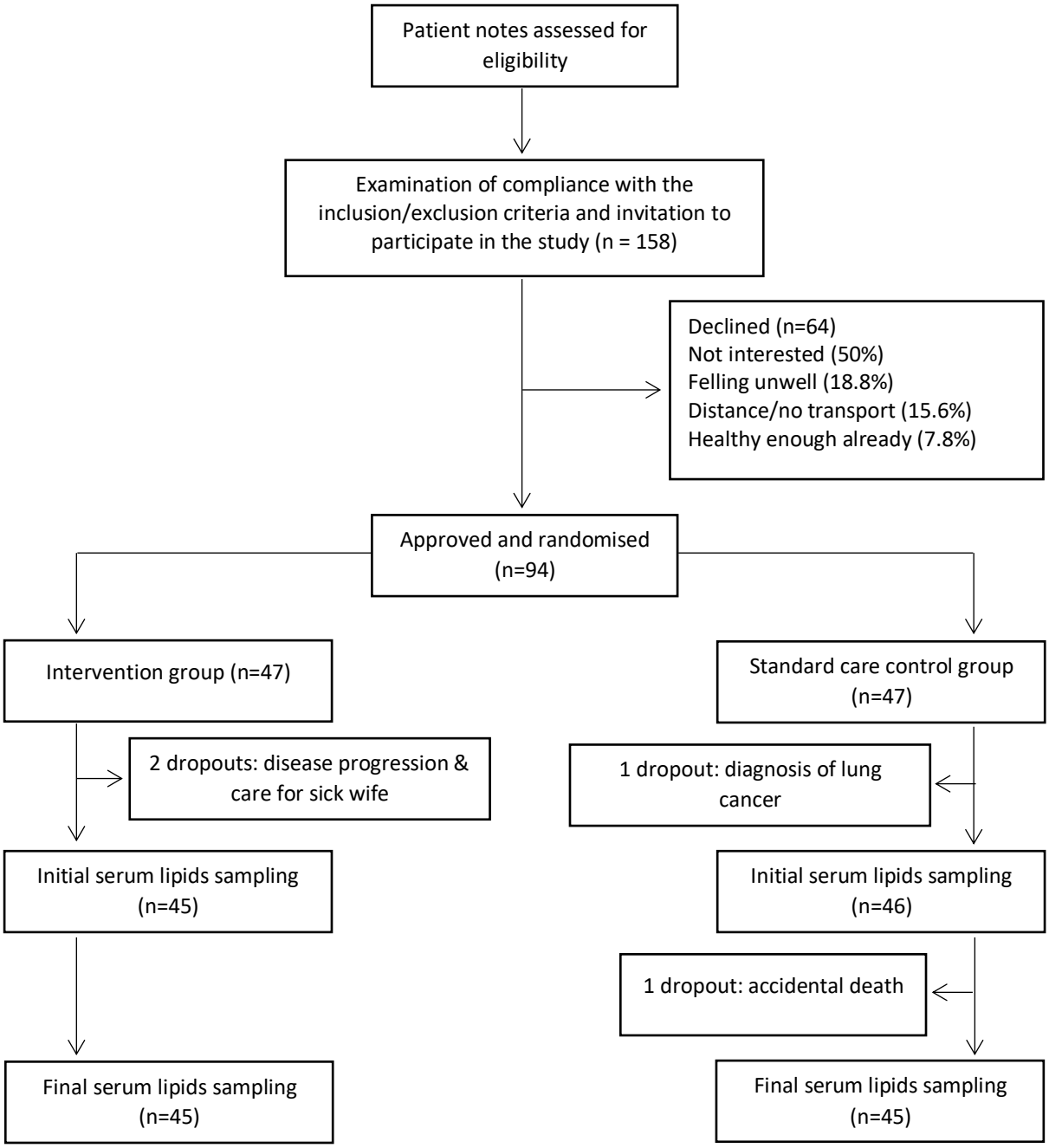


Figure 3.2. The process of patients' recruitment and lipid samples collection during the study

3.4. Intervention

The Intervention was discussed in detail in the study protocol (Haseen et al., 2010b). The given intervention was a combination of dietary advice and self-directed exercise (brisk walking commensurate with UK physical activity guidance) for six months. The intervention was delivered within one week of baseline data collection (O'Neill, 2012). Delivery of the intervention was completed at the patient's home and was attended by a partner or caregiver whenever possible (O'Neill, 2012).

3.4.1. Dietary intervention

The dietary intervention was tailored to the likes and dislikes of the patient based on their food preferences provided in the baseline 7-day food diary. Furthermore, each individual's dietary intervention was designed to be commensurate with UK healthy eating guidelines (Haseen et al., 2010a). Patients were encouraged to improve their habits with the following basic guidelines (O'Neill et al., 2015):

a. ≥5 servings of vegetables and fruits/day,
b. 30-35% of total energy from fat and <10 % energy from saturated fat/day,
c. 10 % of energy from polyunsaturated fat/day,
d. limited consumption of processed meats,
e. 25-35 g of fibre/day,
f. ≤28 units/week of alcohol and
g. limited intake of foods high in salt and/or sugar.

The intervention materials also included suggestions of alternatives/healthy meals and snacks, correct sized portions according to the Food Standards Agency and cooking methods and outside dining suggestions. For patients with overweight or obese conditions, it was recommended to make a reduction of 500 kcal calories daily for the 6 months of the study.

In addition to the above information, there are several things that need to be noted in this study related to dietary intervention as follows: 1) the n-3 fatty acids were not the focus of this study analysis so were not included in the available dataset and results; 2) The health benefits of plant-based foods were discussed in general at intervention delivery and so sterols or stanols would have been mentioned but were not a key focus of intervention delivery or materials; 3) Fruit and vegetable quantification was based on a cut-off of 80 g portions without including beans and pulses or composite foods, which may have had an effect on the overall estimate of fruit and vegetable intake (underestimation) at the end of the study; 4) Because the intervention was delivered 12 years ago there was a difference in the cut-off used (28 units) when compared to the current alcohol recommendation for the UK (14 units).

The dietary intervention was aimed at educating patients to understand the importance of a balanced diet and how to adopt this food pattern. As part of facilitating the adaptation process of each patient, an individual food handbook was provided that was tailored to their respective food preferences (O'Neill et al., 2015, Haseen et al., 2010b).

3.4.2. Physical activity intervention

For the physical activity component of the intervention, each patient was encouraged to complete brisk walking for at least 30 minutes every day for five or more days per week (according to the referral guidelines for UK physical activity) (O'Neill et al., 2015). Patients who had a regular physical activity habit were encouraged to add this 30-minute brisk walking activity onto their usual activity (O'Neill et al., 2015).

Walking was chosen as it is a commonly used exercise, is easily incorporated into the day-to-day lives of patients and involves no cost (O'Neill et al., 2015). Patients were provided with a pedometer and encouraged to count and record their steps (O'Neill et al., 2015). The average weekly number of steps of the patient was monitored with a pedometer (Omron HJ005E vital steps) (O'Neill et al., 2015).

Compliance with the diet and physical activity intervention was assessed every two weeks in the first three months and every three weeks thereafter (O'Neill et al., 2015). Control group monitoring was conducted every six weeks to avoid performance bias (O'Neill et al., 2015). The control group was also given elements of the intervention when the study ended (O'Neill et al., 2015).

3.5. Data collection

Baseline data collection was completed within a week after the assessment for eligibility and consent. A series of self-completion questionnaires were then sent to the patient a week before the scheduled baseline data collection visit. Each patient was advised to fill in all questionnaires and bring them to their scheduled date appointment (O'Neill, 2012).

The main questionnaire given to patients included a structured questionnaire to collect information on socioeconomic and demographic characteristics, as well as medical history, a fatigue severity scale (FSS), functional assessment of cancer treatment questionnaire - prostate (FACT-P) to determine quality of life, a perceived stress scale (PSS), seven-day diet diary, and a questionnaire based on the Transtheoretical Model (TTM) of behaviour change, which aimed to assess the patient's current state of readiness to change aspects of their diet and physical activity (O'Neill, 2012).

The physical measurements were collected during the baseline study visit, including anthropometry measurements to assess body composition, 6-minute walk test (6MWT) as a measure of physical functioning, seven-day physical activity recall assessing the current levels of physical activity (7 Days Physical Activity Recall Questionnaire (7-DPARQ), and fasting blood sample (30 ml) to be used to determine the lipid profile (O'Neill, 2012).

3.6. Outcomes

3.6.1. Body composition

All results of the body composition analysis are the results of previous research conducted by Hanseen et al (2010) and O'Neill (2012) and have previously been reported in another postgraduate thesis. They are reproduced here to allow consideration of context for the newly reported analyses.

3.6.1.1. Weight

Anthropometric measurements were carried out by two nutritionists (Dr. Roisin O'Neill and Dr. Farhana Hanseen) (O'Neill, 2012, Haseen et al., 2010b). Bodyweight was measured using a calibrated SECA704 digital electronic column scale. Patients were advised to remove shoes, heavy clothing, and heavy items from their pockets before being weighed. They were advised to stand straight and still over the centre of the platform, distributing their body weight equally between both feet and looking straight ahead. The measurement was taken twice to ensure an accurate reading. If the second reading differed from the first, a third measurement was taken and the average of the three recorded as the patient's weight. Weight was measured to the nearest 0.1 kg.

3.6.1.2. Height

A SECA Leicester portable height scale was used to measure the standing height of patients. Patients were advised to stand straight on the floorboard of the stadiometer with their arms by their sides, their head held upright, chin parallel to the floor and their neck held in a natural non-stretched position. They were told to place their feet together with their body weight distributed equally across both feet and their heels placed against the base of the vertical board.

The researcher carrying out the measurement ensured the patients' scapula, buttocks and heels were touching the vertical backboard, their head was correctly positioned, and their arms were by their side before the measurement was taken (O'Neill, 2012). The moveable headboard was lowered onto the top of the patient's head and the measurement was recorded. The measurement was taken twice to ensure an accurate reading. If the second reading differed from the first, a third measurement was taken and the average of the three recorded as the patient's height. Measurements were taken to the nearest 0.1 cm.

3.6.1.3. Body mass index

The following formula was used to calculate patients BMI (BMI = $\frac{weight\ in\ kilograms\ (kg)}{(height\ in\ metres\ (m))^2}$). This is a method of assessing an individual's weight relative to height in order to determine if they fall within an appropriate/healthy weight category. The international classification of BMI categories, as defined by the World Health Organisation (WHO) (WHO, 2019a) are underweight <18.5, normal, 18.5- 24.9, overweight ≥25.0 and obese ≥30.0 kg/m^2.

3.6.1.4. Waist circumference

The patient was advised to stand upright with their feet 25-30 cm apart, with weight equally distributed across both feet, arms relaxed and by their side, and their abdomen relaxed (O'Neill, 2012). The tape measure was wrapped around the waist mid-way between the lowest rib and the iliac crest using a flexible, non-elastic tape measure (O'Neill, 2012). The patient was asked to gently exhale, and the measurement was taken to the nearest 0.1 cm (O'Neill, 2012). The procedure was repeated three times and an average of the three measurements recorded (O'Neill, 2012). The classification of risk based on waist measurements by WHO were <94 cm considered low/ideal, 94-102 cm considered high, and >102 cm considered very high (WHO, 2008).

3.6.1.5. Hip circumference

The patient stood straight with their feet positioned together, arms by their side and weight evenly distributed across both feet (O'Neill, 2012). The tape-measure was positioned around the widest portion of the buttocks and the measurement taken to the nearest 0.1 cm and was taken three times and the average of the three values was recorded (O'Neill, 2012).

3.6.1.6. Waist to hip ratio

The patient's WHR was obtained by dividing the mean waist circumference by the mean hip circumference (O'Neill, 2012). A WHR ≥1 classifies an individual as obese and has significant implications for health particularly with cardiovascular disease (WHO, 2008, O'Neill, 2012).

3.6.1.7. Percentage body fat

Two researchers (Dr Roisin O'Neill and Dr Farhana Haseen) took separate skinfold measurements from a subset of patients in order to test the reliability of the measurement. Each patient was asked to remove all clothing from their upper body; for consistency, all measurements were taken on the patient's dominant arm, with the patient instructed to stand straight, in a relaxed position with feet together, weight evenly distributed and hands hanging freely by their side. The measurements were completed using the Harpenden skin-fold callipers and measurements were taken in triplicate at each site.

The Durnin/Wormersley calliper method was used to collect measurements from the following four sites (Durnin and Womersley, 1974):

a. Tricep: measured as the thickness of the vertical fold on the posterior midline of the upper arm, located midway between the acromion process and the Olecranon process.

b. Bicep: measured as the thickness of the vertical fold on the anterior aspect of the upper arm, directly above the pit of the elbow (Cubital fossa), at the same level as the triceps skinfold measurement.
c. Subscapular: measured as the thickness of an oblique fold 1cm below the inferior angle of the scapula; taken at a 45°c angle from the floor.
d. Suprailiac: measured as the thickness of an oblique fold in the midaxillary line immediately above the iliac crest.

The values recorded for each skin-fold site were used to calculate; % body fat, total fat and fat-free mass. Before these measurements could be obtained it was necessary to calculate body density. This was calculated using the formula shown below which uses the log total of all four skinfold sites (Durnin and Womersley, 1974):

a. The first formula is D = $1.1715 - 0.0779 \times (L)$; D = Predicted density of the body (kg/m^3), and L = log10 of the total of the 4 skinfolds (mm)
b. The next calculation is the percentage body fat that was calculated based on body density using the following equation; % body fat = $\left(\frac{4.95}{density}\right) - 4.5 \times 100$
c. Then, total body fat is calculated based on the following formula; total body fat (kg) = $\frac{body\ weight\ (kg) \times \%body\ fat}{100}$
d. The next calculation is fat free mass; fat free mass (kg) = body weight (kg) – body fat (kg)

Body fatness categories are further grouped based on guidelines of American College Sports Medicine (ACSM 2004) as follows 2-5% categorised as essential fat, 6-13% as athletes, 14-17% as fitness, 18-24% as average and ≥ 25% as obese (O'Neill, 2012).

3.6.1.8. Mid upper arm circumference (MUAC)

The patient was instructed to stand straight and sideways to the researcher, with feet apart and arms relaxed by their side. They were directed to bend their arm in order to locate the midpoint of the upper arm; this was marked with a pen. The MUAC measurement was taken at the midpoint of the left upper arm, between the shoulder (Acromion) and the tip of the elbow (Olecranon process). Patients were then instructed to relax their arm with their palm facing towards their thigh; the flexible insertion TALK-MUAC tape measure was wrapped around the marked area of the arm, gently but firmly, taking care to not squeeze the arm. The measurement was taken three times and an average recorded to the nearest 1 mm.

3.6.2. Dietary assessment

The dietary intake data was measured using a 7-day food diary. Energy and nutrient intake were then calculated using a food analysis database (WISP; Tinuviel Software. Warrington, UK) based on UK food composition tables. Patients were advised to keep a record of all food and drink consumed 7 days prior to their measurement day. The diary consisted of 6 meal profiles, these included; breakfast, light mid-morning meal, lunch, light mid-afternoon meal, evening meal and a profile for beverages and snacks. Each meal profile contained a blank table, divided into seven sections; each one labelled Monday to Sunday. Patients were advised to record all food and drink consumed during each meal. They were advised to measure their portion sizes based on household measures such as tablespoons, cups, slices etc. and if possible, packet weights; information on cooking methods and brand names were also recorded. During their measurement visit, the researchers (Dr Roisin O'Neill and Dr Farhana Haseen) reviewed the diet diary to ask about individual foods that were not mentioned in the diary, additional information to confirm the portion size, or for information on brand for foods that had been recorded in the patient's diary. Food intakes were converted into grams and if patients were unsure about the exact portion size then a standard portion

size was entered (Crawley, 1994). The software (NetWisp 3.0; Tinuviel Software) provides a range of dietary information including converting food intakes into an average daily value for the micro and macro nutrients as well as providing information on intakes of specific food groups including meat and meat products, fruit and vegetables, alcoholic beverages and sugar and confectionary (Church, 2002).

3.6.3. Physical activity

The assessment of physical activity was done as follows: taking each day from the previous seven, in turn, patients were first asked to describe their sleeping patterns and time spent in bed. Each day was then divided into morning, afternoon and evening, and patients were asked to describe their daily activities with specific emphasis on activities that were moderate, hard, or very hard, as well as the duration of that activity. Examples of exercises and their associated intensities were used to assist the process, and time spent on each activity was recorded. All remaining daily activity was classified as 'light' intensity. Patients were also asked to report how typical the previous week's exercise was in comparison to their physical activity levels over the previous 3 months. The 7-day physical activity recall provides an estimate of energy expenditure for the previous week (kcal/kg/day) (O'Neill, 2012). Energy expenditure is estimated on the basis of 1 Metabolic Equivalent Task (MET) = 1kcal/kg-1/hour-1 and categorised as sleep (1), light activity (1.5), moderate activity (4), hard activity (6), and very hard activity (10) (Blair et al., 1985).

To produce an estimate of energy expenditure using this method, the total number of hours reported for each category of intensity is multiplied by the appropriate MET value: for example, 8 hours spent sleeping per day equals 8 METs (8hours x 1METs), 1 hour of very hard activity equals 10METS (1hour x 10METs) and the remaining 15 hours of the day is classified as light activity (unless otherwise stated by the patient) and would equal 22.5 METs (15 hours x 1.5METs). This is repeated for the seven days and the total METs for the week (168

hours) provides the total energy expenditure for the week and is independent of body size. In order to establish total caloric expenditure for the week this value is multiplied by the patients' body size in kilograms; to establish the daily total energy expenditure (kcal/kg-1/day-1), this value was divided by 7.

3.6.4. Dietary adherence

Dietary adherence was assessed as a binary variable (yes/no) for each of the recommendations discussed in section 3.7.1.4 including: ≥5 servings of vegetables and fruits/day; 30-35% of total energy from fat; <10 % energy from saturated fat/day; 10 % of energy from polyunsaturated fat/day; 25-35 g of fibre/day, ≤28 units/week of alcohol and salt intake. Due to the nature of the dietary information provided within the study dataset, it was not possible to differentiate between red and processed meat and therefore not possible to determine adherence to the recommendation for 'limiting consumption for processed meat'.

The data used to score each was based on the advice given within the intervention where a person was adherent if their dietary intake met the cut-off recommended within the intervention. For fibre, the assessment was carried out using the Englyst method where the recommended cut-off is 24 g of fibre/day. However, this cut-off was still a matter of debate when this study was conducted, so that a range (25-35 g fibre/day) recommendation was used instead of a cut-off. Participants were classified as adherent if consuming 25 g or more.

3.6.5. Blood collection of lipid profiles analysis

The blood sampling collection was carried out by a research nurse from the clinical trial unit. Each patient was asked to fast (10 hours without eating and drinking except water) prior to their scheduled morning appointments (O'Neill, 2012). A total of 5 x 6 ml vacutainer tubes of blood was extracted, this included: 2 x 6 ml plasma tubes, containing an anticoagulant ethylenediaminetetraacetic acid (EDTA) and 3 x 6 ml serum tubes; blood tubes were labelled

with the patients' study ID number, the date and study time point. Immediately after collection, the plasma tubes were gently shaken to mix the anticoagulant to avoid clotting, they were stored on ice and processed within 2-4 hours of sample collection; serum samples were stored at room temperature in a dark place (an opaque envelope) for at least an hour before processing to assist coagulation. All tubes were transferred to the Centre for Public Health laboratory at Queen's University Belfast for processing before storage.

