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# **EPIDEMIOLOGICAL STUDIES OF DIET QUALITY, BODY SIZE AND PROSTATE CANCER RISK**

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*Till mamma och pappa, med kärlek*

*Not everything that counts can be counted,  
and not everything that can be counted counts.*

*- William Bruce Cameron*



## ABSTRACT

Prostate cancer is the most common male cancer in high-income countries. The etiology of the disease is still poorly understood, but increasing evidence suggests that lifestyle factors such as diet and body size play an important role. As modifiable risk factors, they may serve as potential strategies to prevent prostate cancer. Therefore, this thesis aims to clarify the relationship between overall diet quality as well as body size in a lifetime perspective, and prostate cancer risk.

**Study I-III** are based on a large population-based sample of Swedish men. We used questionnaire data on diet and anthropometric factors collected in 2001-2003 among 1,499 prostate cancer cases and 1,118 controls. **Study IV** is based on a large cohort study of 47,491 American male health professionals, with questionnaire data on anthropometric factors prospectively collected since baseline in 1986.

In **Study I** we evaluated if adherence to the Nordic Nutrition Recommendations (NNR 2004) was associated with prostate cancer risk. We created a score to measure adherence versus non-adherence to the NNR, and found no differences between adherence groups. Additionally, we hypothesized that the potential association was modified by a genetic risk score, but found no statistically significant interaction.

In **Study II** we examined adherence to the Mediterranean diet, as assessed by the Mediterranean Diet Score (MDS), in relation to prostate cancer risk. Secondly, we evaluated the usefulness of the MDS in our Nordic population by comparing five score variants. Overall we found no associations between any of the MDS variants and prostate cancer. The MDS with study-specific intake cut-offs was considered useful to assess a Mediterranean-like diet in a non-Mediterranean population.

**Study III** and **IV** investigated whether childhood and adult body size was associated with prostate cancer risk. The influence of body size varied largely between disease subtypes. Tall men had an increased risk of prostate cancer, especially advanced-stage and fatal disease. Men with a healthy weight in young adulthood had a lower risk of disease overall, while men with a high BMI in young adulthood had a lower risk of late-stage and fatal prostate cancer. Men who were overweight or obese in middle-to-late adulthood had a lower risk of total, early-stage and less aggressive cancer, especially among men  $\leq 65$  years. In addition, **Study III** included analyses on weight change in adulthood; moderate weight gain was associated with an increased risk of disease in short men and in men who were thin at start. We further investigated childhood body size, and the results were inconsistent.

In conclusion, overall diet quality did not appear to influence prostate cancer risk. Tall men had higher risk of the disease compared to short men. Our results further suggest that body size in early adulthood may have larger influence on prostate cancer risk than body size later in life, although maintaining a healthy weight throughout adulthood appears beneficial for disease prevention.

# POPULÄRVETENSKAPLIG SAMMANFATTNING

Prostatacancer är den vanligaste formen av cancer i Sverige idag. Enligt statistiken beräknas 1 av 7 män få prostatacancer före 75 års ålder. Varje år diagnosticeras nästan 10 000 svenska män med sjukdomen, och 2 500 dör av den. Vad som orsakar sjukdomen är inte klarlagt, men forskningen pekar på att både ålder, etnicitet, ärftlighet/genetiska faktorer och faktorer i omgivningen har stor betydelse. Många män undrar vad de själva kan göra för att minska risken att få prostatacancer. Vi vet att livsstilen har stor betydelse för hälsan, men när det gäller livsstilens roll för prostatacancer kvarstår många kunskapsluckor att fylla.

Det övergripande syftet med denna avhandling är att klargöra kopplingen mellan kosten som helhet samt kroppsstorlek i olika åldrar och risken för prostatacancer. Genom studier på populationsnivå har vi jämfört dessa livsstilsfaktorer mellan män diagnosticerade med prostatacancer och friska män. Prognosen kan se väldigt olika ut då sjukdomen kan vara av mer eller mindre elakartad form, därför tittade vi separat på sambandet med olika former av prostatacancer.

I avhandlingens första del undersökte vi om kosten som helhet är kopplad till risken för prostatacancer. Studierna är enligt vår vetskap de första i sitt slag på sambandet med prostatacancer. Vi använde enkätdata på kost och fysisk aktivitet insamlad 2001-2003 i en svensk populationsbaserad studie på 1499 män med prostatacancer och 1118 friska kontroller.

Först utvärderade vi de Nordiska Näringsrekommendationerna (NNR) från 2004 (**delstudie I**). NNR är riktlinjer för energi- och näringsintag samt fysisk aktivitet med syfte att främja god hälsa och förebygga kroniska kostrelaterade sjukdomar i den nordiska befolkningen. Rekommendationerna har dock inte utvärderats tidigare i relation till cancerrisk. Vi använde ett index baserat på åtta kostkomponenter samt en komponent för fysisk aktivitet för att mäta hur väl männen följde rekommendationerna. I vår studiepopulation hittade vi ingen association mellan NNR och risk för prostatacancer. De flesta män hade ett generellt bra näringsintag, varför skillnaderna i kostkvalitet mellan grupperna var små.