Based on established lab protocols, all blood tubes were placed in the centrifuge at 3000 Revolutions per Minute (RPM) for 15 minutes at 4°C in order to separate the plasma/serum from the red blood cells. A plastic transfer pipette was used to transfer serum into 9 x 2 ml aliquot tubes which were sealed with a red lid for storage. Two aliquot tubes were pre-processed for future testing of ascorbic acid; both aliquots had 900 µl of meta-phosphoric acid (MPA) added alongside 100 µl of the plasma and were sealed with a yellow top. The remainder of the plasma sample was equally distributed between 4 aliquot tubes and sealed with a purple lid. Each aliquot tube was labelled using Tubee's high/low-level laser labels; these are designed to withstand long-term freezer storage. Each label included the patient' study ID number, the date and the study time point and was immediately placed in long term freezer storage (-80°C) for future processing (this was completed by Dr Roisin O'Neill and Dr Farhana Hanseen).

3.6.6. Lipid analysis

Blood samples were collected from patients at all three timepoints: baseline, 3 months and 6 months however due to limited study funding, only baseline and endpoint samples were analysed for the purposes of this chapter. One aliquot of serum (500µl) per patient per time point was required to complete a full lipid profile analysis. This included high-density lipoprotein (HDL), triglyceride (TG) and total cholesterol (TC) and the LDL levels were calculated using the Friedewald equation (Knopfholz et al., 2014):

LDL cholesterol = (Total Cholesterol) – (HDL) – (Trig/2.2*)

Note: * where all concentrations are given in mmol/L.

Samples were then processed by Ilab direct analysis method: 1). Cholesterol testing was conducted using a specific cholesterol test kit (IL cholesterol test 0018250540). The I-Lab was calibrated each day and quality control samplers were analysed at least once a day with duplication. The analysis was carried out on the serum obtained from each sample with the measurement results in units of mmol/l; 2). HDL testing was conducted using a commercially available test kit (IL HDL cholesterol test 0018255740), with calibration and quality assurance as for total cholesterol. The analysis was carried out on the serum obtained from each sample with the measurement results in units of mmol/l; and 3). Triglyceride testing was done using a commercially available test kit (IL Triglyceride test 0018255640), with calibration and quality assurance as for the other assays.

Reagents, calibrators, and quality control samples were obtained from Instrumentation Laboratory Ltd. The obtained results were then tabulated and prepared for further analysis.

3.6.7. Calculation of QRisk3 cardiovascular disease risk score

The QRisk3 score builds upon the QRisk2 score including additional parameters and information on a variety of factors to ensure the accuracy of the score: the person's age, gender, ethnicity, smoking status, medical history (including: family history of cardiovascular disease (CVD) and personal history of co-morbidities such as diabetes, Chronic Kidney Disease (CKD), atrial fibrillation, high blood pressure, rheumatoid arthritis, severe mental illness, steroid use, systemic lupus erythematosus and erectile dysfunction) as well as biological markers (i.e. cholesterol, blood pressure measurements and anthropometry including height and weight measurement) (Hippisley-Cox et al., 2017).

The QRisk score is considered to have a performance that is more or less the same as the previously established score, namely Framingham (Hippisley-Cox et al., 2007, Damen et al., 2019). In addition, however, QRisk has also been shown to be more applicable to the UK population than Framingham or ASSIGN (Damen et al., 2019, Hippisley-Cox et al., 2007, van Staa et al., 2014). The advantage in predicting patient risk based on age, sex and social deprivation made QRisk scores a better method of assisting appropriate management and treatment for better outcomes (Hippisley-Cox et al., 2007).

A cardiovascular disease risk score was calculated for all men participating in this study; the QRisk calculation provides:

a. information on an individual's 10-year risk of developing a heart attack or stroke
b. the score of a healthy person with the same age, sex and ethnicity
c. the person's relative risk (the individual's risk of CVD divided by the risk of a healthy person of the same age, sex and ethnicity)
d. the individual's healthy heart age: the age at which a healthy person of the individual's sex, age and ethnicity has the same 10 years risk score.

There are several caveats to the calculation of this risk score in this study: the QRisk has been developed for individuals without a history of heart disease, yet several of the patients recruited to the study had a previous myocardial infarction and pre-existing angina. The score also recommended the inclusion of a blood pressure measurement; however, this was only recorded at the screening visit. The medical history was taken at baseline, some men were receiving cholesterol-lowering medication and therefore receiving an intervention to reduce their CVD risk already. The QRisk score also requires information on the family history of heart disease, however, the information was not available for any patient, so this information was excluded from the score. Researchers did not discuss the QRisk score with

patients participating in the study, it has instead been used as a guide to determine CVD risk in patients and determine if lifestyle intervention can modify risk.

3.6.8. Sample size and statistical analysis

The sample size determination carried out in this study is based on body composition. Data from a previous study on prostate cancer patients treated with hormone therapy reported a mean change in the percentage of fat mass during ADT administration was 9.4% with SD = 9.6% (Smith et al., 2002). Based on the results of the study by Smith et al (2002) assuming the same percentage of fat mass, if there were 72 patients (36 patients in the control group and 36 patients in the intervention group), the study would have 90% power at 5% significance to detect changes in 7.4% fat mass between groups. Subsequently, the sample size was increased by 30% to account for possible drop out among patients. Based on the foregoing, the sample size set for this study was 94 patients, with 47 patients assigned to the control group and the remaining patients assigned to the intervention group (Haseen et al., 2010b).

The normality of data was assessed using normal probability plots. Independent t-tests were used to explore the difference in baseline characteristics between the intervention and control arms. Secondary endpoints (including the lipid profile and CVD risk scores) between the intervention and control group were compared using analysis of covariance (ANCOVA) with baseline scores included in the regression model as covariates. Furthermore, the lipid profiles of patients at endpoint were compared by adherence to the intervention recommendations (high/low) using ANCOVA with baseline scores included in the regression model as covariates. Statistical significance was set at $p < 0.05$, with 95% confidence intervals (95% CIs) used to express uncertainty in estimates. The analysis was performed using STATA software (Release 16; StataCorp LP, College Station, TX).

3.6.9. Quality control

Several measures were implemented throughout the study to ensure good quality data was collected. A standardised protocol was used for each measurement tool. All measurements were taken using previously validated techniques, at a similar time of day and were collected by the same researcher at each time point to avoid intra-interviewer bias. Fasting blood samples were collected by research nurses and the lipid samples were analysed by a lab technician, independent of the study, and using standard operating procedures.

3.6.10. Compliance

Patients recruited to the intervention arm were contacted regularly throughout the study period. These phone calls provided an opportunity for patients to voice any issues or concerns and ask any questions relating to their participation in the intervention. Furthermore, it provided the researcher with an opportunity to gauge the level of participation in both components of the intervention. To try to balance the contact provided to the intervention and control patients, control patients received one phone call mid-way between each of their visits; the purpose of this call was to enquire about their health status and to ask if they had any questions or issues concerning their participation in the study.

3.7. Results

3.7.1. Baseline data

3.7.1.1. Socioeconomic and demographic characteristics

In general, there was no age difference between the control and intervention group patients at baseline with an average age of 69 years ($p = 0.8$). More men in the intervention group were married (91.5%) than in the control group (70.2%), and more men in the control group were single or widowed ($p = 0.009$). There was a significant difference in educational attainment between groups at baseline as 46.8% of men in the intervention group compared

to 25.5% in the control group had received 12 or more years of education (p = 0.03). The majority of patients were retired with no difference between the two groups at baseline (p = 0.7) (**Table 3.1**).

Table 3.1. Baseline socioeconomic and demographic characteristic of prostate cancer patients with ADT who received diet and physical activity interventions

Variables	Control (n = 47)	Intervention (n = 47)	Total (n = 94)	p
Age (mean, SD)	69.9 ± 7.0	69.7 ± 6.8	69.80 ± 6.81	0.8
Marital status (n, %)				
Married	33 (70.2)	43 (91.5)	76 (80.9)	
Single/widowed/divorce	14 (29.8)	4 (8.5)	18 (19.2)	0.009*
Education				
≤12 years (n, %)	35 (74.5)	25 (53.2)	60 (63.8)	
>12 years (n, %)	12 (25.5)	22 (46.8)	34 (36.2)	0.03*
Total years of education (mean, SD)	11.2 ± 2.9	12.15 ± 4.3	11.7 ± 3.7	0.2
Employment status (%, n)				
Retired	43 (91.5)	42 (89.4)	85 (90.4)	
Employed	4 (8.5)	5 (10.6)	9 (9.6)	0.7

- Statistically significant p-value (<0.05) are highlighted with * symbol; p-value from independent t-test of group comparisons
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3.7.1.2. Medical history

Information collected on the baseline medical history of patients included in the intervention is presented in **Table 3.2**. These data include AJCC staging status, Gleason score, months since diagnosis, duration of ADT treatment, PSA both diagnosis and study baseline, number of co-morbidities, and medication and supplement use. Staging information was available for all patients, (using the American Joint Committee on Cancer (AJCC) classification): only 1.1% of patients had stage I, 14.9% had stage II, 46.8% of patients had stage III cancer, 28.7% had stage IV cancer and 8.5 had cancer of unknown classification. There was no difference between the intervention and control groups regarding the Staging (p = 0.3) or Gleason score (p = 0.3). The percentage of patients with a Gleason score 8-10 was 70.2%, Gleason score 7 (20.2%), followed by Gleason score ≤ 6 (8.5%), and unknown (1.1%). The control group patients had an average time of 15 months from diagnosis before the study

started, while the intervention group were diagnosed 16 months before being involved in this study (p = 0.1). Patients had lower mean PSA levels at study baseline than at diagnosis and there were no significant differences between groups at either time point (**Table 3.2**).

Approximately 78.8% of control patients had undergone ≥6 months ADT treatment while in the intervention group the number was slightly lower at 74.5%, but there was no statistical difference between the two groups at baseline (p = 0.9). Most intervention patients had 1-2 comorbidities (48.9%), slightly higher than the control group (44.7%); on the other hand, more control patients had 3-5 comorbidities although this was not statistically significant at baseline (p = 0.9). An analysis of the use of cholesterol-lowering agents was also carried out in both groups of patients; more than half of patients reported not using this drug, however, 48.9% of control patients and 42.6% of intervention patients reported use, although this was not significantly different between groups (p = 0.5). Less than 45% of the patient population in both groups were taking a supplement and this did not differ between groups at baseline (p = 0.8).

Table 3.2. Baseline medical history characteristic of prostate cancer patients with ADT who received diet and physical activity interventions

Variables	Control (n = 47)	Intervention (n = 47)	Total (n = 94)	p
AJCC staging status (%, n)				
I	1 (2.1)	0 (0)	1 (1.2)	
II	8 (17.0)	6 (12.8)	14 (14.9)	
III	23 (49.0)	21 (44.7)	44 (46.8)	
IV	12 (25.5)	15 (32.0)	27 (28.7)	
Unknown	3 (6.4)	5 (10.6)	8 (8.5)	0.3
Gleason score				
≤6	3 (6.4)	5 (10.6)	8 (8.5)	
7	9 (19.2)	10 (21.3)	19 (20.2)	
8-10	35 (74.5)	31 (66.0)	66 (70.2)	
Unknown	0 (0)	1 (2.1)	1 (1.2)	0.3
Months since diagnosis, median (interquartile range)	15 (8-28)	16 (7-57)	15 (7-34)	0.1
Duration of ADT treatment, % (n)				
<6 months	10 (21.3)	12 (25.5)	22 (23.4)	
≥6 months	37 (78.8)	35 (74.5)	72 (76.6)	0.9
PSA, median (interquartile range)				
Diagnosis	24 (11.6-94)	22.5 (16-56)	23.9 (13-63.9)	0.5
Baseline	0.2 (0.1-2.5)	0.7 (0.1-2.7)	0.4 (0.1-2.6)	0.6
Number of co-morbidities (n, %)				
0	2 (4.3)	2 (4.3)	4 (4.2)	
1-2	21 (44.7)	25 (48.9)	46 (48.9)	
3-4	20 (42.6)	14 (36.2)	34 (36.2)	
+5	4 (8.51)	6 (10.6)	10 (10.6)	0.9
7-DPARQ: energy expenditure (kcal/kg/day) (mean, SD)	33.9 ± 3.8	33.2 ± 2.0	33.5 ± 2.9	0.2
Supplement use (taking at least one supplement) (n, %)	19 (40.4)	20 (42.6)	39 (41.5)	0.8
Cholesterol-lowering agent use (%)				
No	51.1	57.5	54.3	
Yes	48.9	42.6	45.7	0.5

- Statistically significant p-value (<0.05) are highlighted with * symbol; p-value from independent t-test; AJCC: American Joint Committee on Cancer; ADT: Androgen Deprivation Therapy; PSA diagnosis: Prostate-Specific Antigen at initial diagnosis of prostate cancer; PSA Baseline: Prostate-Specific Antigen most recently recorded upon entry to the study (generally within 2 weeks prior to baseline measurements); 7-DPAR: 7-Day Physical Activity Recall Questionnaire
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3.7.1.3. Body composition

The majority of patients recruited to the study were overweight, with a BMI of >25 kg/m^2 (83.3%) based on the World Health Organisation's BMI classification categories; 42.6% of these patients had a BMI greater than 30 kg/m^2 thus classifying them as clinically obese

(WHO, 2019a). In terms of central adiposity, an individual is at high risk of developing CVD if they have a waist measurement of >94 cm and are at very high risk if they have a waist measurement of >102 cm; the average waist measurement of patients recruited to this intervention is 107.3 ± 11.4 suggesting central adiposity and an increased risk of cardiovascular disease in this population. In addition, the average percentage of body fat was 32.5 ± 6.0, exceeding the healthy cut-off of <28% for this age group of men (ACSM, 2004). There were no significant differences between the intervention and control group at baseline for any body composition measurements (all p > 0.05) (**Table 3.3**).

Table 3.3. Baseline body composition characteristic of prostate cancer patients with ADT who received diet and physical activity interventions

Variables	**Control (n = 47) (mean, SD)**	**Intervention (n = 47) (mean, SD)**	**Total (n = 94) (mean, SD)**	**p**
Weight (kg)	89.2 ± 14.6	89.1 ± 11.5	89.1 ± 13.1	0.9
BMI (kg/m^2)	29.7 ± 4.6	29.9 ± 4.5	29.8 ± 4.6	0.8
Waist (cm)	107.3 ± 11.8	107.3 ± 11.1	107.3 ± 11.4	0.9
Hip (cm)	106 ± 86	107.3 ± 7.5	107.1 ± 8.0	0.8
Waist-hip ratio	1.00 ± 0.06	1.00 ± 0.06	1.0 ± 0.1	0.9
Mid-upper arm muscle area (cm^2)	6074.5 ± 1175.7	5099.8 ± 1172.2	335.5 ± 35.9	0.8
Fat mass (%)	32.4 ± 5.8	32.6 ± 5.9	32. 47 ± 5.8	0.8
Lean body mass (kg)	59.8 ± 6.7	58.3 ± 8.8	59.1 ± 7.8	0.3

- Statistically significant p-value (<0.05) are highlighted with * symbol; p-value from independent t-test; BMI: Body Mass Index
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3.7.1.4. Dietary

Based on **Table 3.4**, in general, there were no differences in the dietary intakes between the control and intervention groups at baseline, for energy (p = 0.1), total fat (p = 0.4), saturated fat (p = 0.4), monounsaturated fats (p = 0.2), polyunsaturated fats (p = 0.7), cholesterol (p = 0.6), protein (p = 0.2) and sodium (p = 0.06). Carbohydrate intake in the intervention group was significantly higher than the control group at baseline (280.5 g ± 78.7 vs. 248.0 g ± 52.1; p = 0.02). Fibre consumption was also higher in the intervention group than the control at baseline (p = 0.004), and the intervention group consumed more fruit and

vegetables than the control group: 3.9 ± 1.8 compared to 3.2 ± 1.8 in the control group at baseline (p = 0.03).

Table 3.4. Baseline diet characteristics of prostate cancer patients with ADT who received diet and physical activity interventions

Variables	Control (n = 47)		Intervention (n = 47)		Total (n = 94)		p
	(mean, SD)	(%)	(mean, SD)	(%)	(mean, SD)	(%)	
Energy (kcal)	2127.6 ± 376.2,		2271.7 ± 520.6		2199.66 ± 457.6		0.1
Total fat (g)	83.1 ± 18.9	34.7	86.7 ± 25.3	33.8	84.9 ± 22.3	34.2	0.4
Saturated fat (g)	30.7 ± 10.0	12.9	32.6 ± 12.0	12.2	31.6 ± 11.0	12.5	0.4
Monounsaturated fats (g)	25.5 ± 7.4	10.9	27.6 ± 8.2	10.9	26.5 ±7.8	10.9	0.2
Polyunsaturated fats (g)	11.9 ± 4.4	4.9	12.3 ± 4.9	5.5	12.0 ± 4.6	5.2	0.7
Cholesterol (mg)	300.4 ± 105.0	2.1	312.0 ± 117.8	2.4	306.2 ± 111.1	2.2	0.6
Protein (g)	84.8 ± 17.8	16.1	89.1 ± 16.6	17.4	86.9 ± 17.3	16.8	0.2
Total carbohydrates (g)	248.0 ± 52.1	48.1	280.5 ± 78.7	48.8	264.2 ± 68.4	48.4	0.02*
Fibre (g)	14.4 ± 4.4		17.7 ± 6.3		16.1 ± 5.7		0.004*
Sodium (mg)	2953.6 ± 557.2		3206.8 ± 731.1		3080.2 ± 658.9		0.06
Portions of vegetables and fruit	3.2 ± 1.5		3.9 ± 1.8		3.9 ± 2.1		0.03*
Alcohol (units)	14.1±18.4		8.7±16.9		11.4 ± 17.9		0.1
Sugars (g)	113.0 ± 38.1		129.2 ± 58.9		121.1 ± 48.5		0.1

- Statistically significant p-value (<0.05) are highlighted with * symbol; p-value from independent t-test
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3.7.1.5. Lipid profiles

Table 3.5 presents the baseline values for the full lipid profile for all 94 patients at baseline as well as the values for those recruited to the intervention and control arms at baseline. Within the UK, the guidance for adults suggests that a healthy total cholesterol (TC) is ≤5 mmol/L, a HDL of >1 mmol/L, a LDL value of ≤3 mmol/L (men) and Triglyceride of <2.3 (non-fasting) or <1.7 (fasting) (NHS, 2020a, NICE, 2014). Within the full patient sample of n = 94, the average values for TC, HDL, LDL and Triglycerides were within the recommended range. The total cholesterol of the control group at baseline was slightly higher than the intervention, however, levels did not differ significantly (p = 0.2). Likewise, the HDL level for

the total sample was 1.40 ± 0.33 mmol/L and when analysed by group at baseline did not significantly differ between groups (p = 0.3). The average LDL level in the total sample was 2.74 ± 0.95 mmol/L with no significant difference between the groups at baseline (p = 0.6). A significant difference between the intervention and control groups was found in the triglyceride level at baseline, where the level of the control group was higher than the intervention group (1.81 ± 0.85 mmol/L vs. 1.48 ± 0.63 mmol/L; p = 0.03). This chapter also explored the difference in cholesterol levels by treatment with cholesterol lowering medication at baseline and as expected there was a significant difference in levels with the n = 43 patients receiving treatment having lower levels of total cholesterol and LDL cholesterol than the n = 51 not receiving treatment, yet there was no difference in HDL and TG levels according to cholesterol-lowering treatment group (data not presented). As discussed previously, there were no differences in treatment with cholesterol lowering medication between groups at baseline (**Table 3.5**).