Därefter tittade vi på en traditionell Medelhavskost (**delstudie II**), som har visats hälsosam och eventuellt skyddande mot bland annat flera cancerformer. Vi använde ett index för Medelhavskost baserat på intag av åtta livsmedelsgrupper och en komponent för fettkvalitet. Vi hittade ingen association mellan Medelhavskost och prostatacancerrisk. Studien hade också en kvalitativ del, där vi anpassade Medelhavsindexet efter svenska förhållanden och jämförde olika index-varianter för att utvärdera dess användbarhet i en icke-Medelhavspopulation. Skillnaderna mellan indexvarianterna i relation till prostatacancerrisk var små. Vi drog slutsatsen att indexet är användbart även i en nordisk population som skiljer sig i kostvanor jämfört med en Medelhavspopulation.

Avhandlingens andra del syftade till att undersöka om kroppsstorlek har betydelse för utveckling av prostatacancer. Sambandet mellan kroppsstorlek och prostatacancer är sannolikt mycket komplext och involverar bland annat nivåer av tillväxt- och könshormoner i kroppen. Eftersom hormoner har olika påverkan i olika faser i livet ville vi undersöka sambandet ur ett livstidsperspektiv. Få tidigare studier har undersökt kroppsstorlek i unga åldrar och prostatacancer.

**Delstudie III** bygger på självrapporterad data på kroppsstorlek från samma svenska population som i delstudie I-II. **Delstudie IV** bygger på data från en stor amerikansk kohortstudie, där 47 000 män har följts i över 20 års tid med avseende på självrapporterad livsstil, hälsa, prostatacancerdiagnos och död. Drygt 6000 av dessa män diagnosticerades med prostatacancer under uppföljningen. I studierna tittade vi på kroppsfigur i barndomen, längd i vuxen ålder, BMI (body mass index,  $\text{kg}/\text{m}^2$ ) i olika åldrar från 20 år och uppåt, midjeomfång samt viktförändring hos vuxna män. Vi fann att långa män ( $\geq 180$  cm) löpte högre risk att drabbas av prostatacancer, särskilt mer elakartade former, än korta män ( $< 172$  cm). Vi såg inga entydiga samband mellan kroppsfigur i barndomen och prostatacancer. I **delstudie III** såg vi en skyddande effekt av ett hälsosamt BMI i 20-årsåldern, medan övervikt i samma ålder i **delstudie IV** var kopplat till en lägre risk för mer elakartade cancerformer. Övervikt/fetma i medelåldern och framåt var associerat med en lägre risk för tidiga, mindre elakartade former av prostatacancer. En måttlig viktuppgång var kopplad till en svagt ökad risk för prostatacancer i **delstudie III**, särskilt bland korta män samt de som var smala i början av mätperioden.

Sammanfattningsvis såg vi ingen koppling mellan kostens kvalitet och prostatacancer, vilket bekräftas av flera andra studier. Detta kan bero på att kosten som helhet kanske inte har lika stark betydelse för risken att få prostatacancer som man har sett av vissa enskilda kostfaktorer. Det kan också bero på svårigheten att mäta kost. Vidare kunde vi bekräfta tidigare fynd att långa män har en högre risk att drabbas av prostatacancer. Övervikt/fetma i vuxen ålder var kopplat till en lägre risk för sjukdomen, vilket även andra studier har visat. Detta kan tyckas förvånande med tanke på att övervikt/fetma är förenat med övervägande negativa effekter på hälsan. Ytterligare studier krävs dock för att dra slutsatser om det är ett sant samband eller om fyndet kan ha andra förklaringar. Att bibehålla en hälsosam vikt genom vuxenlivet verkar ha en fördelaktig effekt. En viktig observation är att kroppsvikt verkar ha olika betydelse för risken att få prostatacancer i olika skeden i en mans liv, och sannolikt har det störst betydelse i unga år. Detta bör framtida studier på kroppsstorlek och prostatacancer ta hänsyn till.

Denna avhandling, baserad på två stora studiepopulationer med omfattande data, bidrar med flera pusselbitar till den komplexa bilden av hur män genom sin livsstil kanske kan påverka sin risk att utveckla prostatacancer. Ur ett folkhälsoperspektiv är detta betydelsefullt för framtida cancerförebyggande arbete, till exempel ändrade livsstilsrekommendationer för män och identifiering av grupper av män i en högre riskzon att drabbas av sjukdomen. Det sistnämnda är särskilt viktigt för att tidigare kunna upptäcka mer elakartade och dödliga former och kunna ge tidig behandling.

## LIST OF PUBLICATIONS

- I. Möller E, Galeone C, Adami H-O, Adolfsson J, Andersson T, Bellocco R, Grönberg H, Mucci LA, Bälter K. The Nordic Nutrition Recommendations and prostate cancer risk in a Swedish population-based study (CAPS). *Public Health Nutr.* 2012 Oct;15(10):1897-908. Epub 2012 Mar 30.
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- III. Möller E, Adami H-O, Mucci LA, Lundholm C, Bellocco R, Johansson J-E, Grönberg H, Bälter K. Lifetime body size and prostate cancer risk in a population-based case-control study in Sweden. *Cancer Causes Control.* 2013 Sep 19 (Epub ahead of print).
- IV. Möller E, Kasperzyk JL, Wilson KM, Mucci LA, Bälter K, Giovannucci E. Body size across the life course and prostate cancer in the Health Professionals Follow-up Study. *Manuscript.*

## RELATED PUBLICATIONS

(not included in thesis)

- I. Bälter K, Möller E, Fondell E. The effect of dietary guidelines on cancer risk and mortality. *Curr Opin Oncol*. 2012 Jan;24(1):90-102.
- II. Wilson KM, Bälter K, Möller E, Adami H-O, Andrén O, Andersson S-O, Grönberg H, Mucci LA. Coffee and risk of prostate cancer incidence and mortality in the Cancer of the Prostate in Sweden Study. *Cancer Causes Control*. 2013 Aug;24(8):1575-81. Epub 2013 May 24.

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## LIST OF ABBREVIATIONS

ACS	American Cancer Society
AICR	American Institute for Cancer Research
AHEI	Alternate Healthy Eating Index
BMI	Body mass index
CAPS	Cancer of the Prostate in Sweden
CI	Confidence interval
DAG	Directed acyclic graph
DGA	Dietary Guidelines for Americans
DQI	Diet Quality Index
EPIC	European Prospective Investigation into Cancer and Nutrition
FFQ	Food Frequency Questionnaire
HDI	Healthy Diet Indicator
HEI	Healthy Eating Index
HPFS	Health Professionals Follow-up Study
IGF-I	Insulin-like growth factor-I
MDS	Mediterranean Diet Score
MET	Metabolic equivalents
MP:S	Mono- and polyunsaturated to saturated fat ratio
NNR	Nordic Nutrition Recommendations
OR	Odds ratio
PC	Prostate cancer
PSA	Prostate-specific antigen
RFS	Recommended Food Score
RR	Relative risk
SNP	Single-nucleotide polymorphism
TNM	Tumor-Node-Metastasis
WHO	World Health Organization
WCRF	World Cancer Research Fund

# 1 INTRODUCTION

*“There are known knowns; there are things we know that we know.*

*There are known unknowns; that is to say, there are things that we now know we don't know.*

*But there are also unknown unknowns – there are things we do not know we don't know.”*

*- Donald Rumsfeld, US Secretary of Defense*

Epidemiology is the study of the spread and causes of health and disease in a population. The word stems from the Greek *epi* (“upon, among”), *demos* (“people, district”), and *logos* (“study, word, discourse”), in other words meaning “the study of what is upon the people”. We as epidemiologists typically observe associations between an exposure and an outcome in population-based studies in order to make inference about the observed association being potentially causal i.e. that the exposure *may* cause the disease. The observed data is what we measure; the causal model is what we know; and the real world is the truth.

We can only wish to discover the truth and nothing but the truth. Yet, evidence from epidemiological studies with causal interpretation forms the basis for public health strategies to prevent diseases in the population. In this sense, it is particularly interesting to study lifestyle factors that we to a large extent can modify.

Diet is a complex matter. We consume food in combination, and the different components in the food interact with each other as well as with other factors, producing a mix of synergistic and antagonistic effects. In light of this complex interplay, studying the whole diet rather than individual food components is supposedly a preferred alternative to evaluate the impact of diet on health. However, as a nutritional epidemiologist one has to struggle with the inherent difficulty in measuring what people eat. To perfectly measure diet is a “mission impossible”, but we can get close enough. So why did I devote myself to this challenging task? Well the answer is in my strong conviction that what we eat indeed has a crucial effect on our health.

Furthermore, there is an alarming trend in many Western regions; people are getting bigger, mainly as a result of eating more (unhealthy) food and spending more time in front of the TV/computer/smart phone/ipad etc. We are in the middle of an obesity epidemic affecting both children and adults. The epidemic started globally in the 1980s, and between 1980 and 2008 the prevalence of obesity doubled from 5 to 10 % among adult men in the world <sup>(1)</sup>. The prevalence of childhood overweight and obesity increased globally from 4 to 7 % between 1990 and 2010 and is expected to increase to 9 % in 2020 <sup>(2)</sup>. Although there has been a leveling off in the past decade <sup>(3,4)</sup>, we will likely see a continued increase in the prevalence of chronic diseases related to excess body weight in the near future.