Table 3.5. Baseline lipid profiles characteristic of prostate cancer patients with ADT who received diet and physical activity interventions

Variables	Control (n = 47)	Intervention (n = 47)	Total (n = 94)	p
Cholesterol (mmol/L)	5.03 ± 1.12	4.76 ± 1.00	4.89 ± 1.06	0.2
HDL (mmol/L)	1.43 ± 0.33	1.37 ± 0.33	1.40 ± 0.33	0.3
LDL (mmol/L)	2.77 ± 1.03	2.71 ± 0.87	2.74 ± 0.95	0.7
TG (mmol/L)	1.81 ± 0.85	1.48 ± 0.63	1.65 ± 0.76	0.03*
Cholesterol to HDL ratio	3.70 ±1.07	3.58 ± 0.98	3.62 ± 0.92	0.6

Statistically significant p-value (<0.05) are highlighted with * symbol; p-value from independent t-test; HDL: High-Density Lipoprotein; LDL: Low-density Lipoprotein; TG: Triglyceride; TC: Total Cholesterol

3.7.1.6. QRisk score

The average 10 year cardiovascular risk score at baseline was 21.4 ± 8.1 for all patients and there was no difference between the intervention and control groups at baseline (p = 0.8); a score of >20% indicates a high risk of CVD within the next 10 years (Hippisley-Cox et al., 2007). The relative risk, which is the individual's Qrisk score divided by the score of a healthy person of the same age, sex and ethnicity, did not differ across groups at baseline and 70% of

the overall population had a relative risk >1. The heart age of men (the age at which a healthy person of the individual's sex, age and ethnicity has the same 10 year risk score) was generally higher than their actual age across the patient sample, yet the difference in heart age did not differ by groups at baseline (p = 0.6). The average difference between the actual age of patients at baseline and their heart age (based on the Qrisk algorithm) was 3.38 ± 3.8 for the entire sample and 3.21 ± 3.8 and 3.55 ± 3.9 for the intervention and control groups respectively (**Table 3.6**).

Table 3.6. Baseline cardiovascular disease risk score of prostate cancer patients with ADT who received diet and physical activity interventions

Variable	Control (n = 47) (mean, SD)	Intervention (n = 47) (mean, SD)	Total (n = 94) (mean, SD)	p
10 years QRisk	21.9 ± 8.6	21.0 ± 7.6	21.4 ± 8.1	0.5
Relative risk	1.28 ± 0.4	1.23 ± 0.3	1.25 ± 0.38	0.5
Heart age	73.5 ± 6.89	72.9 ± 6.6	73.2 ± 6.7	0.6
Actual Age at Baseline	69.9 ± 7.0	69.7 ± 6.8	69.8 ± 6.8	0.8
Difference in actual and healthy heart age	3.55 ± 3.9	3.21 ± 3.8	3.38 ± 3.8	0.6

P-values from an independent T-test: 10 years QRisk: person's risk of developing a cardiovascular event in next 10 years; Relative risk*: the individual's QRisk divided by the QRisk of a healthy person of the same age, sex and ethnicity; Healthy heart age: the age at which a healthy person - of the individual's sex, age and ethnicity - has the same 10 years risk score

3.7.2. Outcomes

3.7.2.1. Body composition

The six-month dietary and physical activity intervention led to number of significant changes in anthropometry at endpoint in the intervention group when compared to the control group and the results have been already published (O'Neill et al., 2015), but are presented here to allow interpretation of the further new analyses. As described in **Table 3.7**, the body weight of patients in the control group increased while the intervention group decreased at study endpoint. The between group difference in weight (kg) between the intervention and control group at study endpoint -3.3 kg (95%CI -4.5, -2.1) was statistically significant (p = 0.001). A significant reduction in BMI was also observed between the

intervention and control group at endpoint after adjusting for baseline values (-1.1 kg/m^2 (95% CI -1.5, -0.7)) (p = 0.001). At study endpoint, the mean hip measurements of patients in the intervention group decreased from 107.3 cm ± 7.5 at baseline to 105.3 cm ± 7.0 at endpoint yet increased in the control group with a statistically significant between group difference at study endpoint of -2 cm (95% CI -3.0, -1.0) (p = 0.001). A similar decrease was also found in the waist measurement of the intervention group at endpoint with a between group differences of -3.3 cm (95% CI -4.6, -1.9) (p = 0.001). The decrease in hip and waist measurements ultimately helped improve the waist-hip ratio in the intervention group from 1.00 ± 0.06 at baseline to 0.98 ± 0.1 at endpoint with a significant between group difference of -0.02 (95% CI -0.03, -0.004) after adjustment for baseline values within the analysis (p = 0.009).The percentage fat mass decreased in the intervention group from 32.6% ± 5.9 at baseline to 30.8% ± 5.8 at endpoint yet increased from 32.4 ± 5.8 to 32.8 ± 5.8, a statistically significant between group difference -2.1% (95% CI -2.8, -1.4) (p <0.001). On the other hand, the intervention group showed an increase in lean body mass of 0.4 kg at six months but the between group difference at endpoint was not significant (p = 0.34) and no change between the intervention and control group for mid-upper arm muscle area (p = 0.1) (**Table 3.7**).

Table 3.7. Outcome of body composition of prostate cancer patients with ADT who received diet and physical activity interventions

Variables	Control (n = 47)		Intervention (n = 47)		Endpoint between-group difference (95% CI)	p
	Baseline (mean, SD)	Endpoint (mean, SD)	Baseline (mean, SD)	Endpoint (mean, SD)		
Weight (kg)	89.2 ± 14.6	90.0 ± 14.3	89.1 ± 11.5	85.9 ± 10.5	-3.3 (-4.5, -2.1)	0.001*
BMI (kg/m^2)	29.7 ± 4.6	30.0 ± 4.5	29.9 ± 4.5	29.0 ± 4.5	-1.1 (-1.5, -0.7)	0.001*
Waist (cm)	107.3 ± 11.8	107 ± 12.1	107.3 ± 11.1	103.6 ± 10.7	-3.3 (-4.6, -1.9)	0.001*
Hip (cm)	106 ± 86	107.5 ± 8.6	107.3 ± 7.5	105.3 ± 7.0	-2.0 (-3.0, -1.0)	0.001*
Waist-hip ratio	1.00 ± 0.06	1.0 ± 0.1	1.00 ± 0.06	0.98 ± 0.1	-0.02 (-0.03, -0.004)	0.009*
Mid-upper arm muscle area (cm^2)	6074.5 ± 1175.7	6045.5 ± 1121.7	5099.8 ± 1172.2	6107.1 ± 1189.8	135.5 (-29.7, 300.7)	0.1
Fat mass (%)	32.4 ± 5.8	32.8 ± 5.8	32.6 ± 5.9	30.8 ± 5.8	-2.1 (-2.8, -1.4)	0.001*
Fat mass (kg)	29.5 ± 9.9	30.1 ± 9.6	28.8 ± 9.2	26.9 ± 7.8	-2.4 (-3.5, -1.0)	0.001*

Lean body mass (kg)	59.8 ± 6.7	59.1 ± 5.2	58.3 ± 8.8	59.8 ± 6.6	0.4 (-1.3, 2.0)	0.34

- Statistically significant p-value (<0.05) are highlighted with * symbol; [a]p-value from ANCOVA for endpoint scores, adjusting for baseline values; BMI: Body Mass Index
- Reproduced with permission from O'Neill et al 2015

3.7.2.2. Dietary intakes

As previously published, but presented here to allow interpretation of the later analyses (O'Neill, 2012), the total energy intake decreased by -234.1 kcal (95% CI -379.3, -89.0) between the intervention and control groups at endpoint; this was a significant between group difference after adjusting for the baseline values (p = 0.002). In terms of fat, the total fat consumption of the intervention group decreased from 86.7 g ± 25.3 at baseline to 66.5 g ± 20.2 at endpoint; the between group difference of 15.9 g (95% CI -23.1, -8.8) at six months was statistically significant after adjusting for baseline values (p = 0.001). A statistically significant between group decrease in consumption of saturated fat by -8.0g (95% CI -11.2, -4.8) (p = 0.001) as well as monounsaturated fat by -5.8 g (95% CI -8.2, -3.4) (p = 0.001), and cholesterol by -19.2 mg (95% CI -58.6, 20.1) (p = 0.33) was also demonstrated at the end of the study, whilst also adjusting for baseline scores. No statistically significant difference in polyunsaturated fat was observed between groups at endpoint (0.7 g (95% CI -0.9, 22.2)) (p = 0.3)). In terms of protein consumption, dietary intakes of protein did not differ between groups at study endpoint with a non-significant between group difference of -2.5 g (95% CI-9.8, 4.8) (p = 0.5) at six months. Total carbohydrate consumption decreased in the intervention group from 280.5 g ± 78.7 at baseline to 238.1 g ± 59.2 at endpoint and in the control group from 248.0 g ± 52.1 at baseline to 237.0 g ± 65.0 in the control group with a non-significant between group difference (-17.9 g (95% CI -39.3, 3.5)) (p = 0.1)). A significant increase in fibre was observed in the intervention group at endpoint; the between group difference of 2.0 g (95% CI 0.2, 3.9) was observed at six months after adjusting for baseline measurements (p = 0.03). Patients in the intervention group reduced their salt intake between baseline and endpoint whilst those in the control group increased their intakes over the six-

months study period. The between group difference was -402.0 mg (95% CI -803.8, 0.23) (p = 0.05) at endpoint after adjusting for baseline values. Fruit and vegetable intakes increased in the intervention group from 3.9 ± 1.8 at baseline to 1.3 (95% CI 0.7, 1.9) six months yet decreased in the control group from 3.2 ±1.5 at baseline to 3.0 ± 1.6 at six months. There was a significant between group difference of p = 0.001 (**Table 3.8**).

Table 3.8. Outcomes of dietary intake reporting between-group difference of prostate cancer patients with ADT who received diet and physical activity interventions

Variables	**Control (n = 47)**		**Intervention (n = 47)**		**Endpoint between-group difference (95% CI)**	**p**
	Baseline (mean, SD)	**Endpoint (mean, SD)**	**Baseline (mean, SD)**	**Endpoint (mean, SD)**		
Energy (kcal)	2127.6 ± 376.2	2016.8 ± 476.0	2271.7 ± 520.6	1889.2 ± 418.9	-234.1 (-379.3, -89.0)	0.002*
Total fat (g)	83.1 ± 18.9	80.6 ± 21.4	86.7 ± 25.3	66.5 ± 20.2	-15.9 (-23.1, -8.8)	0.001*
Saturated fat (g)	30.7 ± 10.0	30.2 ± 9.6	32.6 ± 12.0	22.8 ± 8.7	-8.0 (-11.2, -4.8)	0.001*
Monounsaturated fats (g)	25.5 ± 7.4	25.9 ± 7.2	27.6 ± 8.2	21.3 ± 7.2	-5.8 (-8.2, -3.4)	0.001*
Polyunsaturated fats (g)	11.9 ± 4.4	11.4 ± 4.3	12.3 ± 4.9	12.2 ± 4.5	0.7 (-0.9, 22.2)	0.3
Cholesterol (mg)	300.4 ± 105.0	280.2 ± 97.0	312.0 ± 117.8	264.1 ± 115.9	-19.2 (-58.6, 20.1)	0.33
Protein (g)	84.8 ± 17.8	83.4 ±22.2	89.1 ± 16.6	84.2 ± 18.0	-2.5 (-9.8, 4.8)	0.5
Total carbohydrates (g)	248.0 ± 52.1	237.0 ± 65.0	280.5 ± 78.7	238.1 ± 59.2	-17.9 (-39.3, 3.5)	0.1
Fibre (g)	14.4 ± 4.4	14.4 ± 5.4	17.7 ± 6.3	19.0 ± 6.0	2.0 (0.2, 3.9)	0.03*
Sodium (mg)	2953.6 ± 557.2	3022.0 ± 1091.5	3206.8 ± 731.1	2727.2 ± 835.5	-402.0 (-803.8, 0.23)	0.05*
Portions of vegetables and fruit	3.2 ±1.5	3.0 ± 1.6	3.9 ± 1.8	4.9 ± 2.1	1.3 (0.7, 1.9)	0.001*
Alcohol (units)	14.1 ± 18.4	8.8 ± 13.6	8.7 ± 16.9	7.3 ± 13.2	0.6 (-2.8, 4.0)	0.7
Sugars (g)	113.0 ± 38.1	100.9 ± 43.7	129.2 ± 58.9	108.0 ± 48.3	-0.39 (-18.2, 12.3)	0.7

- Statistically significant p-value (<0.05) are highlighted with * symbol; [a]p-value from ANCOVA for endpoint scores, adjusting for baseline values
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3.7.2.3. Adherence to dietary and physical activity

The analysis explores adherence to the intervention recommendations at endpoint by group assignment and, as expected, the intervention group had higher adherence for several recommendations when compared to the adherence of the control group at endpoint. The adherence of ≥ 5 serving of vegetables and fruit/day in the intervention group was

significantly higher than the control group; 48.9% of patients within the intervention group adhered to this recommendation in comparison to only 11.1% in the control group at study endpoint (p <0.001). In terms of adherence to the recommendation for 30-35% of total energy from fat: 42.2% of the intervention group complied with this guidance compared to only 13.3% by the control group at study endpoint (p = 0.02). The percentage of participants adhering to <10% energy of saturated fat/day was shown to differ significantly (p = 0.004) as 40% of the intervention group were adhering to this recommendation at the study endpoint while only 13.3% of the intervention group managed to adhere to it. Compliance with 25-35 g fibre per day was achieved in 11% of the intervention group and no one in the control group at the endpoint (p = 0.02). There were no differences between adherence to alcohol, and physical activity between the groups at endpoint (**Table 3.9**).

Table 3.9. Adherence to dietary and physical activity recommendations at endpoint by group of prostate cancer patients with ADT who received diet and physical activity interventions

Recommendation	Adherence		Non-adherence		P
	Control (n, %)	Intervention (n, %)	Control (n, %)	Intervention (n, %)	
≥5 servings of vegetables and fruits/day	5 (11.1)	22 (48.9)	40 (88.9)	23 (51.1)	<0.001*
30-35% of total energy from fat	6 (13.3)	19 (42.2)	39 (86.7)	26 (57.8)	0.02*
<10 % energy from saturated fat/day	13 (13.3)	18 (40)	39 (86.7)	27 (60)	0.004*
10% of energy from polyunsaturated fat/day	44 (97.8)	43 (95.6)	1 (2.22)	2 (4.44)	0.5
25-35 g of fibre/day	0 (0)	5 (11.1)	45 (100)	40 (88.9)	0.02*
≤28 units/week of alcohol	36 76.6)	41 (87.2)	11 (23.4)	6 (12.8)	0.2
Physical activity 30 minutes/5 days per week (yes/no)	23 (50)	21 (44.7)	23 (50)	26 (55.52)	0.6
Salt (6g or less)	30 (66.7)	15 (33.3)	33 (73.3)	12 (26.7)	0.4

Statistically significant p-value (<0.05) are highlighted with * symbol; p-value from ANCOVA

3.7.2.4. Lipid profiles

The six-month dietary and physical activity intervention had no significant impact on the lipid profile of patients at study endpoint. Total cholesterol levels increased slightly between baseline and endpoint in the control group and remained steady within the

intervention arm but there was no significant between group difference at six months after adjustment for the baseline values (-0.16 mmol/l (95%CI -0.50, 0.13) (p = 0.2)). Similarly, LDL levels increased in the control group from 2.77 mmol/L ± 1.03 at baseline to 2.93 ± 1.05 endpoint and remained steady in the intervention arm: 2.72 ± 0.87 at baseline and 2.73 ± 0.96 at endpoint however the between group difference was non-significant -1.57 mmol/L (95% CI -0.49, 0.06), (p = 0.1). There was a non-significant decrease in HDL levels in patients in the control group from 1.43 ± 0.33 at baseline to 1.38 ± 0.28 at six months compared to an increase in the intervention group from 1.37 ± 0.33 at baseline to 1.38 ± 0.33 at study endpoint. At the end of the intervention, there was a between group difference of +0.01 mmol/L (95% CI -0.06, 0.07), between the intervention and control arm, however, this was not statistically significant (p = 0.8). In terms of triglycerides, there was a decrease observed in the average values of both the control and intervention groups between baseline and endpoint but there was no between group difference in triglyceride values at endpoint after adjusting for baseline values (-0.17 mmol/L (95% CI -0.21, 0.18) (p = 0.9) (**Table 3.10**).

Table 3.10. Outcomes of lipid profiles at endpoint by group of prostate cancer patients with ADT who received diet and physical activity interventions

Variables	Control (n = 47)		Intervention (n = 47)		Endpoint between-group difference (95% CI)	p
	Baseline (mean, SD)	Endpoint (mean, SD)	Baseline (mean, SD)	Endpoint (mean, SD)		
Cholesterol (mmol/L)	5.03 ± 1.12	5.10 ± 1.09	4.76 ± 1.00	4.77 ± 1.09	-0.16 (-0.50, 0.13)	0.2
HDL (mmol/L)	1.43 ± 0.33	1.38 ± 0.27	1.37 ± 0.33	1.38 ± 0.33	0.19 (-0.06, 0.07)	0.8
LDL (mmol/L)	2.77 ± 1.03	2.93 ± 1.05	2.72 ± 0.87	2.73± 0.96	-1.57 (-0.49, 0.06)	0.1
TG (mmol/L)	1.81 ± 0.85	1.75 ± 0.78	1.48 ± 0.63	1.44 ± 0.67	-0.17 (-0.21, 0.18)	0.9
Cholesterol to HDL ratio	3.70 ± 1.07	3.80 ± 0.9	3.58 ± 0.98	3.62 ± 1.1	-0.08 (-0.34 -0.18)	0.5

Statistically significant p-value (<0.05) are highlighted with * symbol; p-value from ANCOVA for endpoint scores, adjusting for baseline values; HDL: High-Density Lipoprotein; LDL: Low-density Lipoprotein; TG: Triglyceride

3.7.2.5. QRisk score scores

The QRisk score increased from 21.9% ± 8.6 at baseline to 23.4 ± 8.8 at endpoint in the control group and 21.0 ± 7.6 at baseline to 22.2 ± 8.4 at endpoint in the intervention group

however there were no significant between group differences at endpoint 0.24 (95% CI -0.9, 1.3). As a result, the relative risk: the individual's QRisk divided by the risk of a healthy person of the same age, sex and ethnicity, remained steady across the duration of the study and also did not differ by group (intervention and control) at study endpoint. The difference in heart age, the age at which a healthy person of the individual's sex, age and ethnicity has the same 10 years risk score minus the person's actual age also did not change at endpoint by group after adjusting for baseline values with a between group difference of -0.14 (95% CI -0.89, 0.6) (p = 0.7) (**Table 3.11**).