What is also increasing worldwide is prostate cancer, now ranked as the second most common cancer among men globally <sup>(5)</sup>. The understanding of the causes of the disease is still a rather blurry puzzle, but lifestyle factors such as diet and body size seem to

play important roles. Reducing the incidence and mortality of prostate cancer is a major public health priority, and as modifiable risk factors, dietary changes and weight control are potential strategies for disease prevention. The goal of this thesis has therefore been to provide scientific evidence for such strategies by clarifying the role of overall diet quality as well as body size in childhood and adulthood in the development of prostate cancer.

## 2 BACKGROUND

### 2.1 PROSTATE CANCER

#### 2.1.1 Disease description

The prostate is part of the male reproductive system, with the function to produce the seminal fluid that protects and nourishes the sperm cells. The gland is situated below the urinary bladder and in front of the rectum, surrounding the upper part of the urethra. The growth and function of the prostate is regulated by sex hormones, primarily dihydrotestosterone, which is a converted form of testosterone. The prostate starts to develop already before birth and during puberty it takes on a rapid process of growth and maturation, reaching its full size around age 20.

A normal, healthy prostate has the size of a walnut, but in older men it is often enlarged due to a common condition called *benign prostatic hyperplasia*. This fairly harmless condition can cause problems with urination but is not linked to cancer. However, an enlarged prostate may also be due to a growing cancer. The predominant form of prostate cancer, referred to as *adenocarcinoma*, arises in the gland cells. Symptoms of the disease often occur quite late in the disease process and include frequent urination, difficulties when urinating, blood in the urine, problems with erection and ejaculation, and pain. Many of these symptoms resemble those of a harmless enlargement of the prostate. Late symptoms also include pain in the back, hips or ribs caused by metastases, as well as weight loss and fatigue that are common for most cancers in advanced stages.

Most prostate cancers are slow-growing; it can take several decades from tumor initiation to symptoms being shown. In fact, many men with prostate cancer, whether diagnosed or undiagnosed, can live many years without any symptoms and may die from other causes before they even notice having a cancer. However, in some cases the tumor is more aggressive and may spread to other parts of the body, i.e. form metastases and lead to premature death. Distant metastases of prostate cancer are primarily found in the bone and lymph nodes.

#### 2.1.2 Diagnosis & prognosis

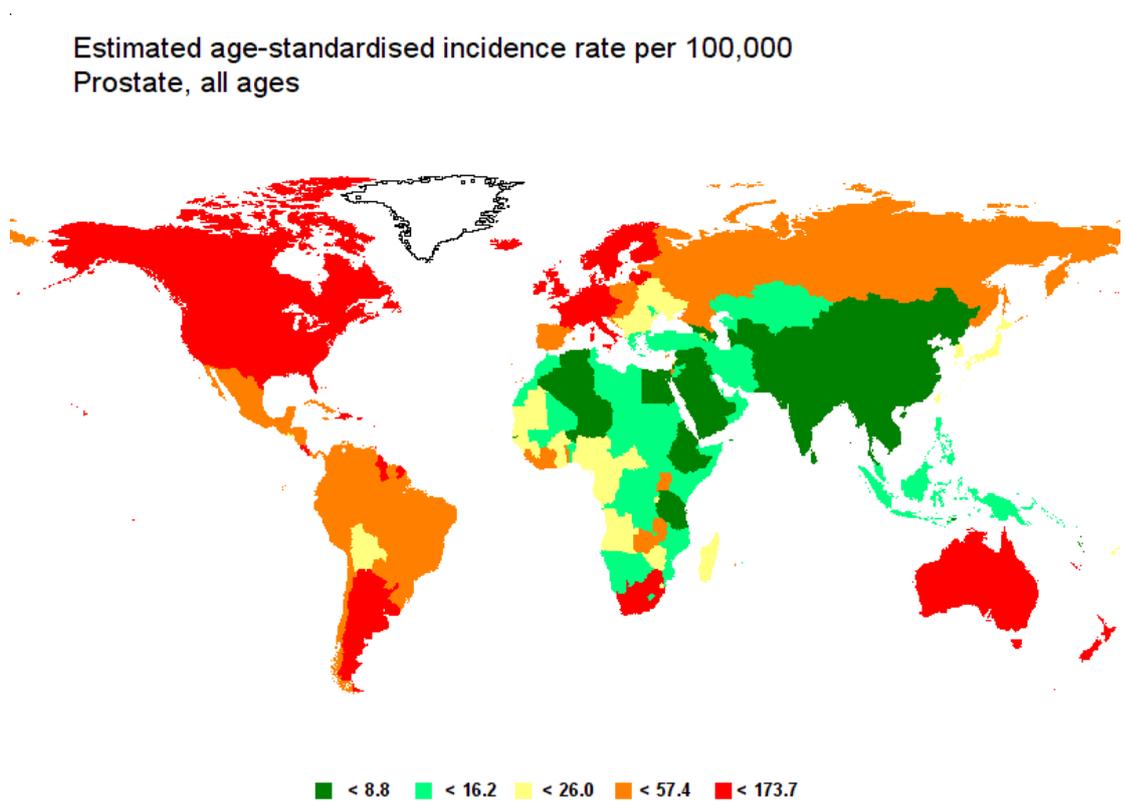
A prostate cancer is normally detected as a result of symptoms or a blood test showing elevated levels of prostate-specific antigen (PSA). Diagnosis is subsequently made based on physical examination and biopsies.