Table 3.11. Change in cardiovascular risk scores at endpoint by group of prostate cancer patients with ADT who received diet and physical activity interventions

Variable	Control		Intervention		Endpoint between group difference (95%CI)	p
	Baseline (mean, SD)	Endpoint (mean, SD)	Baseline (mean, SD)	Endpoint (mean, SD)		
10 years QRisk	21.9 ± 8.6	23.4 ± 8.8	21.0 ±7.6	22.2 ± 8.4	0.24 (-0.9, 1.3)	0.7
Relative risk [a)]	1.28 ± 0.4	1.28 ± 0.3	1.23 ± 0.3	1.26 ± 0.4	0.02 (-0.0.5, 0.09)	0.6
Healthy Heart age	73.5 ± 6.9	74.6 ± 6.37	72.9 ± 6.6	73.7 ± 6.4	0.03 (-0.74, 0.81)	0.9
Difference in actual and healthy heart age	3.55 ± 3.9	3.82 ± 3.3	3.21 ± 3.8	3.29 ± 4.24	-0.14 (-0.89, 0.60)	0.7

Statistically significant p-value (<0.05) are highlighted with * symbol; p-value from ANCOVA for endpoint scores, adjusting for baseline values: person's risk of developing a cardiovascular event in next 10 years; [a)]Relative risk: the individual's QRisk divided by the QRisk of a healthy person of the same age, sex and ethnicity; Healthy heart age: the age at which a healthy person of the individual's sex, age and ethnicity that has the same 10 years risk score

3.7.2.6. Lipid scores change by adherence of intervention

An overall adherence score was created to evaluate the difference in lipid measurement at endpoint by high/low adherence to the diet and lifestyle recommendations made within the intervention. If patients adhered to less than four of the recommendations, they were categorised into the low adherent group and if they adhered to four or more recommendations they were categorised as high adherence.

Adherence to the diet and lifestyle recommendations did not lead to significant change in the lipid profile at study endpoint after adjusting for baseline values. As shown in

Table 3.12, total cholesterol was higher in the group adhering to more than four recommendations with an average total cholesterol of 5.06 ± 1.07 compared to 4.77 ± 1.11 in the low adherence group (less than four recommendations; with a between group difference of -0.8 mmol/L (95% CI -0.4, 0.25). This difference, however, was not statistically significant (p = 0.65) after adjustment for baseline values. HDL levels were lower in the adherent group (1.36 ± 0.30) compared to the low adherence group (1.40 ± 0.34) after adjustment for baseline values +0.02 mmol/L (95% CI -0.05, 0.08) (p = 0.64)). On the other hand, LDL was lower in the adherent group compared to the non-adherent group where the result was a difference between groups of -0.06 (95% CI -0.35, 0.23) although, again, this difference was not statistically significant (p = 0.7). The same was found for triglycerides in the adherent group that was lower than the non-adherent group, with a difference between the groups of -0.03, which was not statistically significant (95% CI -0.22, 0.16) (p = 0.2) (**Table 3.12**).

Table 3.12. Change in lipid scores at endpoint by adherence to diet and lifestyle recommendations (high/low) of prostate cancer patients with ADT who received diet and physical activity interventions

Outcome	High adherence (≥4) (n = 40)	Low adherence (< 4) (n = 50)	Between group difference	p
Cholesterol	5.06 ± 1.07	4.77 ± 1.11	-0.8 (-0.4, 0.25)	0.6
HDL	1.36 ± 0.30	1.40 ± 0.34	0.02 (-0.05, 0.08)	0.6
LDL	2.74 ± 1.0	2.90 ± 1.0	-0.06 (-0.35, 0.23)	0.7
TG	1.48 ± 0.69	1.68 ± 0.77	-0.03 (-0.22, 0.16)	0.2

Statistically significant p-value (<0.05) are highlighted with * symbol; p-value from ANCOVA for endpoint scores, adjusting for baseline values; HDL: High-Density Lipoprotein; LDL: Low-density Lipoprotein; TG: Triglyceride

3.7.2.7. Anthropometry change by adherence of intervention

Adherence to the diet and lifestyle recommendations influenced anthropometric changes at the end of the study after the baseline value adjustment was carried out. Weight in the high adherence group (with more than four recommendations) was lower (86.5 ± 11.3) than the low adherence group (with less than four recommendations) (89.04 ± 13.6) and there was a significant decrease of -1.99 kg (95% CI -2.8, 0.0009), (p = 0.05). BMI in the high adherence group experienced a significant change at the end compared to the low adherence

group of -2.3 kg/m^2 (95% CI -1.03, -0.07) (p = 0.02). Waist circumference also decreased by -2.0 cm between groups at end (95% CI -3.0, 0.003) (p = 0.05). Meanwhile, the waist to hip ratio in the high adherence group (1.0 ± 0.07) was not different from the low adherence group (1.0 ± 0.06), (p = 0.2). Similar results were also seen in the MUAC results where there was no difference in the decrease (-1.1 mm (95% CI -6.0, 1.7)), (p = 0.3) between adherence groups. However, a significant result was found for changes in fat mass (%) between the two groups of -2.5% (95% CI -1.9, -0.2), (p = 0.01). Meanwhile, the high adherence group showed no significant change in lean body mass compared to the low adherence group (+0.03% (95% CI -1.6, 1.7)) (p = 1.0) (**Table 3.13**).

Table 3.13. Change in anthropometry at endpoint by adherence to diet and lifestyle recommendations (high/low) of prostate cancer patients with ADT who received diet and physical activity interventions

Outcome	High adherence (≥4) (n = 40)	Low adherence (< 4) (n = 50)	Between group difference	p
Weight	86.5 ± 11.3	89.04 ± 13.6	-1.99 (-2.8, 0.0009)	0.05
BMI	28.2 ± 3.9	30.4 ± 4.7	-2.3 (-1.03, -0.07)	0.02*
Waist	102.8 ± 10.7	108 ± 11.7	-2.0 (-3.0, 0.003)	0.05
Waist to hip ratio	1.0 ± 0.07	1.0 ± 0.06	-1.2 (-0.02, 0.004)	0.2
MUAC	328.4 ± 29.4	339 ± 40.6	-1.1 (-6.0, 1.7)	0.3
Fat mass (%)	30.9 ± 5.8	32.5 ± 5.9	-2.5 (-1.9, -0.2)	0.01*
Lean body mass	59.4 ± 5.7	59.5 ± 6.2	0.03 (-1.6, 1.7)	1.0

Statistically significant p-value (<0.05) are highlighted with * symbol; p-value from ANCOVA for endpoint scores, MUAC: mid-upper arm muscle area

3.8. Discussion

This chapter explored the effect of a diet and physical activity intervention on lipid levels and cardiovascular risk as secondary outcomes in prostate cancer patients. The effect of different levels of adherence on both primary and secondary outcomes was also assessed.

3.8.1. Socioeconomic and demographic

Based on the socio-economic and demographic data obtained in this study at baseline, there was a higher number of single or widowed men in the intervention group. As this was a randomised controlled trial, any differences between groups will have occurred by

chance, but these factors have been associated with prostate cancer risk in general. A preliminary study has reported that marital status determined morbidity and mortality associated with all causes of death (Hu and Goldman, 1990). Poor health has also been identified consistently in single or divorced men (Robards et al., 2012). Men who were single or separated, divorced or widowed (SDW) have a higher risk of developing cancer and all-cause mortality (Sammon et al., 2012). Unmarried men have a 40% higher risk of death from prostate cancer and only have an 8.6% lower survival rate than married men (Tyson et al., 2016). Even with all the available evidence, the impact of marital status on morbidity and mortality, especially in prostate cancer, still requires further ascertainment (Klaassen et al., 2014).

Meanwhile, higher levels of education in the intervention group in this study can be associated with the incidence of prostate cancer. Education was reported to be significantly associated with prostate cancer incidence (Liu et al., 2001) which has been suggested to be due to increased awareness among men with higher educational background (Kroese et al., 2014). Conversely, low education was linked with increased deaths (Schwartz et al., 2009). Less-educated men tended not to recognise prostate cancer due to a lack of disease understanding (Pudrovska and Anishkin, 2015).

An interesting observation from the analysis is that these differences in socioeconomic and demographic characteristics were found between the intervention group and the control group at baseline. Several design characteristics that can contribute to overall study robustness are the randomisation process, concealment of allocation and blinding. This study was randomized to try to minimize differences in baseline characteristics (Jager et al., 2008, Pourhoseingholi et al., 2012). However, the randomization process does not always eliminate the differences between groups as expected, this process can only reduce as much as possible the variation between arms in the prevalence of existing conditions (Jager et al.,

2008). It is necessary to consider the combination of block randomisation that has been used with the use of stratified randomisation (Farrokhyar et al., 2010). This combination can be used to ensure the balance between the intervention and control groups while increasing the power of the study. Concealment of allocation may also allow for bias if the person making the decision on the eligibility of study subjects knows where patients will be allocated. This process intentionally or unintentionally can tend to encourage an enrolment process based on the favourable characteristics needed to obtain the intended outcome. What can be done to minimize this is ensure that individuals responsible for recruiting and allocating patients to treatments remain unaware of the next assignment in the sequence and ensure that the individual who generates the allocation scheme is not involved in ascertaining eligibility, administering treatment or assessing outcomes (Farrokhyar et al., 2010). It is most challenging, yet best practice, to blind allocation from patients and research personnel. People who set up follow-up visits may (intentionally or unintentionally) make extra efforts for complete follow-up for patients who received experimental treatment than for those who received conventional treatment if they are not blinded for treatment allocation. This may create differential follow-ups between study groups and introduce attrition bias. What can be done to reduce bias due to inadequately blinded processes is to blind the process to as many people involved as possible, but if not, ensure that people who are randomly assigning patients are independent of the study and not involved in patient care (Farrokhyar et al., 2010).

3.8.2. Body composition

Body composition did not differ between the intervention and control groups at baseline. As expected, patients in the intervention group had significantly decreased weight, BMI, waist, hip, the waist-hip ratio, fat mass both in percentage and kg at the endpoint. This

intervention group also experienced a modest increase in MUAC and an increase in lean muscle mass, however, the changes were not statistically significant.

A systematic review reported an association between exercise and general health improvement in prostate cancer patients with ADT (Teleni et al., 2016). Meanwhile, another stated that a combination of diet and physical activity plays a role in weight loss in the same patients (Mohamad et al., 2014). Other evidence also agreed and reported that the combination of exercise and diet can improve both whole body mass and fat mass in patients with ADT (Galvao et al., 2010).

Evidence suggests that calorie restriction and exercise lead to significantly reduced body weight and improved body composition and fat distribution (Donnelly et al., 2013, Redman et al., 2007). While Caudwell et al 2012 stated that exercise and diet have a mutually beneficial effect. Exercise-induced energy expenditure and intake can control appetite and be useful in a successful diet program (Caudwell et al., 2011). Furthermore, another study showed that there were a short-term energy deficit and a delay in eating that resulted from exercise, this effect created a delay in short energy compensation after exercise and can be very important in appetite regulation (Schubert et al., 2013).

When examining the anthropometric changes by adherence, all anthropometric outcomes decreased more at the endpoint in those who were most adherent to the intervention, except for lean body mass. Anthropometric changes associated with adherence to recommendations were noted to be significant in terms of decreased body weight, BMI, waist circumference, and fat mass (%). Another study conducted in Korea has reported that changes from overweight or obesity to a healthy weight were only obtained from the high adherence group within behaviour change interventions (An et al., 2019) as also found in this chapter.

A narrative review by Leung et al (2017) stated that the relationship between dietary and physical activity may actually be less supported by strong evidence and it is important to include a measure of adherence and account for adherence within a behaviour change intervention. This chapter shows that the high adherence group had more anthropometric improvement compared to the low adherence group although not all of the outcomes were statistically significant. However, what needs to be underlined is that adherence can provide important information for program improvement, especially improving the effectiveness and cost-effectiveness of behaviour change or life-style modification interventions (Leung et al., 2017).

On the other hand, the significance of anthropometric changes may decrease with time and become weaker at follow-up; adherence to behaviour change interventions does have more effect on changes in body weight in the short term and adherence may decrease over time (Coupe et al., 2019). The use of rigorous methods, commitment devices such as behavioural contracts, and the effective follow-up time of the population studied may be a consideration for improving adherence generated by behaviour change interventions (Coupe et al., 2019).

3.8.3. Dietary

Regardless of a higher total carbohydrate, the portion of vegetables, and fruit at baseline, the intervention group had a significant change in dietary outcomes at endpoint i.e. decreased energy, total fat, saturated fat, carbohydrate, and sodium; increased fibre and increased number of portions of fruit and vegetables. There were no changes in polyunsaturated fat, cholesterol, protein, total carbohydrates, and alcohol intake in the intervention group at endpoint.

The improvement of several nutrients that occurred between groups at the endpoint could have an important effect on obesity-related cancer. Total energy, total fat, saturated fat and carbohydrates are important components of Dietary-Energy Density (DED) which are directly associated with adiposity, weight gain and BMI (Rouhani et al., 2016). Other evidence suggests that DED certification is an important part of a dietary intervention to reduce the risk of obesity-related cancer (Thomson et al., 2018). Meanwhile, the amount of fibre has been suggested to play a role in preventing the development of prostate cancer (Deschasaux et al., 2014, Sawada et al., 2015). Meanwhile, the level of fruit and vegetable consumption may have the same effect in preventing prostate cancer (Petimar et al., 2017).

Dietary changes were not consistent, i.e. there was variation in adherence related to several recommendations given as part of the intervention. Changes in servings of vegetables and fruit, limitation of total energy from fat, choice of the type of fat used, the fulfilment of fibre intake targets recorded at the end of the study were noted in the intervention group. Meanwhile, adherence to alcohol consumption recommendations was not proven to have changed at study endpoint.

Average nutrient intakes at baseline were high in total energy, protein, saturated fat, yet low in polyunsaturated fat and fibre. Although the intervention given encouraged an improvement, it is obvious that nutrient intake was initially poor at baseline. Family support is a factor that can affect the level of adherence, family support is needed so that someone can carry out the recommendations given (Mostafavi-Darani et al., 2020), this concept may not have been involved in the results of this chapter because, through observing baseline data, it can be seen that most of the subjects were single or widowed. Another factor related to poor dietary intake relates to the fact that food habits have been formed for a long time, efforts to change a habit have very varied results and require different time for everyone

(Mostafavi-Darani et al., 2020). Stress due to illness is also a potential barrier that could hinder someone's compliance (Ayele et al., 2018).

Regarding alcohol consumption, the results of this chapter have shown that alcohol consumption did not change at the study end. It might relate to the initial average alcohol consumption that was within general consumption guidelines (UK: 14 units/week) (NHS, 2018). The adherence cut-off was quite high (28 units), which might be the reason why the difference in alcohol adherence did not differ between intervention and control groups.

3.8.4. Lipid profile

There was no significant difference in any lipid measurements at the endpoint between the groups after adjustment for the baseline values, although the results suggested the expected direction of change, such as a decrease in LDL, triglyceride, and cholesterol, as well as an increase in HDL in the intervention group. The results of a recent study by Jimenez et al (2020) reported that changes in lipid profiles were only achieved after a 40% reduction in body weight for 24 months postoperatively in obese patients (Jimenez et al., 2020). Although the described weight loss process differed compared with patients in this chapter, this suggested that a desired improvement in the lipid profiles needed more significant weight loss, perhaps over a longer period of time. As these were secondary outcomes, the study was also potentially underpowered (see Conclusion for retrospective power calculation).

3.8.4.1. HDL

HDL level in the intervention group showed improvements but was not significantly different from the control group. HDL improvement in the high adherence group was slightly below that in the low adherence group, although this was not statistically significant.

The use of a combination of physical activity and dietary interventions has been used in other cancer survivor studies and has generated positive outcomes on HDL. According to

Mefferd et al (2007), there was an increase in HDL by 10% after the patient was given a multifaceted 12-month intervention that involved the CBT method in its implementation. However, these results were obtained when the intervention was given to breast cancer patients (Mefferd et al., 2007). Another study also reported improvements in HDL experienced by men with non-aggressive prostate cancer without ADT after a 6-week evaluation since whole-grain diet interventions combined with vigorous activity were administered to patients (Eriksen et al., 2017). A recent study reported the opposite result where the provision of dietary interventions and light physical activity failed in improving HDL levels in cancer survivors (Spees et al., 2019).

In cancer, HDL plays an important role in the management of reactive oxygen species (ROS), with a potential antioxidant role (Ruscica et al., 2018). The moderating effect of ROS by HDL has been suggested to control pathogenesis and tumour development (Ruscica et al., 2018). Evidence has also shown that low HDL levels were associated with the risk of locally advanced prostate cancer (Lebdai et al., 2018). Meanwhile, high HDL levels have been associated with reduced aggressiveness of prostate cancer (Mondul et al., 2011).

3.8.4.2. LDL

This chapter has shown decreased LDL levels in the intervention group, although these were not statistically significant. Patients in the high-adherence group showed slightly lower LDL levels than those in the low-adherence group, however, the difference was also not statistically significant.

In another study, an 11% reduction in LDL levels was reported when CBT behaviour change interventions were administered (Mefferd et al., 2007), a decrease in LDL levels was also noted to occur during moderate and vigorous interventions in cardiovascular disease patients (Silva et al., 2016). However, Spees et al (2019) stated that overweight cancer

patients did not experience a decrease in LDL after being given daily steps physical activity intervention and dietary advice (no specific diet mentioned). Whereas in non-aggressive prostate patients, a whole grain diet and physical intervention had only a weak effect on reducing LDL (Eriksen et al., 2017).

LDL through its receptors (LDLR) plays an active role in prostate tumour cells. Impaired LDL receptor expression due to unbalanced LDL levels have been linked to more lethal cancers (Stopsack et al., 2017). Although this suggestion has been disputed by others (Jacobs et al., 2012), improvement of LDL homeostasis may influence the course of cancer (Stopsack et al., 2017). Another study stated that higher levels of total cholesterol and LDL were associated with a high Gleason score and therefore related to risk of high grade prostate cancer (Murtola et al., 2019).Therefore, it is important that interventions to encourage maintenance of LDL at healthy levels are considered to give potential advantage to cancer patients.

3.8.4.3. TG

The result of TG shows no significant changes in response to the diet and physical activity intervention. Although in the high adherence group the TG level was lower than the low adherence group, the difference was also not statistically significant.

A reduction in TG levels in breast cancer patients was reported to be 8.4% after receiving 12 months of a multifaceted intervention (Mefferd et al., 2007), but this result cannot, of course, be directly compared with the results in this chapter. Furthermore, in cancer survivors, intervention with moderate physical activity combined with diet has also been demonstrated to reduce patient's TG levels (Spees et al., 2019). These changes in TG were found to vary in previous studies, where TG levels actually increased after moderate and vigorous physical activity interventions were given to patients with cardiovascular disease (Silva et al., 2016). Similar results were reported in an intervention in non-aggressive prostate

patients, where the study reported increased TG levels after physical activity and diet intervention for 6 months (Eriksen et al., 2017).

According to Arthur et al (2016) hypertriglyceridemia was a risk factor for prostate cancer. High TG levels have been linked to disease aggressiveness and the development of prostate cancer (Arthur et al., 2016). Moreover, hypertriglyceridemia has linked with higher Gleason score (≥ 8) that was also related with aggressiveness (Hayashi et al., 2012).

3.8.4.4. TC

The total cholesterol level in the intervention group was lower than the control group but not statistically significant at the endpoint. Patients with high adherence had slightly higher total cholesterol levels than the opposite group, although the difference between the two groups was not statistically significant.

Non-aggressive prostate patients have been demonstrated to respond to an intervention with whole grain and vigorous physical activity by showing improved levels of total cholesterol (Eriksen et al., 2017). Women with breast cancer who were given a behaviour change intervention with the CBT method for one year also showed improvement in cholesterol (Mefferd et al., 2007). The same thing was reported by a study by Spees et al (2019) in a breast and prostate cancer survivor group.

Total cholesterol has been linked to prostate cancer outcomes, Jamnagerwalla et al (2018) states that cholesterol levels are associated with prostate-specific antigen (PSA) levels and the growth of high-grade prostate cancer. Furthermore, it was reported that when there is an increase in total cholesterol, this condition will play an important role in the failure of coordination between healthy prostate cells and an increase in prostatic secretion which will trigger the growth of cancer cells (Di Vizio et al., 2018).