As mentioned above, the prognosis of a prostate cancer can vary largely between individuals depending on the tumor type. The critical part at diagnosis is therefore to determine whether the tumor is likely to progress into advanced stages and metastasize, in which case treatment should be considered, or whether it is a slow-growing tumor with a good prognosis <sup>(6)</sup>. Tumor stage refers to the spread of the tumor, whereas differentiation grade refers to the aggressiveness of the tumor. Early-stage or non-aggressive tumors are normally followed up by active surveillance. For tumors that have spread outside of the prostate or more aggressive tumors, curative treatments may

be considered; these include radical prostatectomy (surgical removal of the prostate), radiation therapy, hormonal therapy or chemotherapy <sup>(6)</sup>.

### 2.1.3 Disease occurrence

Prostate cancer ranks as the most common cancer among men in economically developed countries <sup>(5)</sup>. The rates of new cases per year vary largely across geographical regions as seen in **Figure 1**; the highest incidence rates are found in Scandinavia/Western Europe, North America, and Australia/New Zealand, and the lowest in South-Central Asia <sup>(5)</sup>.

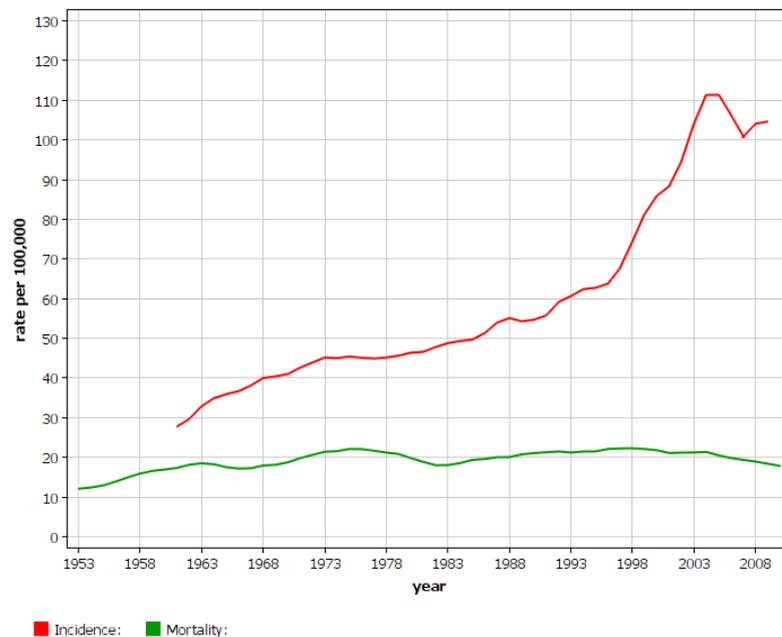


**Figure 1.** Age-standardized prostate cancer incidence rates per 100,000 men in the world, all ages. Rates are age-standardized to the world population. Source: GLOBOCAN 2008 (IARC) (15.10.2013).

In Sweden, the incidence of prostate cancer has increased steadily during the last five decades, as shown in **Figure 2**. In 2010, the age-standardized incidence rate was 104 per 100,000 individuals <sup>(7)</sup>. Today roughly 80,000 Swedish men are living with the disease, and based on current statistics, about 1 in 7 men will be diagnosed with prostate cancer before age 75 <sup>(7)</sup>.

In the United States (US), the estimated yearly age-standardized incidence rate was 152 per 100,000 individuals in the years 2006-2010 <sup>(8)</sup>. In 2010, over 2.5 million American men were living with a prostate cancer, and about 1 in 7 American men are expected to get diagnosed with prostate cancer during their lifetime <sup>(8)</sup>. However, a decreasing trend in prostate cancer incidence has been observed since 2000 <sup>(9)</sup>.

Sweden  
Prostate  
ASR (World) age 0-85+



**Figure 2.** Age-standardized rates for prostate cancer incidence (upper line) and mortality (lower line) per 100,000 men in Sweden, all ages, 1952-2011. Rates are age-standardized to the Nordic population in year 2000. Source: NORDCAN © Association of the Nordic Cancer Registries (15.10.2013)

Prostate cancer mortality rates have not followed the increasing incidence trends, as can be seen in **Figure 2**. In Sweden and the US they have been relatively stable during the last decades, with a decreasing trend since early-mid 1990s <sup>(5)</sup>. Still, prostate cancer is estimated as the second leading cause of cancer death in American men in 2013 <sup>(10)</sup>, and accounts for 21 % of all cancer deaths in Sweden <sup>(7)</sup>. The 5-year survival rate in Sweden was 91 % in 2010 <sup>(7)</sup>, and 99.2 % in the US 2003-2009 <sup>(8)</sup>.