3.8.5. QRisk score

Non-significant results were obtained from the variables associated with QRisk. Although there were anthropometric changes as a result of the intervention, lipids did not change, which may have influenced the overall QRisk score. In addition, medical history data were only available at baseline, making it difficult to use as supporting data regarding the possible effects of the intervention given on the QRisk score. These data suggest that the intervention was not able to alter overall CVD risk as estimated using this tool.

However, these results may be important and need attention because various studies have reported a risk of cardiovascular disease in prostate cancer patients, especially with the application of ADT. Furthermore, a cohort study in Canada has reported that prostate cancer sufferers on androgen therapy are more likely to develop hypertension and have a high prevalence of cardiovascular disease (Davies et al., 2015). Another study conducted on prostate cancer survivors found an increased risk of ischemic heart disease and stroke compared to controls (Shin et al., 2016). Further investigation of the prostate cancer survivor group also reported that different therapies presented a risk of cardiovascular disease, where the risk of stroke was found to be increased on ADT application (HR 1.16 95% CI 1.02, 1.32) but no increased risk was found in patients with surgery (Shin et al., 2016). Another recent study reinforces previous findings where there was a 30% increase in cardiovascular events in prostate cancer patients who were given ADT, especially GnRH agonists and Degarelix (Cardwell et al., 2020). Therefore, it will be important to find ways of effectively reducing cardiovascular risk in prostate cancer patients given ADT to reduce their chances of prostate cancer recurrence.

3.8.6. Limitations and strengths

This six-month dietary and physical activity intervention did not have a significant impact on lipids, although it cannot be denied that there was a trend towards improvement in all lipids. However, the intervention did improve the patient's body composition and these results would support the encouragement of prostate cancer patients to improve dietary intake and physical activity in general.

Strengths of this study include its strong and well-prepared methodology, and inclusion of a range of secondary outcomes allowing the testing of the current hypotheses, even if the study was not originally powered to detect changes in these, perhaps explaining the non-significant trends in lipids. Weaknesses in this study include the influence of the use of lipid-lowering drugs by both control and intervention patients; treatments that might have had an impact on the outcome of the lipid profile, and the ability of the intervention to effect a change in lipids against this pharmacological background. The percentage of lipid-lowering drug users was more than half of the patients involved, which may well have affected the sensitivity of the measured lipid profile results, although there were no differences in lipid levels by lipid therapy use at baseline. The QRisk score was used to determine CVD risk, yet there were some variables missing (e.g. blood pressure; medical history at endpoint) that made the calculation of this score less than optimal, and this could have affected study findings.

The combination of dietary and physical activity intervention, i.e. that this was a complex intervention, is difficult to establish, which does result in it being challenging to determine the efficacy of the intervention. The control group could also have adopted the intervention or changed their dietary habits during the study. In addition, the measurement of intervention outcomes was not conducted by a researcher blinded to group assignment.

As discussed, even though the randomization process has been carried out to prevent bias, there were also some differences at random between intervention and control groups.

There were several potential explanations of why this RCT result is different from other studies. First, the different patient profiles included by sex or type of cancer (Mefferd et al., 2007, Spees et al., 2019, Beeken et al., 2017), or baseline levels of lipids, so that there may have been fundamental differences involving metabolism and the role of related hormones in determining lipid levels. Second, the dietary modifications tested by other studies were different; as an example another study added a specific whole-grain diet alongside a guided-dietary intervention (Eriksen et al., 2017). Third, the physical activity intervention used differed between studies in terms of type, intensity level, and duration (Demark-Wahnefried et al., 2018, Bourke et al., 2011, Nobes et al., 2012), and, in fact, in the current study reported changes in physical activity levels did not differ between the intervention groups. Fourth, the different pharmacological therapies used by these patient groups may have affected lipid response. These reasons might affect the demonstrated results and lead to differences in findings between studies.

3.9. Conclusion

The 6-month dietary and physical activity intervention was delivered to prostate cancer patients being treated with ADT and, although previously published work suggested that the intervention led to significant improvements in body composition, a significant change in the lipid profile of patients was not observed in this analysis of patient biomarkers. However, the direction of change in the intervention arm at study endpoint was positive (i.e. in the direction of a healthier lipid profile) for all lipids. One potential reason for these null findings in lipid profile between the intervention and the control groups at endpoint is that the intervention was designed with body composition as the primary outcome and was not powered to detect statistically significant changes in lipid parameters. Based on the mean change and standard

deviation from this RCT, at 90% power it would have required 1030 control patients and 1030 intervention patients to detect a significant change in total cholesterol; 64 control patients and 64 intervention patients for each of HDL and LDL detection. For triglyceride, 526 control patients and 526 intervention patients would have been needed to detect a significant change. These retrospective power calculations confirm that the study was underpowered for the lipid secondary outcomes. Therefore, further studies are needed which are designed to focus on the lipid outcomes and perhaps with the intervention designed to maximise lipid-lowering to effect a significant change, for example considering the type, intensity and duration of a given physical activity. On the other hand, such a specific intervention design to lower lipids will mean that it will be less similar to general dietary guidelines, relevant for a wider population, and therefore this is an important consideration (the current study focused on implementing general dietary and physical activity guidelines).

4. Association between adipokines, lipid and prostate cancer- and all cancer-mortality in the PRIME cohort.

4.1. Introduction

According to WHO (2016), 13% of the adult population worldwide was obese. In general, men with obesity (11%) were less likely than women to be obese (15%) (WHO, 2019b). However, in the United States and Europe, the obesity rates in men reported by the Global Health Observatory 2016 was higher than that of women (Kim and Shin, 2020). A systematic review revealed that men tend to be less concerned about weight problems than women and have lower basic knowledge of nutrition that might induce the difference in obesity prevalence based on gender (Kim and Shin, 2020). The 2008 data show that there were 26.9% of the population aged ≥ 20 years who were obese in the United Kingdom of Great Britain and Northern Ireland (WHO, 2013). The WHO has stated that 26% of men and 27.7% of women were obese and this was predicted to increase both in men (36%) and women (33%) by 2030 (WHO, 2013). This was also associated with an increased number of hospital admissions attributable to obesity (23%) that has reported on 2017/2018 by NHS (NHS, 2020b).

Obesity is an independent factor for various cardiovascular disorders (Carbone et al., 2019, Csige et al., 2018). Atherosclerosis has been linked to obesity, both of which are considered chronic inflammatory conditions (Csige et al., 2018). Lipid oxidation and free fatty acids activate inflammation that triggers atherosclerosis (Csige et al., 2018). In addition to obesity, fatty tissue also mediates the release of adipocytokines to initiate insulin resistance, endothelial dysfunction, hypercoagulability, and systemic inflammation leading to atherosclerosis (Csige et al., 2018).

Being overweight and obese increases the risk of advanced prostate cancer as stated by the WCRF-CUP (WCRF, 2018). Suggestions of an association between obesity and the aggressiveness and progression of prostate cancer as well as associated prostate cancer mortality

have been reported by a systematic review, but the results are inconsistent when compared between pre-diagnosis and post-diagnosis (Parekh et al., 2012). A review analysing the relationship between overweight and obesity with the average mortality rate for people with liver and pancreatic cancer has also not been able to confirm whether there is a definite relationship (De Pergola and Silvestris, 2013). Another cohort study, namely the Surveillance Epidemiology and End Result (SEER) in breast cancer patients resulted in a relationship that tends to be inconsistent, especially if it is associated with hormone conduction (Blair et al., 2019). However, retrospective studies on the shared equal access to regional cancer hospital (SEARCH) database have reported that obesity is associated with prostate cancer specific-mortality (PCSM) (Vidal et al., 2017). The Prospective Epidemiology Study of Myocardial Infarction (PRIME) collected biological (including leptin and adiponectin) and lifestyle data that can be used to determine the relationship between obesity and cancer development, although it originally focused on CVD outcomes. The collected database includes various information which has also been used to analyse the contribution of these various factors to other health problems, one of which was cancer (Cardwell et al., 2014).

Based on the results of the systematic review and meta-analysis in chapter 2, there is an inconsistency in the relationship between leptin and adiponectin with risk, aggressiveness, and progression of prostate cancer. Meanwhile, in chapter 3, and based on known increased CVD risk in prostate cancer patients, potentially due to the use of ADT therapy, the results of physical activity and diet interventions did not significantly improve lipid profiles in prostate cancer patients, although on the other hand there was an improvement in BMI and other anthropometric indicators. Finally, based on the still inconsistent results of other studies on the association of adipokines, obesity and cancer, this chapter was dedicated to exploring the relationship between leptin and adiponectin, lipids and other biological risk factors related to obesity and considered important in CVD aetiology and overall cancer or prostate cancer-specific mortality using PRIME data. This was done to complement the review in this thesis which had

previously been started with a systematic review and meta-analysis, coupled with the analysis of the RCT results and then completed with the results of cohort data analysis. It was hoped that this combined analysis would explain the relationship between obesity and prostate cancer in a comprehensive manner.

4.2. Method

The Prospective Epidemiological Study of Myocardial Infarction (PRIME) is an ongoing population-based cohort study exploring the contribution of a range of environmental, lifestyle and biological risk factors, and their interaction, to the development of ischemic heart disease and other cardiovascular endpoints (Appleton et al., 2016, Luc et al., 2002, Luc et al., 2006, Yarnell, 1998) in both French and Northern Irish populations. This was a prospective study, based in four centres: three in France: in the South (Toulouse), East (Strasbourg) and North (Lille) of France and one in Northern Ireland (Belfast).

The study design and sampling methods have been described in detail elsewhere (Bataille et al., 2006, Yarnell, 1998); briefly, a total of 10,592 men aged 50-59 years were recruited from 1991 to 1994 (n = 2745 within Northern Ireland and n =7847 in France) within the NI sample, Participants were recruited in the general population through prevention and screening centres in General Medicine Practices, in industry, the Civil Service or administration through occupational medicine channels (Bataille et al., 2006). The Northern Ireland sample represented approximately 5% of the adult male population in the greater Belfast area at the time of recruitment. In the French centres, two-third of the subjects were recruited through prevention centres and one third through occupational medicine (Bataille et al., 2006). The sampling framework was developed so that participants broadly matched the social class structure of the background population (Luc et al., 2006). Ethical approval for this cohort study was provided by the QUB Faculty of Medicine, Dentistry and Biomedical Sciences, Research Ethics Committee. All participants provided informed written consent prior to baseline data collection.

4.2.1. Baseline data collection

Each participant completed a range of self-reported questionnaires that received via mail and completed at home and researchers checked this during the measurement visit to the clinic to ensure completion. These self-report questionnaires were used to collect information on demographic and socioeconomic characteristics including education and marital status, a detailed personal and family medical history, as well as lifestyle factors, including alcohol consumption, smoking history, physical activity levels and dietary behaviours. Information on smoking included if the participant was a current, ever or never smoker; alcohol consumption was collected in grams of alcohol per week, dietary intake (via a short self-administered 16 item food frequency questionnaire measuring the frequency and consumption of a range of food items including overall intake of fruit and vegetables) and physical activity was based on the average weekly net energy expenditure for Physical activity expressed in metabolic equivalents per hr/week.

4.2.2. Anthropometry

Physical measurements including standardised measures of height, weight, waist and hip circumferences and blood pressure (Bataille et al., 2006).

4.2.3. Biological measurement

A blood sample was taken after a 12-h fast (Bataille et al., 2006). Plasma for lipid measurements was prepared immediately and was sent weekly at 4°C to Lille for a centralised measurement at the beginning of the study (Bataille et al., 2006). Circulating concentrations of adiponectin and leptin were measured in plasma and serum respectively using an Elisa (R&D Systems, Billerica, MA, USA). For quality control purposes, R&D assay internal standards and laboratory internal plasma and serum quality controls were used within each 96-well plate (Neville et al., 2016). Clinical information was validated from hospital and

GP records (Yarnell, 1998)). Demographic characteristics were similar in all centres (Yarnell, 1998) and participants were examined for evidence of ischemic heart disease at baseline (Logan et al., 2020, Yarnell, 1998).

Follow-up of PRIME participants, at a face to face visit, only for Belfast men, was carried out at 10 years and only 2.9% of the men were missing (Yarnell et al., 2012). The follow-up data collection included electrocardiogram (ECG), laboratory analyses, and radiological diagnostic results (Yarnell et al., 2012). Since that follow-up, annual questionnaires have been posted to participating men, as well as monitoring of deaths through data linkage. Where indicated, information on death, if possible, was collected through family or subject's practitioner. All relevant medical records were consulted and the cardiovascular events verified by two independent committees consisting of a cardiologist for cardiovascular events and a neurologist for stroke events (Yarnell et al., 2012).

4.2.4. Cancer follow-up and outcome data

Death from all cancer and prostate cancer specific mortality was ascertained by review of death certificates, classified using the International Classification of Diseases 10th Revision (ICD 10). If prostate or any cancer (excluding non-melanoma skin cancer) was recorded as the “Disease or condition directly relating to death” (1a, 1b or 1c on the person’s death certificate), this was coded as a death from cancer.

4.2.5. Statistical analysis

Statistical analysis was performed using the STATA software package (Release 14. College Station, TX StataCorp LP). Data were summarised by means and standard deviations for normally distributed variables and if positively skewed were logarithmically transformed and presented as geometric means and Interquartile ranges. Pearson correlation coefficients were used to examine associations between the adipokines and a range of health-related risk

factors. Chi square tests (for categorical variables) and independent samples t-test (for continuous variables) were used to compare baseline characteristics between participants who died from cancer and those who did not. The association between levels of baseline biomarkers (adiponectin, leptin, insulin, and lipid profile) and cancer specific mortality were examined using Cox proportional hazard regression models. Follow up time for each participant was calculated from baseline (date of examination/biological sample collection) until the date of death or until the end of study follow-up 11th November 2019.

All analyses were initially adjusted for age and multivariate models were adjusted for age, education, BMI, WHR, alcohol, smoking, and, for the adiponectin and leptin models, were mutually adjusted for adiponectin/leptin. For all analyses, statistical significance was set at $p < 0.05$.

4.3. Results

The characteristics of the men involved in the PRIME study from France (Toulouse, Strasbourg, Lille) and Northern Ireland (Belfast) are presented in **Table 4.1**. In general, all variables differ significantly between the two countries, except for physical activity. The ages of both men involved in the two countries were around 54 years. The men with the most overweight came from France (52%), while the men with obesity were more likely to be reported by Belfast (14.7%). The waist circumference of French men (95.88 95% CI 95.66-96.10) was significantly greater than that of their Belfast counterpart (91.29 95% CI 90.94-91.64; $p < 0.001$). This was also evident in the waist to hip ratio where the ratio of French men was greater than that of Belfast men ($p < 0.001$).

Lower figures for total cholesterol and triglycerides were found in the French group of men compared to the Belfast men. On the other hand, the HDL and LDL levels of French men

were higher than that of Belfast men. The cholesterol to HDL ratio of Belfast men (5.31 95% CI 5.25-5.37) was higher than that of men from France (4.72 95% CI 4.69-4.75) (p <0.001).

French men smoked more on average 5173.33 cigarettes / year (95% CI 5082.80-5263.85) than Belfast men who only averaged 3842.47 cigarettes / year (95% 5922.77-6210.38) (p <0.001). Alcohol consumption was also reported to be higher in French men at 287.26 ml/week (95% CI 281.62-292.90) compared to Belfast men 193.61 ml/week (95% CI 182.03-205.19). Meanwhile, data on insulin, adiponectin, leptin, and leptin to adiponectin ratio are only available in Belfast men, so they cannot be compared with French men.

Table 4.1. PRIME baseline characteristic by country (French and Belfast)

	French (n = 7,855)	**Belfast (n = 2,745)**	**p**
Age (year, mean, CI)	54.95 (54.88-55.01)	54.79 (54.68-54-90)	0.016*
BMI (%)			
Underweight	0.33	0.47	
Normal	31.03	36.54	
Overweight	52.84	50.49	
Obese	12.17	14.71	< 0.001*
Waist (cm, mean, CI)	95.88 (95.66-96.10)	91.29 (90.94-91.64)	< 0.001*
Waist to hip ratio (mean, CI)	0.96 (0.96-0.97)	0.94 (0.93-0.94)	< 0.001*
Total cholesterol (mmol/L, mean, CI)	5.69 (5.67-5.71)	5.90 (5.86-5.94)	< 0.001*
HDL (mmol/L, mean, CI)	1.28 (1.27-1.29)	1.18 (1.17-1.19)	< 0.001*
LDL (mmol/L, mean, CI)	1.27 (1.26-1.29)	1.23 (1.21-1.25)	0.0003*
Triglyceride (mmol/L, mean, CI)	1.59 (1.56-1.61)	1.99 (1.94-2.04)	< 0.001*
Cholesterol to HDL ratio (mean, CI)	4.72 (4.69-4.75)	5.31 (5.25-5.37)	< 0.001*
Insulin (mean, CI) [a)]	n/a	6.97 (6.72-7.22)	n/a
Leptin (ng/mL, mean, CI) [a)]	n/a	5937. 23 (5716.80-6157.66)	n/a
Adiponectin (µg/mL, mean, CI) [a)]	n/a	6132.11 (5953. 28-6310.93)	n/a
Leptin to adiponectin ratio [a)]	n/a	1.57 (1.47-1.67)	n/a
Smoking (cigarettes/year, mean, CI)	5173.33 (5082.80-5263.85)	3842.47 (5922.77-6210.38)	< 0.001*
Alcohol (ml/week, mean, CI)	287.26 (281.62-292.90)	193.61 (182.03-205.19)	< 0.001*
Physical activity (mean, CI)	69.99 (68.81-71.18)	70.10 (68.27-71.93)	0.93

Statistically significant (< 0.05) are highlighted with * symbol; p-value from independent t-test, [a)] data available only for Belfast

The magnitude and direction of the correlation between lipid profile (at both baseline and 10 year follow up) and anthropometry measurements is presented in **Table 4.2**. The direction of the correlation between cholesterol and anthropometric measures was significantly positive

except for height at follow-up. A fair correlation was found between cholesterol and BMI ($r = 0.085$, $p = 0.0001$), followed by the waist and waist to hip ratio. BMI again demonstrated a positive correlation with HDL ($r = 0.113$, $p = <0.001$) in Belfast men at follow-up, followed by waist and hip. For LDL, the strongest correlation was also related to BMI even though the direction was negative ($r = -0.128$) while waist and waist to hip ratio followed afterward. On the other hand, out of a total of 1,919 Belfast men, TG levels had also positively the highest correlation with BMI ($r = 0.122$, $p = <0.001$). Meanwhile, the same pattern was also found in the correlation between cholesterol to HDL ratio and BMI ($r = 0.127$, $p <0.001$).