#### 2.1.4 Prostate-specific antigen (PSA) testing

A likely explanation for variations in prostate cancer incidence across regions and time periods are differences in use of the PSA test <sup>(11)</sup>. PSA is an enzyme produced as part of the prostate’s normal function, and low blood levels are present in men with a healthy prostate. Elevated levels are a sign of malfunctions of the prostate such as prostatitis (inflammation), benign prostatic hyperplasia, or prostate cancer. The PSA test was introduced as a clinical test for prostate cancer in the US in the late 1980s <sup>(9)</sup>, followed by Sweden and other Western countries in the 1990s, causing a marked increase in the number of detected prostate cancers <sup>(11)</sup>. The rationale for the test is to detect prostate cancer early so that treatments can be given earlier for tumors deemed to be more severe, thereby saving lives. However, the test creates a lot of false positives and also results in men being diagnosed at a much earlier stage compared to 20 years ago <sup>(6)</sup>. Since most prostate tumors are slow-growing, many of these men will suffer from the heavy psychological burden of “having a cancer diagnosis”, without having any physical symptoms. Also, to date there is limited evidence that PSA testing actually reduces mortality from prostate cancer <sup>(12)</sup>.

The use of PSA testing is a debated issue. A major concern is the risk of over-diagnosis and overtreatment of small, slow-growing prostate tumors. In the US, annual PSA testing is recommended for men  $\geq 50$  years after being thoroughly informed about the risks and benefits of such a test so that they can make an informed decision; for men at higher risk (African-American men, or men having close relatives diagnosed with prostate cancer) the recommended age is 40-45<sup>(10)</sup>. In Sweden, there is no general PSA screening recommendation. It has been estimated that during the years 2000-2007, about one third of all Swedish men between age 50-75 had taken at least one PSA test<sup>(13)</sup>.

## 2.2 RISK FACTORS FOR PROSTATE CANCER

Established risk factors for prostate cancer are age, family history of the disease, and race/ethnicity<sup>(11)</sup>. Prostate cancer mainly affects older men; 98 % are  $>55$  years at diagnosis<sup>(8)</sup>. The mean age of diagnosis is 70 years in Sweden<sup>(7)</sup>, and the median age in the US is 66 years<sup>(8)</sup>. Men with a father or brother diagnosed with prostate cancer are at 2-3 times higher risk than men with no close relatives having the disease<sup>(14)</sup>. Furthermore, men with African ancestry have the highest disease risk; incidence rates in the US are 70 % higher among African-American men than among white men, and they are twice as likely to die from the disease compared to white Americans<sup>(9)</sup>. However, white men have higher risk than other ethnic groups living in the US, such as Hispanic, American Indian, or Asian men<sup>(9)</sup>. These ethnic differences in prostate cancer risk are probably explained by both genetic and environmental factors such as lifestyle. Several genetic factors have been associated with prostate cancer risk<sup>(15-17)</sup>.

Prostate cancer is a hormone-dependent cancer, and levels of sex hormones, insulin, and insulin-like growth factor (IGF)-I have been shown to be associated with risk of the disease<sup>(18-21)</sup>. Other hormones such as adipokines may be involved through pathways related to inflammation<sup>(18,19)</sup>. Androgens are vital for the growth and differentiation of the prostate gland, and high circulating levels of testosterone was long thought to promote prostate tumor growth, but in fact there is no convincing evidence for an association<sup>(20)</sup>. However, men with *low* testosterone levels seem to be at higher risk of poorly differentiated tumors, i.e. more aggressive prostate cancer<sup>(19,22)</sup>. Furthermore, insulin resistance and prolonged diabetes have been shown to be associated with a reduced risk of prostate cancer<sup>(20,23)</sup>; this association is likely mediated through changes in levels of insulin, IGF-I, and testosterone<sup>(20)</sup>.

Lifestyle factors are likely to have an important impact on prostate cancer risk. This is supported by migration studies showing that the incidence of prostate cancer among Asian men having settled in North America or Europe is much higher compared to men in their home countries<sup>(11)</sup>. Also, there has been a dramatic rise in prostate cancer incidence and mortality in many Asian populations going through a process of “Westernization” in food and cultural habits<sup>(24)</sup>. However, little is still known about the influence of lifestyle factors on prostate cancer development. Smoking seems to have little or no impact on the risk of prostate cancer<sup>(11)</sup>, whereas high physical activity may be associated with a modestly reduced disease risk<sup>(25)</sup>. The current evidence for associations with diet and body size is presented in the next two sections.

## 2.2.1 Diet and prostate cancer

Many studies have been performed investigating the association between diet and prostate cancer risk. However, findings have been largely inconsistent and therefore we still know little about what men should eat in order to reduce their risk.