Table 4.2. Associations between anthropometric measurements and lipid profiles at baseline and follow up for Belfast only (n = 1,919)

Anthropometry measurements	Lipid profiles									
	Cholesterol		HDL		LDL		TG		Cholesterol to HDL ratio	
	Baseline	Follow up	Baseline	Follow up	Baseline	Follow up	Baseline	Follow up	Baseline	Follow up
Height (r, p)	-0.025, 0.009*	-0.46, 0.037*	-0.037, 0.0001*	-.0.043, 0.053	0.005, 0.560	0.062, 0.007*	-0.016, 0.100	-0.051, 0.021*	0.011, 0.252	-0.049, 0.026*
Weight (r, p)	0.042, <0.001*	0.050, 0.024*	-0.236, <0.001*	0.078, 0.0004*	-0.083, <0.001*	-0.076, 0.0009*	0.191, <0.001*	0.071, 0.0013*	0.209, <0.001*	0.087, 0.0001*
BMI (r, p)	0.062, <0.001*	0.085, 0.0001*	-0.244, <0.001*	0.113, <0.001*	-0.097, <0.001*	-0.128, <0.001*	0.224, <0.001*	0.112, <0.001*	0.228, <0.001*	0.127, <0.001*
Waist (r, p)	0.054, <0.001*	0.078, 0.0004*	-0.205, <0.001*	0.104, <0.001*	-0.009, <0.001*	-0.114, <0.001*	0.208, <0.001*	0.109, <0.001*	0.195, <0.001*	0.115, <0.001*
Hip (r, p)	0.019, 0.050	0.058, 0.009*	-0.149, <0.001*	0.087, <0.0001*	-0.067, <0.001*	-0.088, 0.0001*	0.128, <0.001*	0.083, 0.0002*	0.126, <0.001*	0.093, <0.001*
Waist to hip ratio (r, p)	0.068, <0.001*	0.060, 0.006*	-0.159, <0.001*	0.071, 0.0013*	-0.079, <0.001*	-0.094, <0.001*	0.187, <0.001*	0.085, 0.0001*	0.170, <0.001*	0.084, 0.0001*

Statistically significant (< 0.05) are highlighted with * symbol; p-value from Pearson

In **table 4.3**, the overview of the correlation between anthropometry measurement and adipokines and insulin is presented. The association between leptin and anthropometry measurement was positive, with the strongest correlation shown in BMI (r = 0.605, p <0.001). Leptin did not correlate only with height (p = 0.128). Height also did not correlate with adiponectin (p = 0.206). Adiponectin showed a significant negative correlation with other anthropometry measurements where the correlation with BMI was the strongest (r = -0.207). Meanwhile, BMI also appears to have a strong positive correlation with the leptin to adiponectin ratio with a value of r = 0.480 (p <0.001). For insulin, the correlation was statistically significant with body weight, BMI, waist, hip, and waist to hip ratio, while height did not show any correlation with insulin (p = 0.727). BMI again showed the strongest positive correlation with insulin (r = 0.365, p <0.001).

Table 4.3. Associations between anthropometric measurements and adipokines at baseline for Belfast only (n = 1,919)

Anthropometry measurements	**Adipokines**			**Insulin**
	Leptin	**Adiponectin**	**Leptin to adiponectin ratio**	
Height (r, p)	-0.030, 0.128	-0.027, 0.206	-0.017, 0.456	-0.007, 0.727
Weight (r, p)	0.525, <0.001*	-0.199, <0.001*	0.420, <0.001*	0.324, <0.001*
BMI (r, p)	0.605, <0.001*	-0.207, <0.001*	0.480, <0.001*	0.365, <0.001*
Waist (r, p)	0.560, <0.001*	-0.182, <0.001*	0.425, <0.001*	0.341, <0.001*
Hip (r, p)	0.525, <0.001*	-0.145, <0.001*	0.412, <0.001*	0.298, <0.001*
Waist to hip ratio (r, p)	0.348, <0,001*	-0.151, <0.001*	0.252, <0.001*	0.237, <0.001*

Statistically significant (< 0.05) are highlighted with * symbol; p-value from Pearson

Anthropometric differences and lipid profiles in Belfast men who were recorded at 10-year follow-up generally indicated an increase over time (**Table 4.4**). Weight was found to be significantly increased by 2.80 kg (95% CI 1.88-3.71) (p <0.001). An increase of 2.01 kg/m^2 BMI was also found after 10 years of follow-up (p <0.001). These men also experienced an increase in waist size of 6.32 cm (p <0.001) and hip size of 7.34 cm (p <0.001) followed by an increase in the value of the waist to hip ratio by 0.004 (95% CI 0.001-0.007) (p = 0.0023).

HDL experienced a significant increase (0.16 mmol/L (95% CI 0.13-0.18), p <0.001), although this increase was accompanied by a decrease in total cholesterol by 0.53 mmol/L and an increase in LDL by 1.98 mmol/L (p <0.001). Changes in cholesterol and HDL values ultimately resulted in a reduction in the cholesterol to HDL ratio of -1.03 (-1.09- (-0.97) (p <0.001).

Table 4.4. Anthropometry and lipid profiles differences after 10 years in Belfast men (n = 1,919)

	Baseline	Follow up	Differences	p
Weight (kg, mean. CI)	79.42 (78.94-79.91)	82.23 (81.18-83.27)	2.80 (1.88-3.71)	<0.001*
BMI (kg/m^2, mean, CI)	26.15 (26.01-26-30)	27.41 (27.25-27.58)	2.01 (1.17-1.34)	<0.001*
Waist (cm, mean, CI)	90.95 (90.54-91.35)	97.27 (95-67-98.86)	6.32 (4.77-7.86)	<0.001*
Hip (cm, mean, CI)	96.83 (96.55-97.12)	104.18 (102.01-106.34)	7.34 (5.19-9.48)	<0.001*
Waist to hip ratio (mean, CI)	0.93 (0.93-0.94)	0.94 (0.93-0.94)	0.004 (0.001-0.007)	0.0023*
Cholesterol (mmol/L, mean/CI))	5.89 (5.85-5.94)	5.37 (5.32-5.41)	-0.53 (-0.57-(-0.48))	<0.001*
HDL (mmol/L, mean, CI)	1.18 (1.17-1.20)	1.34 (1.31-1.37)	0.16 (0.13-0.18)	<0.001*
LDL (mmol/L, mean, CI)	1.28 (1.25-1.30)	3.26 (3.22-3.30)	1.98 (1.94-2.02)	<0.001*
TG (mmol/L, mean, CI)	1.95 (1.90-2.00)	1.77 (1.73-1.82)	-0.18 (-0.23-(-0.13)	<0.001*
Cholesterol to HDL ratio (mean, CI)	5.28 (5.21-5.35)	4.25 (4.20-4.30)	-1.03 (-1.09-(-0.97))	<0.001*

Statistically significant (< 0.05) are highlighted with * symbol; p-value from paired t-test

Table 4.5 shows that men who died from cancer were significantly older that those who did not die, and they also had a lower number of years of education, but marital status was similar between the groups. There was no difference in the value of the waist circumference, hip circumference, or the ratio between the two groups who died from cancer or not.

In terms of lifestyle behaviours, only smoking status was associated with risk of dying from cancer, and not fruit and vegetable or alcohol intake or levels of physical activity, which were similar between these groups.

At baseline, the group of men who later died from cancer showed slightly higher levels of adiponectin than the group of men who did not later die from cancer, and this approached

statistical significance. None of the other measured biological markers differed significantly between these two groups (**Table 4.5**).

Table 4.5. All-mortality baseline characteristics of Belfast men from PRIME data analysis

Variables	Total (n=2745)	Death from Cancer		p
		Yes (n = 406)	No (n = 2339)	
Age *	54.8 (2.89)	55.3 (2.90)	54.7 (2.89)	0.0001*
Education (%)				
< 12 years	1870 (68.2)	314 (77.3)	1556 (66.6)	
12-14 years	554 (20.2)	63 (15.5)	491 (21.0)	
15 years	319 (11.6)	29 (7.1)	29 (12.4)	<0.001*
Marital Status (%)				
Single	2349 (85.6)	351 (86.5)	1998 (85.42)	
Married/cohabiting	362 (13.2)	48 (11.8)	314 (13.4)	
Widowed/divorced/separated	34 (1.2)	7 (1.7)	27 (1.2)	0.444
Anthropometry				
Weight*	79.4 (11.6)	79.8 (11.3)	79.3 (11.6)	0.445
BMI (kg/m2)				
Normal	1012 (36.9)	90 (38.8)	922 (33.7)	
Overweight	334 (12.2)	34 (14.7)	300 (11.9)	
Obese	1280 (50.9)	107 (46.1)	1280 (50.9)	0.451
Waist Circumference -cm (SD)	91.3 (9.4)	91.8 (9.2)	91.2 (9.5)	0.660
Hip Circumference –cm (SD)	96.9 (6.8)	96.9 (6.8)	96.9(6.7)	
WHR	0.94 (0.5)	0.94 (0.5)	0.94 (0.5)	0.412
Lifestyle behaviours				
Smoking				
Never	903 (32.9)	94(23.2)	809 (34.6)	
Former	1738 (63.3)	1435 (61.4)	303 (74.6)	
Current	103 (3.8)	9 (2.2)	94 (4.0)	<0.001*
Alcohol				
No drinker	1095 (39.9)	150 (37.0)	945 (40.4)	
≤ 168 g (21units)	782 (28.5)	119 (29.3)	663 (28.4)	
> 168 g	868 (31.6)	137 (33.7)	731 (31.3)	0.151
Fruit and Veg consumption	3.7 (1.8)	3.6(1.7)	3.7 (1.9)	0.198
Total PA	70.1 (47.9)	70.8 (47.9)	70.0 (45.0)	0.767
Biological Markers				
Adiponectin (µg/ml)	5.0 (3.3, 7.6)	5.1 (3.1, 7.2)	4.6 (3.4, 7.7)	0.050*
Leptin (ng/ml)	4.4 (2.4, 7.4)	4.6 (2.4, 7.8)	4.4 (2.4, 7.3)	0.344
SBP (mmHg)	133.9 (20.6)	135.1 (20.1)	133.7 (20.6)	0.218
DPB (mmHg)	81.7 (11.5)	81.6 (11.4)	81.8 (11.5)	0.727
Leptin to adiponectin ratio	1.1 (0.5, 2.02)	1.0 (0.5, 2.5)	1.13 (0.5, 2.0)	0.136

Continuous variables are presented as mean (SD) or geometric mean (IQR) for skewed variables. Categorical variables are presented as n (%). Differences between groups analysed using independent samples t-test for continuous variables and chi-square test for categorical variables

Table 4.5. All-mortality baseline characteristics of Belfast men from PRIME data analysis (continue)

Variables	Total (n=2745)	Death from Cancer		p
		Yes (n = 406)	No (n = 2339)	
Insulin	5.9 (4.1, 8.4)	6.1(4.1, 8.2)	5.9 (4.1, 8.9)	0.471
CRP (mg/L)	1.7 (0.9, 3.3)	2.0 (1.0, 3.9)	1.7 (0.83, 3.2)	0.712
Triglycerides (mmol/L)	1.7 (1.2, 2.4)	1.8 (1.3, 2.5)	1.7 (1.2, 2.4)	0.152
HDL (mmol/L)	1.18 (3.3)	1.17 (0.33)	1.19 (0.33)	0.368
Total cholesterol (mmol/L)	5.9 (1.0)	5.9 (1.0)	5.9 (1.1)	0.889

Continuous variables are presented as mean (SD) or geometric mean (IQR) for skewed variables. Categorical variables are presented as n (%). Differences between groups analysed using independent samples t-test for continuous variables and chi-square test for categorical variables

During an average of 24 years of follow up (28 years max), there were 406 cancer related deaths within the Belfast PRIME cohort, 56 of which were deaths from prostate cancer. **Table 4.6** describes the association between adiponectin, leptin, leptin to adiponectin ratio, insulin and the lipid profile and cancer-specific death, analysed using Cox regression analysis. Each biological measurement was categorised into thirds.

This analysis suggests a non-significant inverse association between adiponectin and cancer related death as men in the highest tertile (>6.62 µg/ml) had a 8% reduced risk of a cancer specific death compared to those in the lowest tertile <3.81 µg/ml (T3 vs T1 HR 0.92, 95%CI 0.7, 1.2). This association was attenuated after adjustment for age (T3 vs T1 HR 0.90, 95%CI 0.69, 1.19) and further in the fully adjusted model (T3 vs T1 HR 0.97 95% CI 0.7, 1.3), and was not statistically significant.

Higher levels of leptin (T2 v T1) were associated with a 7% reduced risk of death from cancer (T2 vs T1 HR 0.93 (0.7, 1.21) in the unadjusted model, yet a 17% increased risk was observed between the highest tertile and the reference group (T3 vs T1 HR 1.17 (0.9, 1.49); this was attenuated for the fully adjusted model (T3 vs T1 HR 1.13 (0.79, 1.61).

The leptin to adiponectin ratio was also categorised into tertiles and, although non-significant, suggested a 17% increased risk of death from cancer in the highest tertile (a ratio >1.82) compared to the reference category (<0.67) (T3 vs T1 HR 1.17 (0.88, 1.56)); this risk was

attenuated in the age adjusted model (T3 vs T1 HR 1.15, 95%CI 0.86, 1.5)), and the fully adjusted model suggested a 13% reduction in risk between the highest and lowest tertile (T3 vsT1 HR 0.87, 95%CI 0.54, 1.40).

Higher levels of insulin (T3: >7.2) were associated with a 20% increased risk of death from cancer in the unadjusted model (T3 vs T1: HR 1.2, 95%CI 0.96, 1.6) and the HR remained the same in the age-adjusted model (T3 vs T1: HR1.2 (1.0, 1.6)). This was attenuated slightly in the multivariate model which suggests a 16% increased risk of death from cancer in the highest compared to the lowest categories of insulin (T3 vs T1 HR 1.16, 95%CI, 0.8, 1.7); however, these results were not significant.

For total cholesterol, there was no change in risk between tertile 2 (5.44-6.23 mmol/L) vs T1 (<5.44 mmol/L) (T3 v T1 HR1.0, 95%CI 0.76, 1.22) however higher levels of total cholesterol appeared to have a protective effect with a 15% reduced risk of cancer death in tertile 3 (T3 vs T1 HR 0.85, (0.67, 1.1) in the unadjusted model. These results are not significant, and the values did not change with the additional adjustment for potential confounding variables in the fully adjusted model.

Table 4.6. Association between adiponectin, leptin, leptin to adiponectin ratio and the lipid profile and cancer specific death in the PRIME cohort

Categories	Cases/non cases	Unadjusted	Age adjusted	Fully adjusted
Adiponectin (µg/ml)				
Q1 (<3.81)	109/594	1.0	1.0	1.0
Q2 (3.81-6.62)	102/601	0.94 (0.7, 1.2)	0.93 (0.7, 1.2)	1.01 (0.79, 1.4)
Q3 (>6.62)	97/606	0.92 (0.7, 1.2)	0.90 (0.69, 1.19)	0.97 (0.7, 1.3)
Leptin (ng/ml)				
Q1 (<3)	119/689	1.0	1.0	1.0
Q2 (3-6.2)	112/696	0.93 (0.7, 1.21)	0.93 (0.72, 1.20	0.9 (0.70, 1.29)
Q3 (>6.2)	133/675	1.17 (0.9, 1.49)	1.12 (0.88, 1.44)	1.13 (0.79, 1.61)

Fully adjusted model: age, education, BMI, WHR, Alcohol, Smoking and were mutually adjusted for adiponectin/leptin

Table 4.6. Association between adiponectin, leptin, leptin to adiponectin ratio and the lipid profile and cancer specific death in the PRIME cohort (continued)

Categories	Cases/non cases	Unadjusted	Age adjusted	Fully adjusted
Leptin to adiponectin ratio				
T1 (<0.67)	87/616	1.0	1.0	1.0
T2 (0.67-1.82)	86/617	0.98 (0.73, 1.32)	1.0 (0.7, 1.4)	0.90 (0.64, 1.30)
T3 (>1.82)	101/602	1.17 (0.88, 1.56)	1.15(0.86, 1.5)	0.87(0.54, 1.40)
Insulin				
T1 (<4.6)	115/685	1.0	1.0	1.0
T2 (4.6-7.2)	102/675	0.9(0.68, 1.2)	0.9 (0.70, 1.2)	0.9 (0.66, 1.3)
T3 (>7.2)	132/634	1.2(0.96, 1.6)	1.2 (1.0, 1.6)	1.16 (0.8, 1.7)
Total cholesterol				
T1 (<5.44)	143/ 776	1.0	1.0	1.0
T2 (5.44-6.23)	138/770	1.0 (0.76, 1.22)	1.0 (0.76, 1.2)	1.0 (0.75, 1.3)
T3 (>6.23)	123/787	0.85 (0.67, 1.1)	0.85(0.67, 1.1)	0.83 (0.62, 1.1)
HDL				
T1 (<=1.01)	T1 (<=1.01)	T1 (<=1.01)	T1 (<=1.01)	T1 (<=1.01)
T2 (>1.01-1.27)	T2 (>1.01-1.27)	T2 (>1.01-1.27)	T2 (>1.01-1.27)	T2 (>1.01-1.27)
T3 (>1.27)	T3 (>1.27)	T3 (>1.27)	T3 (>1.27)	T3 (>1.27)
LDL				
T1 (<3.45)	T1 (<3.45)	T1 (<3.45)	T1 (<3.45)	T1 (<3.45)
T2 (3.45-4.2)	T2 (3.45-4.2)	T2 (3.45-4.2)	T2 (3.45-4.2)	T2 (3.45-4.2)
T3 (>4.2)	T3 (>4.2)	T3 (>4.2)	T3 (>4.2)	T3 (>4.2)
Triglycerides				
T1 (<1.21)	T1 (<1.21)	T1 (<1.21)	T1 (<1.21)	T1 (<1.21)
T2 (1.22-1.87)	T2 (1.22-1.87)	T2 (1.22-1.87)	T2 (1.22-1.87)	T2 (1.22-1.87)
T3 (>1.87)	T3 (>1.87)	T3 (>1.87)	T3 (>1.87)	T3 (>1.87)
Cholesterol to HDL ratio				
T1 (<4.82)	T1 (<4.82)	T1 (<4.82)	T1 (<4.82)	T1 (<4.82)
T2 (4.82-5.83)	T2 (4.82-5.83)	T2 (4.82-5.83)	T2 (4.82-5.83)	T2 (4.82-5.83)
T3 (>5.8)	T3 (>5.8)	T3 (>5.8)	T3 (>5.8)	T3 (>5.8)

Fully adjusted model: age, education, BMI, WHR, Alcohol, Smoking and were mutually adjusted for adiponectin/leptin

During an average of 24 years of follow up (28 years max), there were 56 deaths from prostate cancer and therefore analyses were repeated focusing specifically on prostate cancer. **Table 4.7** describes the association between adiponectin, leptin, leptin to adiponectin ratio, insulin and the lipid profile and prostate cancer-specific death. Each biological measurement was categorised into thirds.

This analysis suggests similar associations between all variables in prostate cancer specific death as for all cancer deaths, in that there were trends towards an association, but that, ultimately,

all estimates were non-significant and particularly attenuated towards null in the fully adjusted model, suggesting no major differences in associations between these variables and all cancer and prostate cancer mortality. Associations tended to suggest a protective effect of increasing adiponectin and reducing leptin and the leptin to adiponectin ratio, but these estimates were variable depending on the level of adjustment made, were not always linear, and were not statistically significant.

Table 4.7. Association between adiponectin, leptin, leptin to adiponectin ratio and the lipid profile and prostate cancer specific death in the PRIME cohort

Categories	Cases/non cases	Unadjusted	Age adjusted	Fully adjusted
Adiponectin (µg/ml)				
Q1 (<3.81)	18/685	1.0	1.0	1.0
Q2 (3.81-6.62)	9/694	0.50(0.23, 1.12)	0.50 (0.22, 1.11)	0.59 (0.26, 1.40)
Q3 (>6.62)	16/687	0.93 (0.90, 0.47)	0.90 (0.46, 1.77)	0.94(0.44, 2.0)
Leptin (ng/ml)				
Q1 (<3)	18/790	1.0	1.0	1.0
Q2 (3-6.2)	17/773	0.94 (0.48, 1.83)	0.93 (0.48, 1.81)	0.98 (0.46, 2.1)
Q3 (>6.2)	15/793	0.89 (0.45, 1.76)	0.84(0.42, 1.67)	1.2 (0.36, 4.1)
Leptin: Adiponectin Ratio				
T1 (<0.67)	11/603	1.0	1.0	1.0
T2 (0.67-1.82)	14/594	1.26 (0.57, 2.8)	1.33 (0.6, 2.9)	1.12(0.40, 3.2)
T3 (>1.82)	13/609	1.15 (0.5, 2.6)	1.18 (0.5, 2.6)	0.87 (0.2, 3.6)
Insulin				
T1 (<4.6)	18/782	1.0	1.0	1.0
T2 (4.6-7.2)	15/762	0.84 (0.43, 1.7)	0.87 (0.44, 1.73)	0.86 (0.39, 1.4)
T3 (>7.2)	14/752	0.85 (0.42, 1.7)	0.83 (0.4, 1.7)	0.81(0.3, 2.18)
Total cholesterol				
T1 (<5.44)	18/901	1.0	1.0	1.0
T2 (5.44-6.23)	18/889	1.05 (0.55, 1.99)	1.04(0.54, 1.98)	1.24(0.55, 2.8)
T3 (>6.23)	18/910	0.99(0.5, 1.89)	0.98(0.5, 1.89)	1.23 (0.60, 2.96)
HDL				
T1 (<=1.01)	20/987	1.0	1.0	1.0
T2 (>1.01-1.27)	20/934	1.02(0.55, 1.90)	1.04 (0.56, 1.93)	1.05(0.47, 2.36)
T3 (>1.27)	15/776	0.95(0.49, 1.85)	0.97(0.49, 1.89)	1.57(0.67, 3.36)

Fully adjusted model: age, education, BMI, WHR, Alcohol, Smoking and were mutually adjusted for adiponectin/leptin

Table 4.7. Association between adiponectin, leptin, leptin to adiponectin ratio and the lipid profile and prostate cancer specific death in the PRIME cohort (continued)

Categories	Cases/non cases	Unadjusted	Age adjusted	Fully adjusted
LDL				
T1 (<3.45)	17/845	1.0	1.0	1.0
T2 (3.45-4.2)	15/847	1.04(0.55, 1.98)	1.03(0.54, 1.94)	1.0(0.43, 2.32)
T3 (>4.2)	19/841	0.99(0.5, 1.86)	0.97(0.54, 1.86)	1.16 (0.5, 2.56)
Triglycerides				
T1 (<1.21)	19/906	1.0	1.0	1.0
T2 (1.22-1.87)	19/888	1.05(0.55, 1.98)	1.03 (0.54, 1.93)	1.05 (0.48, 2.29)
T3 (>1.87)	17/889	0.97(0.50, 1.86)	0.97 (0.5, 1.86)	0.9 (0.39, 2.16)
Chol/HDL Ratio				
T1 (<4.82)	16/896	1.0	1.0	1.0
T2 (4.82-5.83)	21/891	1.3(0.68, 2.5)	1.3(0.68, 2.5)	1.25 (0.55, 2.82)
T3 (>5.8)	18/894	1.15(0.59, 2.26)	1.14(0.59, 2.26)	1.06(0.44, 2.5)

Fully adjusted model: age, education, BMI, WHR, Alcohol, Smoking and were mutually adjusted for adiponectin/leptin

4.4. Discussion

This chapter aimed to explore the associations between adiponectin, leptin, lipids and other CVD-related risk factors and both all cancer and prostate cancer-specific death in Belfast men enrolled in the PRIME study and followed up over a period of >20 years.

In addition, it was possible to examine the initial comparison in these and other factors between men in France and Northern Ireland, as well as exploring the change in anthropometric and lipid variables over a 10 year period, due to the design of the PRIME study and the inclusion of a second data collection period in person, with anthropometric and biological sample collection.

4.4.1. Baseline characteristics

In general, it appears that there are differences between French and Belfast men as follows: the incidence of overweight was found to be higher in French men, while obesity was more common in men in Belfast. The waist circumference and waist to hip ratio were reported to be greater in French men. Lipid profiles at baseline showed that Belfast men had higher

cholesterol and TG but have lower HDL and TG compared to French men. Adipokines and insulin data were available only from Belfast men.

BMI and lipid profiles reported in the PRIME cohort have been reported to be associated with various risks of vascular disorders and heart disease in published studies (Luc et al., 2002, Luc et al., 2006, Yarnell et al., 2012).

A prospective study (Framingham Heart Study) in 2002 has found that cardiovascular risk was increased in people with overweight (male: RR 1.21 95% CI 1.05, 1.40) and obese (male: RR 1.46 95% CI 1.20-1.77) through increased risk attributes. in the form of hypertension, angina pectoris, and coronary disease (> 20% in men) (Wilson et al., 2002). Other studies have also explained that when adiposity occurs it will trigger adipose circulation disorders as part of obesity-related metabolic syndrome, the emergence of excess interstitial fluid, increased blood volume and cardiac output, and left ventricular diastolic function which was all associated with cardiovascular disease (Poirier et al., 2006). Recent studies regarding the underlying mechanisms of obesity and cardiovascular disease have found that obesity results in changes in the structure and function of the heart (Csige et al., 2018).

The PRIME study was originally designed to explore the phenomenon of the French Paradox, where a high level of alcohol consumption, in this case, wine, in the French population and a high intake of saturated fat appears to be associated with a protective effect against the incidence of CVD. However, this result is apparently not only related to alcohol consumption but also due to the recent time lag in increasing consumption of animal fats and serum cholesterol levels in French men compared to men from the UK who experienced this earlier (Law and Wald, 1999). Another explanation may be that moderate wine consumption in French men produces HDL or thrombolysis which causes more beneficial effects (Walsh, 1995). Whilst only Belfast data were included from the PRIME study for the current analysis, the contrasting risk factor profiles and lifestyle behaviours seen in the French and Northern

Irish populations would have been of interest when exploring our research questions, but follow-up and adipokine analysis were only available in the Belfast centre.

4.4.2. Anthropometry and lipid profiles

The relationship between cholesterol and anthropometric variables showed a significant positive direction. The direction of a positive relationship was also shown between BMI and HDL, LDL, and cholesterol to HDL ratio (all-p <0.001), and associations were similar at baseline and follow-up. These results further clarify the significant association between all anthropometric variables and lipid profile, with few differences depending on the anthropometric variable assessed.

PRIME-related publications that have been carried out report that metabolic syndrome including HDL and TG levels are strong predictors of cardiovascular disease (CVD) (Bataille et al., 2006). Another earlier study reported a significant direct relationship between cholesterol, HDL, TG, and HDL and cystatin-C (which is an inhibitor that plays a role in coronary ischemic including degradation of the extracellular matrix in atherosclerosis) (Luc et al., 2006).

4.4.3. Anthropometry, adipokine, and insulin

The results obtained from this chapter indicated a positive relationship between leptin and BMI, while adiponectin was noted to have a negative relationship with BMI. When the analysis was done, a strong relationship was shown between the leptin to adiponectin ratio, and these observed associations were stronger than those observed between anthropometric variables and lipid profile.

However, inconsistent results were reported in 2010, where the results of PRIME data analysis associated with coronary heart disease stated that adiponectin was not a contributing factor while leptin was only proven to play a role as a risk factor for disease when unadjusted data analysis was carried out (Luc et al., 2010). Meanwhile, from the PRIME data, analysis of

leptin and adiponectin has been reported to have a greater role in the formation of Type 2 diabetes mellitus, where leptin plays a role in increasing risk (HR 4.27 95% CI 2.67, 6.83) and adiponectin plays a role in reducing risk (HR 0.24 95% CI 0.14, 0.42) (Neville et al., 2016).

The result of a previous cohort study in 2002 (Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) / Cooperative Health Research (KORA) stated that leptin and adiponectin each interact and play a role in the risk of developing Type 2 DM where adiponectin plays a more dominant role than leptin (Thorand et al., 2010). While, the more recent cohort study which was the Singapore Chinese Health Study (SCHS) also confirmed the role of adiponectin in type 2 DM (Wang et al., 2018).

4.4.4. Anthropometry and lipid profiles difference

In the current chapter, 10-year follow-up of Belfast men reported a significant increase in anthropometric measures including body weight, BMI, waist, hip, and waist to hip ratio. Meanwhile, the lipid profile also showed a significant increase, especially HDL and LDL, but a decrease in cholesterol, TG and cholesterol to HDL ratio was observed.

The results in this chapter are supported by the results of a study that states that anthropometric measures and lipid profiles have been reported to be associated with increasing age (BMI, waist and hip circumference increasing with age) but this study used a relatively much younger age group (18-35 y) (Al-Ajlan, 2011). However, other studies reported results refuting the PRIME analysis results in this chapter, where age was positively associated with total cholesterol in subjects ≤ 40 years, LDL in subjects ≤ 60 years) and TG in subjects ≤ 40 years, yet the reverse (negative) associations were observed in men who were older (Feng et al., 2020). Furthermore, as the association between HDL and age was observed to be inconsistent (Feng et al., 2020). Our analyses do suggest that the major CVD risk factors do

increase with age, hence the need for dietary and lifestyle advice to reduce or minimise these age-associated deteriorations in risk factor status.

4.4.5. Association between biological markers and all cancer and prostate cancer mortality

Regarding all cancer mortality, there were no significant differences in the level of leptin and leptin to adiponectin ratio between men who later died from cancer and those who did not. However, on the other hand, the difference in baseline adiponectin approached statistical significance between these groups. In the further survival analysis, where adjustment for potential confounders was included, all analyses (leptin, adiponectin, ratio of these) were not statistically significant, although trends in estimates for adiponectin were in the same direction as in the less complex analysis.

When this chapter result is linked to the results of the systematic review and meta-analysis in chapter two, the trend of the PRIME cohort data analysis shows the same direction for both adiponectin and leptin. But the weakness of the existing association makes this result unable to provide adequate supporting evidence for the results in the previous chapter, even when the methodological weaknesses of some of the studies included in chapter two were dealt with in the current analysis (prospective cohort design; comprehensive adjustment for potential confounders; consideration of adiponectin to leptin ratio).

Other analyses have been conducted by Grossmann and Cleary (2012), who explored the relationship between leptin, adiponectin and the balance between the two and mortality from breast cancer (leptin to adiponectin ratio), finding that the balance between leptin and adiponectin was associated with mortality (Grossmann and Cleary, 2012). In another study, adiponectin was reported to provide a protective effect against cancer progression (breast, liver, pancreatic, prostate, ovarian, and colorectal) (Parida et al., 2019) and poor prognosis (hepatocellular carcinoma) was associated with leptin deviations (Zhang et al., 2020).The role

of adiponectin in predicting prostate cancer specific mortality was previously reported in the Physicians' Health Study but leptin was not associated with risk of death (Li et al., 2010). Meanwhile, in studies on adiponectin receptor expression, it was reported that low AdipoR1 expression was a predictor of improving overall survival (Howard et al., 2014). Another study reported that adiponectin was also a significant predictor of time of death (Siegel et al., 2015). Results from a recent study reported a role for adiponectin in relation to overall survival but found no association with leptin (Zhang et al., 2020).

This chapter also showed that insulin levels were not related to either all cancer or prostate cancer mortality. This is in contrast to a cohort study (the Israel GOH 29 follow-up study) stating that higher fasting insulin levels were associated with mortality in all cancer patients (Dankner et al., 2012). Likewise, another study on insulin also states that hyperinsulinemia/insulin resistance was associated with cancer mortality (Perseghin et al., 2012).

Men who later died from cancer had TG levels and HDL levels which were not significantly difference from the levels in those who did not later die from cancer. A relationship between HDL and cancer outcomes is still controversial, the results of a review recently showed that HDL has a relationship with cancer risk but the meta-analysis results included in the same paper did not show a strong relationship (Pirro et al., 2018). Further analysis of total cholesterol showed a protective effect in the men with the highest tertile although these results were, again, not statistically significant. The results of the analysis of total cholesterol in this chapter also contradict previous studies that stated cholesterol was inversely related to male cancer mortality (Cowan et al., 1990). Cohort studies a decade later continue to report that high cholesterol levels are associated with cancer-related death (Nago et al., 2011).

The lack of statistically significant results between lipid profiles and all-cancer and prostate cancer mortality in this cohort do not then provide support for lipid changes, as had been hypothesised, though not demonstrated, in the previous chapter, impacting on cancer-related mortality outcomes. Lipid changes would be, however, very likely to result in changes in cardiovascular-related and also therefore all-cause mortality.

4.4.6. Limitations and strengths

The aim of this chapter was to use data from the PRIME study to resolve the mixed evidence discovered within the earlier systematic review and meta-analysis regarding association between adiponectin and leptin and prostate cancer risk, aggressiveness and mortality. Strengths of the approach taken include the use of a cohort study with more than 20 years of follow-up, the adjustment for a broad range of potential confounders, and the inclusion of the adiponectin to leptin ratio within the analysis. This is in contrast to many of the studies included within the systematic review and meta-analysis, which were mostly cross-sectional or case control, and where analysis rarely included the adiponectin to leptin ratio and where the degree to which the main analyses were adjusted for potential confounders was limited, heterogeneous between studies and sometimes unclear.

The limitations of this chapter include that the follow-up was only done in Belfast men, and, amongst these men, although the follow-up period was more than twenty years, there were a limited number of both overall cancer and prostate cancer deaths, which make power to detect associations with serum adiponectin and leptin limited. Furthermore, any mention of prostate cancer on a death certificate was included in our analyses, because of the small number of cases, but this may then have meant that a patient was included who died with but not necessarily from prostate cancer, and ideally these should have been confirmed through linkage with a cancer registry. However, PRIME participants did not ever consent to linkage with cancer registry data, so this cannot be completed. Furthermore, only data for

serum leptin and adiponectin were available, whereas genetic polymorphisms linked to these factors and tissue expression were not included, which may be linked to longer term exposure, within the systematic review. Finally, the adiponectin isoforms were not measured in the PRIME participants.

4.5. Conclusion

Cardiovascular risk factor status, some of which, like BMI and waist to hip ratio, and lipid profile, have also been suggested to be associated with prostate cancer risk, differ amongst men in Northern Ireland and France enrolled in the PRIME study. Amongst Belfast men, anthropometric and lipid profiles altered over time, confirming an age-associated increase in CVD risk and suggesting that lifestyle behaviour change to manage this age-associate increase in risk factor status, is important.

When exploring the association between adiponectin and leptin and prostate cancer mortality in this cohort study with more than twenty years of follow up, trends in reduction in both overall cancer and prostate cancer mortality with increasing adiponectin and reduction in leptin were seen, but these were not statistically significant, and, particularly for leptin, were not linear, and the estimates were affected by the degree of adjustment for confounders within the model. This was also true for the adiponectin to leptin ratio. Therefore the association between serum adiponectin and leptin and both all cancer and prostate cancer mortality is uncertain and requires confirmation in further studies which have an adequate number of formally confirmed prostate cancer deaths, and where, ideally, information on adiponectin and leptin polymorphisms or tissue levels are available, and where data exist on a broad range of potential confounders, to allow the construction of robust models.

5. Final discussion

5.1 General

The incidence of prostate cancer is estimated to continue to increase, as it is estimated that, by 2040, there will be more than one million additional new cases worldwide (IARC, 2020c). Meanwhile, the number of deaths will continue to rise by more than 90% or reach seven hundred thousand deaths in 2040 (IARC, 2020d). Prostate cancer is cancer with an aetiology that is still not well understood at present due to the complexity of the factors involved (ACS, 2020).

Obesity has been identified as a contributing factor to at least twelve types of cancer, including prostate cancer (WCRF, 2018). High-fat stores during obesity promote insulin resistance, growth hormone production and inflammation that supports cancer growth (WCRF, 2018). BMI has been the major indicator focused on in studies exploring the link between obesity and prostate cancer (Langlais et al., 2019). Apart from BMI, waist circumference and the ratio of waist to hip circumference have also been examined in terms of link with risk of prostate cancer (Lavalette et al., 2018).

Furthermore, in the condition of obesity, it has been reported that changes in the level and function of leptin are disrupted which result in an increase in adiposity, causing an increase in the production of growth hormone needed by cancer cells (Pan and Myers, 2018). On the other hand, adiponectin interacts with insulin and causes an energy balance disorder which has been thought to be involved in cancer growth (Iwabu et al., 2019). Thus, it has been suggested that overweight and obesity may be associated with increased prostate cancer risk via the action of the adipokines.

While ADT is a therapy option that is widely used in the treatment of prostate cancer, it has reported side effects in the form of changes in body composition (Allan et al., 2014, Haseen

et al., 2010a). ADT has also been reported to be associated with obesity, increased insulin resistance, changes in lipid profiles, and the emergence of metabolic syndrome markers (Allan et al., 2014). This means that patients who are given ADT will be at an increased risk of death from cardiovascular disease, because of the effect of the therapy on cardiovascular disease risk factors (Haque et al., 2017).

This thesis has been structured with the main objective of providing an overview of how the adipokines (leptin and adiponectin) and lipid profiles contribute to the interaction between obesity and prostate cancer, with each chapter using a different study design and research question in order to get a more complete picture of how obesity is linked to prostate cancer.

In the intro chapter, the available scientific literature relating obesity globally to cancer (including prostate cancer) was summarised. The intro chapter also includes information about current prostate cancer statistics.

The next chapter examined the role of leptin and adiponectin (adipokines associated with metabolic changes in obesity) in terms of risk, aggressiveness, and progression of prostate cancer through the conduct of a comprehensive systematic review. Through a combination of narrative review and meta-analysis, this chapter described the roles of the two adipokines, both serum, receptor expression, and DNA in each stage of prostate cancer (risk, aggressiveness, and progression).

This was followed by a chapter describing the post-hoc analysis of an RCT diet and physical activity intervention over 6 months in prostate cancer patients who were receiving ADT. This chapter attempted to reveal the relationship between the interventions given and changes in lipid profiles and cardiovascular disease risk scores, as well as exploring whether different degrees of adherence were associated with all outcomes measured.

A number of limitations were identified within the available literature included in the systematic review, and therefore a survival analysis of adipokines, anthropometry and lipid profiles and all cancer and prostate cancer mortality, attempting to deal with some of these limitations, is presented within the next chapter.

5.2 Leptin and adiponectin in relation to prostate cancer risk, aggressiveness, and progression – systematic review and meta-analysis

The objective of this chapter was to comprehensively investigate the relationship of leptin and adiponectin through exploring serum levels, receptor expression and genetic polymorphisms in relation to prostate cancer risk, aggressiveness, and progression. The results of this review have added evidence helping explain the relationship, which may be complex, between adipokines, obesity, and clinically relevant prostate cancer. This chapter involved a total of 42 studies considered in the narrative review and a total of 14 studies for meta-analysis.

In the beginning, narrative analyses were carried out for all available studies. Starting by study selection based on adipokines (leptin or adiponectin), studies measuring each adipokine studies were separated according to whether the association with risk or aggressiveness or progression of prostate cancer was being assessed. Studies were also examined based on their biological measurement which was in serum or DNA or receptor. From this grouping, it was then mapped how many studies were available, the direction of association for each individual study, and an outline of the findings. After that, a narrative explanation was compiled, for example, a narrative of the studies which have explored serum leptin and the association with risk of prostate cancer, and this process was repeated until all sub-groupings had been narratively explained.

The next step was a meta-analysis, all study groups were explored as to whether they could be analysed through a meta-analysis, i.e. were data presented appropriately. Data were

available for studies measuring serum leptin related to prostate cancer risk and aggressiveness. For serum adiponectin, data were also available from studies related to risk and aggressiveness of prostate cancer.