Most previous studies have focused on single dietary factors. The current evidence suggests that a high intake of *dairy products*, mainly as a rich source of *calcium*, potentially increases the risk of prostate cancer<sup>(10)</sup>. High intake of *red or processed meat*<sup>(26)</sup>, *carbohydrates*, *saturated fat*, and *omega-6 fat*<sup>(27)</sup> has also been suggested to increase the risk. In contrast, a diet rich in *plant foods*, especially *tomatoes*, *cruciferous vegetables*, *legumes*, and *soy products*, as well as *fatty fish* rich in *omega-3 fat* may be beneficial in prostate cancer prevention<sup>(10,26,27)</sup>. Recent studies suggest that high *coffee* consumption may lower the risk of the disease<sup>(28-32)</sup>, though not in all studies. There is conflicting evidence for a protective effect of vitamin D and E and selenium, although men with low serum levels of these nutrients are likely to benefit from an increased dietary intake<sup>(33-36)</sup>.

Few studies have examined overall diet in relation to prostate cancer risk. Among studies using data-driven methods, several have shown that “Western-like” dietary patterns characterized mainly by high intakes of red/processed meat and refined grains may increase the disease risk<sup>(37-39)</sup>, whereas other studies have shown no associations with neither healthy or less healthy dietary patterns<sup>(40-42)</sup>.

Furthermore, interactions between dietary and genetic factors have been shown to influence prostate cancer risk in a number of studies. For instance the effect of dietary fatty fish and phytoestrogens on prostate cancer seems to be modified by variations in specific genes<sup>(43-45)</sup>, and polymorphisms in genes coding for antioxidative enzymes seem to influence the effect of dietary antioxidants on disease risk<sup>(46,47)</sup>.

### 2.2.1.1 Dietary recommendations

Dietary recommendations aiming to promote health on a population level have been around for over a century, with an increasing relevance for public health practice in the last 30-40 years. In 1980 came the first version of the Dietary Guidelines for Americans (DGA) that was most recently updated in 2010<sup>(48)</sup>. A decade later the WHO published dietary guidelines for prevention of chronic diseases in a global perspective<sup>(49)</sup>. Subsequently, the American Cancer Society (ACS) and the American Institute for Cancer Research (AICR) issued global recommendations for cancer prevention, lastly updated in 2012 and 2007, respectively<sup>(50,51)</sup>. Dietary recommendations are based on the most up-to-date available scientific knowledge for prevention of major chronic diseases, and are often specific for the population to which they are targeted. Some recommendations additionally include lifestyle factors other than diet such as physical activity, weight control, and smoking.

*The Nordic Nutrition Recommendations* (NNR) are guidelines jointly issued by the Nordic countries: Denmark, Finland, Iceland, Norway, and Sweden<sup>(52)</sup>. The overall goal of the NNR is to promote good health and prevent chronic diet-related diseases in the Nordic population. They include recommendations for intake of energy, nutrients,

alcohol, fiber, salt, and levels of physical activity. The recommendations are evidence-based and specific to the Nordic habits and nutritional needs, forming the basis for national dietary guidelines. The NNR was first issued in 1980 and are updated regularly, the fourth version in 2004 <sup>(52)</sup>, and the fifth edition being launched in 2013 <sup>(53)</sup>. The most recent version puts a stronger focus on the whole diet and quality of food choices compared to previous versions, in line with the aim of this thesis.

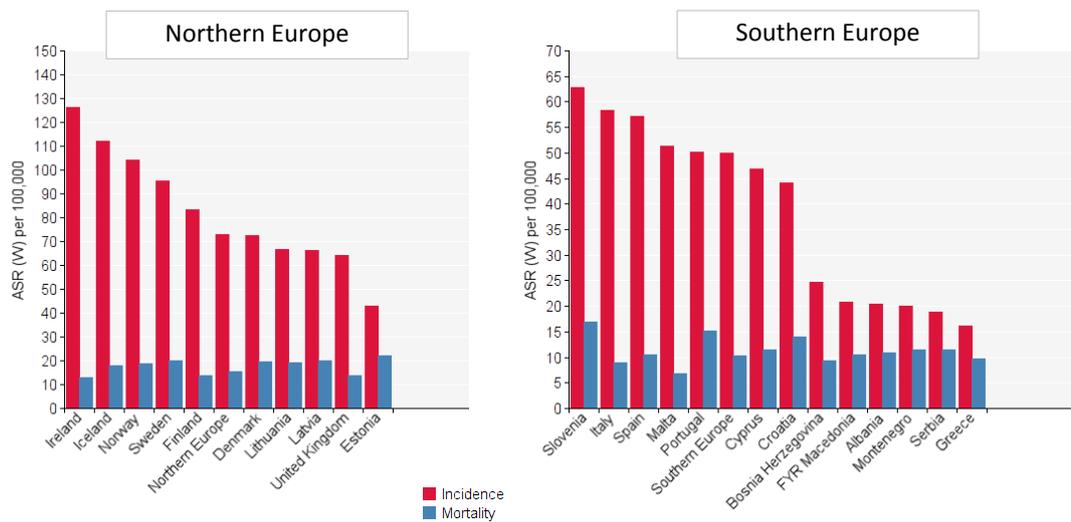
Considering the aim of the NNR, it is pertinent to evaluate their potential to reduce the risk of common chronic diseases in the Nordic population. To our knowledge, only one study has previously evaluated the NNR 2004 in relation to health outcomes, showing no association with upper respiratory tract infections <sup>(54)</sup>. Since prostate cancer is the most common cancer among Nordic men, comprising about 36 % of all male cancer in Sweden <sup>(7)</sup>, it is highly relevant to investigate the association between adherence to recommendations for the Nordic population and prostate cancer risk.