The association between leptin and prostate cancer risk was supported by most case-control studies, this was less consistently supported by nested case-control studies, which would be considered methodologically stronger, and was not supported by a weaker, cross-sectional study. The association between leptin and prostate cancer aggressiveness was supported by the cohort studies and most cross-sectional studies and case-control studies, but this was less convincing within nested case-control studies. There were no studies found within this systematic review that explored the association between leptin and the progression of prostate cancer. Meanwhile, the meta-analysis found no relationship between serum leptin and risk or aggressiveness of prostate cancer.

The association between adiponectin and prostate cancer risk was supported by the majority of case-control studies, this was less consistently supported by nested case-control studies, which would be considered methodologically stronger, and was supported by one, and rejected by another one, weaker cross-sectional studies. The mixed association between adiponectin and prostate cancer aggressiveness was reported by the case-control studies and nested case-control studies and cross-sectional studies. The association between adiponectin and prostate cancer progression was supported by both cross-sectional study and cohort, however, the overall number of studies was small. The results of the meta-analysis did not show a significant association between serum and adiponectin with prostate cancer risk or aggressiveness.

Overall, an inconsistent association was found between leptin (risk and aggressiveness) and adiponectin (risk, aggressiveness, and progression) and prostate cancer in the narrative review results. There were no significant associations in the meta-analysis between serum leptin

and prostate cancer risk or aggressiveness, whereas the results of the adiponectin meta-analysis did not find an association between risk or aggressiveness of prostate cancer.

The limitations of the included studies were the small number of studies involved, particularly the cohort studies and the difficulty of maintaining consistency in terms of confounders that were included during analysis. Limitations in the studies included in this systematic review and meta-analysis chapter were attempted to be answered by the PRIME cohort data analysis performed in the later part of the thesis.

5.3 The efficacy of a six-month dietary and physical activity intervention on the dietary intake, lipid profiles and cardiovascular risk profile of prostate cancer patients receiving ADT

The results of this chapter describe the impact of a 6-month intervention on dietary and physical activity in prostate cancer patients with ADT on dietary behaviour, lipid profiles and cardiovascular (QRisk) values, also considering whether adherence affected outcome response. The results obtained showed no difference in lipid profiles between intervention and control groups, although the direction of change for all lipids were in the expected direction, including when results were explored according to level of adherence. In the QRisk score analysis, there was no difference in cardiovascular risk between groups, although this result may be related to issues regarding available data when determining cardiovascular disease risk. On the other hand, the lack of statistical significance could also be due to the retrospective power, where the initial design of this RCT was to measure anthropometric changes in patients and was not intended to detect changes in lipid profile, whereas detecting lipid changes required a different (and larger) sample size.

5.4 Association between adipokines, lipid profile and prostate cancer- and all cancer-mortality in the PRIME cohort.

The group of men who later died from cancer showed slightly higher levels of adiponectin measured at baseline than the group of men who did not later die from cancer, but there was no significant difference between the two groups. The association between adiponectin, leptin, leptin to adiponectin ratio, insulin and the lipid profile and all cancer-specific death, analysed using Cox regression analysis, was not statistically significant, in unadjusted or fully adjusted models. Furthermore, the association between adiponectin, leptin, leptin to adiponectin ratio, insulin and the lipid profile and prostate cancer-specific death was also not statistically significant. Hence, although these analyses can be considered more robust than most of the studies included in the systematic review and meta-analysis presented earlier in the thesis, these analyses can still not confirm the link between adipokines and prostate cancer.

5.5 Overall summary findings in this thesis

While obesity has been related to prostate cancer, the role for adipokines in terms of risk, aggressiveness and progression of prostate cancer is still uncertain, with the work conducted in this thesis systematically reviewing the literature and highlighting weaknesses within that literature, which new analysis of an available prospective cohort study, the PRIME study, attempted to rectify. Ultimately, findings from this survival analysis suggested trends in terms of associations between adipokines and prostate cancer mortality, but results were not statistically significant, likely due to a low number of cases, and therefore further robust studies are required considering method of assessment of adipokine exposure and development of robust models using appropriate confounders, which will allow conclusions regarding this potential association.

Once men have been diagnosed with prostate cancer, the range of therapies available are likely to include ADT, which increases risk of CVD. Post-hoc analysis of a diet and lifestyle

intervention has demonstrated that, although previously analysed anthropometric outcomes and dietary intake were altered, there was no significant effect on lipid profile and CVD risk outcomes, while level of adherence also did not seem to be associated with these secondary outcomes, although adherence was associated with the primary anthropometry outcome. As for the survival analysis, a lack of statistical power is likely to have been an issue for the secondary lipid outcomes, and a retrospective power calculation confirmed this. Given this lack of power, and the already observed effect of the dietary and lifestyle intervention on the anthropometric outcomes, additional work should explore the acceptability of such an intervention in prostate cancer patients and how it could be rolled out at scale.

Such qualitative work, to explore acceptability of diet and physical activity intervention in prostate cancer patients, including consideration of timing and intensity of intervention, had been planned as part of this PhD thesis, and ethical and governance approval was in the final stages in March 2020. However, given the national lockdown introduced as a result of COVID-19, and, from a university perspective, that all research had to be conducted remotely, and patient contact not being possible, then this element of the research could not be completed. It would be useful, however, given the results of the analyses that could be conducted within the thesis, to consider the advice currently given surrounding prostate cancer and lifestyle factors, including when ADT is being prescribed.

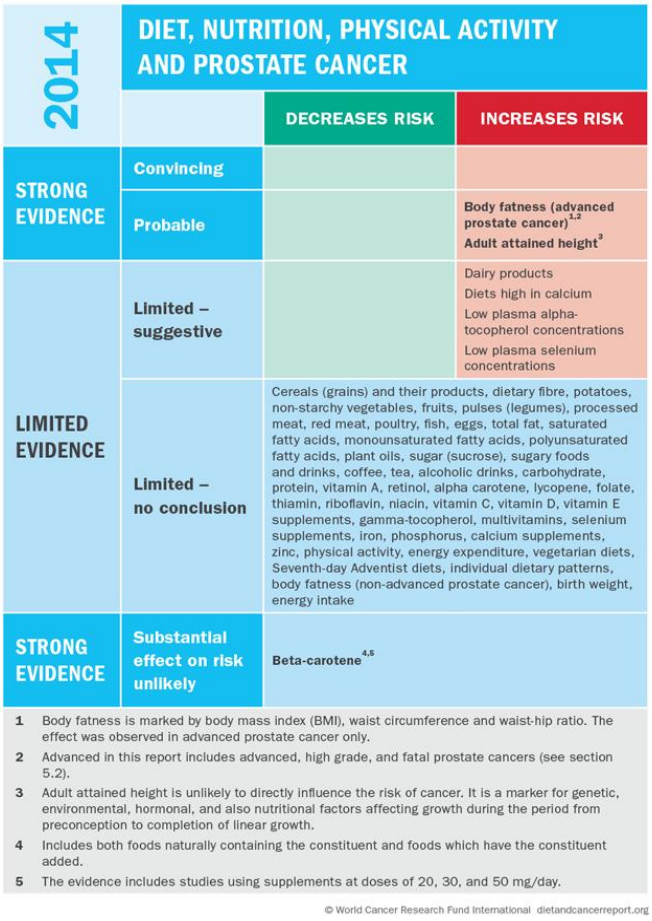
5.6 Available current guidelines for prostate cancer

The following are some of the guidelines currently available regarding diet, physical activity and prostate cancer, and the known side-effects of ADT:

1. Evidence summary according to the WCRF-CUP (WCRF-CUP, 2020), summarised in **Figure 5.1**:
    a. there is strong evidence that being overweight or obese increases the risk of advanced prostate cancer, being tall increases the risk of prostate cancer, and consuming beta-

carotene (in the diet or as supplements) is unlikely to have a substantial effect on the risk of prostate cancer.

b. Meanwhile, there is some evidence for higher consumption of dairy products might increase the risk of prostate cancer, diets high in calcium might increase the risk of prostate cancer, low plasma alpha-tocopherol concentration (vitamin E) might increase the risk of prostate cancer, and low plasma (blood) selenium concentrations might increase the risk of prostate cancer.



2014

DIET, NUTRITION, PHYSICAL ACTIVITY AND PROSTATE CANCER

		DECREASES RISK	INCREASES RISK
STRONG EVIDENCE	Convincing		
	Probable		Body fatness (advanced prostate cancer)[1,2] Adult attained height[3]
LIMITED EVIDENCE	Limited – suggestive		Dairy products Diets high in calcium Low plasma alpha-tocopherol concentrations Low plasma selenium concentrations
	Limited – no conclusion	Cereals (grains) and their products, dietary fibre, potatoes, non-starchy vegetables, fruits, pulses (legumes), processed meat, red meat, poultry, fish, eggs, total fat, saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, plant oils, sugar (sucrose), sugary foods and drinks, coffee, tea, alcoholic drinks, carbohydrate, protein, vitamin A, retinol, alpha carotene, lycopene, folate, thiamin, riboflavin, niacin, vitamin C, vitamin D, vitamin E supplements, gamma-tocopherol, multivitamins, selenium supplements, iron, phosphorus, calcium supplements, zinc, physical activity, energy expenditure, vegetarian diets, Seventh-day Adventist diets, individual dietary patterns, body fatness (non-advanced prostate cancer), birth weight, energy intake	
STRONG EVIDENCE	Substantial effect on risk unlikely	Beta-carotene[4,5]	

1 Body fatness is marked by body mass index (BMI), waist circumference and waist-hip ratio. The effect was observed in advanced prostate cancer only.
2 Advanced in this report includes advanced, high grade, and fatal prostate cancers (see section 5.2).
3 Adult attained height is unlikely to directly influence the risk of cancer. It is a marker for genetic, environmental, hormonal, and also nutritional factors affecting growth during the period from preconception to completion of linear growth.
4 Includes both foods naturally containing the constituent and foods which have the constituent added.
5 The evidence includes studies using supplements at doses of 20, 30, and 50 mg/day.

Source: WCRF-CUP

Figure 5.1. Diet, nutrition, physical activity, and prostate cancer recommendation (2014)

2. Guidelines about cancer prevention according to the WCRF-CUP (WCRF-CUP, 2020)

    a. Be healthy weight

    b. Move more

c. Enjoy more grains, vegetables, fruit, and beans

d. Avoid high calorie foods

e. Limit consumption of red and processed meat

f. Limit consumption of sugar-sweetened drinks

g. For cancer prevention, do not drink alcohol

h. Supplement would not prevent cancer

i. Breastfeed your baby

3. Guidelines about post cancer diagnosis according to the WCRF-CUP (WCRF-CUP, 2020)

    a. Follow the general advice for cancer prevention except you got specific advice by a health professional

    b. During loss of appetite: try to change the portion sized to see what sized can be tolerate, avoid drinking in mealtimes, sit upright when eating, make food look as appealing as possible

    c. During loss of weight: prioritise slowing down or stopping weight loss, eat healthy high calorie foods

4. Guidelines according to Cancer Research UK (CRUK, 2019):

    a. Obese means being very overweight with a body mass index (BMI) of 30 kg/m^2 or higher. And being overweight means having a BMI of between 25 and 30 kg/m^2.

    b. Try to keep a healthy weight by being physically active and eating a healthy, balanced diet.

    c. There is some evidence that being active might help to lower your risk of developing prostate cancer.

    d. Being overweight or obese increases your risk of advanced prostate cancer. Researchers have found a link between being obese or overweight and cancers being higher grade (faster growing).

5. Guidelines according to Prostate Cancer UK (PCUK, 2020):

    a. There is also strong evidence that being overweight raises the risk of aggressive or advanced prostate cancer. So, it may be particularly important for men with prostate cancer to stay a healthy weight.

    b. Being a healthy weight may mean your prostate cancer is less likely to spread after surgery or radiotherapy. Hormone therapy might also be less effective if you're very overweight. And staying a healthy weight may help you manage or reduce some of the side effects of treatments, such as urinary problems after surgery.

6. Guidelines according to Prostate Cancer UK (ADT side effect) (PCUK, 2020):

    a. Weight gain: physical activity and a healthy diet can help you stay a healthy weight.

    b. Strength and muscle loss: regular gentle resistance exercise, such as lifting light weights or using elastic resistance bands, may help to prevent muscle loss and keep your muscles strong.

    c. A healthy diet and regular physical activity are important for general health and can help you stay a healthy weight. This may be particularly important if you have prostate cancer, as there is strong evidence that being overweight raises the risk of aggressive (more likely to spread) or advanced prostate cancer.

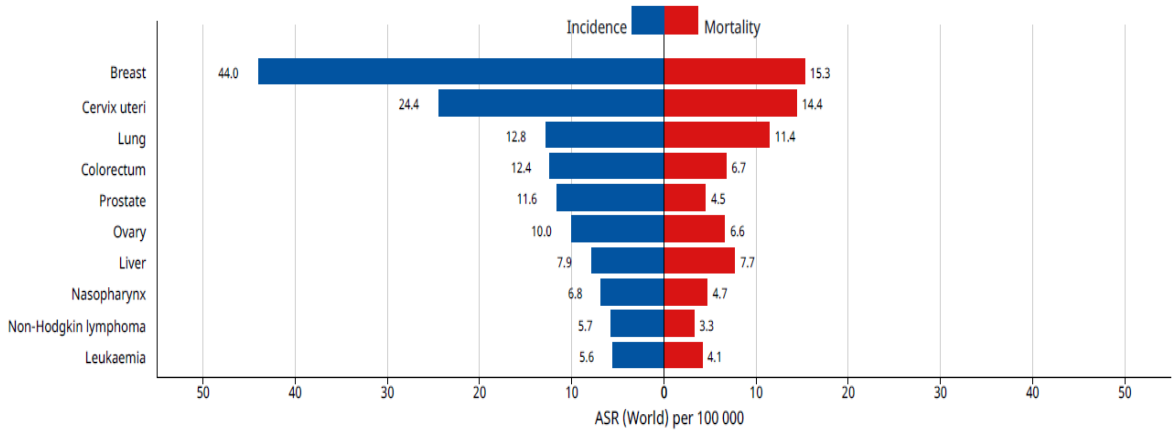
    d. A healthy lifestyle can also help manage many of the side effect of treatments for prostate cancer.

7. Guideline according to NICE (ADT side effect) (NICE, 2020):

    a. Fatigue: Offer people who are starting or having androgen deprivation therapy supervised resistance and aerobic exercise at least twice a week for 12 weeks to reduce fatigue and improve quality of life

Clearly, the results presented in each chapter in this thesis do not argue against the importance of weight control (preventing obesity) in prostate cancer patients, whether due to treatment side effects (ADT) or not, and in terms of prevention of progression of prostate cancer and preservation of cardiovascular health. The application of diet combined with physical activity does appear to be a feasible method of inducing behaviour change with resulting beneficial effects on anthropometric measures. The thesis does, however, highlight the challenges of determining whether the action of obesity on prostate cancer risk and progression occurs via the adipokines and suggests the need for further study. Regardless of the insignificant or inconsistent results observed in this thesis, there is no doubt that the results presented in this thesis do not contradict the recommendations published by the various organisations/charities mentioned above.

The guides above focus mostly on English language and UK-focused guidance. Until now, no guidelines have been reported from centres originating from Asia, particularly Indonesia. Prostate cancer is currently not a major problem in Indonesia, prostate cancer is ranked 4th out of 5 most frequent cancers in Indonesia, with around 11.6 incidences per 100.000 (age-standardize) and 4.5 mortality per 100.000 **(Figure 5.2)** (IARC, 2020a). On the other hand, the Ministry of Health of the Republic of Indonesia has reported an increase in the prevalence of obesity by 4% according to the latest data (2010-2013) (Kemenkes, 2017), even though in Southeast Asia, Indonesia still has a prevalence of obesity <10% (Obesity, 2011). It is very important to pay attention to the potential association between obesity and prostate cancer in Indonesia and consider recommendations or guidelines for prevention and management now, when disease burden is still relatively low, as it is likely to increase.



Source: IACR 2020

Figure 5.2. Age-standardised (World) incidence and mortality rates, total 10 cancers in Indonesia (December 2020)

In addition, Indonesia also needs national and international networks to develop research capacity in the field of cancer epidemiology and an understanding of the risk factors that contribute to the risk of and mortality from prostate cancer locally.

5.7 Limitations and strengths

This thesis was structured to review the relationship between obesity and prostate cancer, which has not to date been fully explained. The overall objective of this project was to study the role of adipokines (leptin and adiponectin), insulin, and lipid profiles as possible contributors to the interactions between obesity and prostate cancer. Limitations in this thesis include:

1. Within the systematic review and meta-analyses: the studies involved had various methodological variations, definitions of prostate cancer, different levels of reliability, and various biological measurement differences as well as a limited number of studies that restricted the pooled analysis that could be conducted, although the overall aim of the chapter was still completed

2. Within the RCT: there was no control over the use of lipid-lowering agents in patients included and there are missing variables when calculating QRisk data which may have affected the results of the analysis. Furthermore, these were secondary analyses, which may have suffered from a lack of statistical power, as illustrated by the retrospective power calculation
3. Within the survival analysis of the PRIME study: power is likely to have been low due to the small number of prostate cancer patients, while the lack of confirmation of these cases via a cancer registry is also a limitation.

On the other hand, the strengths of this thesis are:

1. Within systematic reviews and meta-analyses: the results are an overall picture of the relationship between leptin and adiponectin and the risk, aggressiveness, and progression of prostate cancer stemming from all biological measurements different from similar studies that have been performed. In addition, all studies used in the meta-analysis were from high-quality studies. Some of the limitations observed within the studies included in the systematic review were rectified within the additional survival analysis of the PRIME study conducted.
2. Within the RCT study: this study utilised a strong and robust methodology and was well conducted. Analyses presented in this thesis explored the effects of different levels of adherence to the intervention.
3. All chapter results do not dispute the current recommendations regarding diet and regulation of physical activity in relation to obesity and prostate cancer

5.8 Conclusion

Research regarding the association between obesity and prostate cancer, and the involvement of the adipokines, needs to be continued. This thesis has demonstrated that the association between the adipokines and prostate cancer risk, aggressiveness and progression is uncertain, with some methodological challenges that should guide further analyses and study designs. Conducting survival analysis of serum adipokine levels and prostate cancer death more than twenty years later in the PRIME study did not, however, confirm an association, even those this analysis did have a long period of follow-up, included a range of confounders, and was prospective in nature. Finally, ADT-associated weight gain and body composition change, although improved by a diet and physical activity intervention, led to no change in lipid levels and CVD risk, even when adherence to the intervention was factored into the analysis.

This research should consider the toughest challenge when researching in this area, i.e. that prostate cancer is a slow growing cancer. However, as prostate cancer is classified as the leading cause of death in men, and the increasing number of people with obesity as a modifiable risk factor of prostate cancer, then research to explore the mechanism by which obesity influences prostate cancer (i.e. role of the adipokines) and interventions to reduce obesity and, therefore, prostate cancer risk and progression, are of great importance.

The results of this thesis can be used as a guide for men with or at risk of prostate cancer, especially how obesity may have a role in the risk, aggressiveness, and progression of prostate cancer. In addition, the results of this thesis also fully support the existing guidelines regarding the positive effects of being physically active and regulating eating according to existing healthy eating guidelines as an important part of prostate cancer therapy.

Finally, this research should be accompanied by guideline updates, as the evidence accrues, regarding dietary and physical activity, particularly during prostate cancer

therapeutic support, although research results on this are currently still mixed and guidelines therefore very general. Inclusion of such guidance could at least reduce the effect of the therapy which has been shown to induce body composition changes in the patient and reduce the likelihood of co-morbidities, which is particularly important as prostate cancer is such a slow growing cancer.

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