Several dietary scores have been developed to measure adherence to dietary or nutrient guidelines such as the Healthy Eating Index (HEI), <sup>(55)</sup>; the Recommended Food Score (RFS) <sup>(56)</sup>; the Diet Quality Index (DQI) <sup>(57)</sup>; the ACS cancer prevention guidelines score <sup>(58)</sup>; the 1997 AICR cancer prevention recommendations score <sup>(59)</sup>, and the Healthy Diet Indicator (HDI) that evaluates the WHO dietary recommendations <sup>(60)</sup>. Other scores are based on current knowledge regarding foods and nutrients beneficial for chronic disease prevention, such as the Alternate Healthy Eating Index (AHEI) <sup>(61)</sup>.

Many of the abovementioned diet quality scores have been associated with reduced risk or mortality of major chronic disease, as reviewed previously <sup>(62-65)</sup>. Studies on overall cancer risk in men have mostly shown no association <sup>(61,66-69)</sup>, but two studies evaluating recommendations specific for cancer prevention showed significantly lower total cancer risk <sup>(70)</sup> or mortality <sup>(58)</sup> among individuals who followed the recommendations. To our knowledge, only two studies have evaluated adherence to dietary guidelines in relation to prostate cancer <sup>(70,71)</sup>, both published within the last year and a half. Adherence to the 2005 DGA and the AHEI score was inversely associated with total prostate cancer risk among US men who had taken a recent PSA test <sup>(71)</sup>. In contrast, adherence to the cancer prevention guidelines of the World Cancer Research Fund (WCRF) and the AICR was not associated with prostate cancer in European men <sup>(70)</sup>.

### 2.2.1.2 *Mediterranean diet*

Prostate cancer incidence varies largely within the European region as illustrated in **Figure 3**. Rates are considerably lower in the Mediterranean countries compared to the Nordic countries (age-standardized incidence rates per 100,000 years in 2008: Italy 58; Spain 57; Cyprus 47; Croatia 44; Albania 21; Greece 16; and Turkey 15, compared to Iceland 112; Norway 104; Sweden 95; Finland 83; and Denmark 73) <sup>(5)</sup>. It is probable that lifestyle factors may in part explain these regional differences.



**Figure 3.** Age-standardized incidence and mortality rates for prostate cancer in Northern (left panel) and Southern (right panel) Europe, all ages. Rates are age-standardized to the world population. **Note that the scale of the rates differ between the two panels.** Source: GLOBOCAN 2008 (IARC) (15.10.2013).

An increasing pool of epidemiological evidence indicates that the “traditional” Mediterranean diet has beneficial effects on health <sup>(72)</sup>. These effects include reduced risk of all-cause mortality, cardiovascular disease and mortality, and possibly overall cancer risk and mortality <sup>(72,73)</sup>. The “traditional” Mediterranean diet refer to the culture and dietary habits of especially Crete and other parts of Greece as well as southern Italy and Spain in the 1950s and early 1960s <sup>(74)</sup>. It is characterized by high consumption of olive oil, vegetables, fruits, nuts, beans, cereals, and lean fish (by the coast), moderate consumption of alcohol (mainly wine with meals), and low intakes of dairy products and red meat.

Mediterranean diets are rich in many of the foods and nutrients that have been suggested as protective against prostate cancer, for example vegetables, nuts, beans, and a healthy balance of fatty acids <sup>(10,26,27,50,75,76)</sup>. Also, they generally contain lower amounts of red meat and milk products, foods that have been associated with an increased risk of prostate cancer <sup>(10,26)</sup>. Trichopoulou *et al.* <sup>(77)</sup> reviewed current knowledge on the individual components of the Mediterranean diet in relation to common cancers and estimated that shifting to a Mediterranean diet could prevent up to 10 % of the prostate cancer cases in Western high-income countries. However, up to recently no individual study had directly investigated the Mediterranean diet as a whole in relation to prostate cancer risk. Two investigations published within the last year did not show any association between the Mediterranean diet and prostate cancer <sup>(71,78)</sup>.

There is a variety of scores assessing adherence to the Mediterranean diet. The most widely used is the Mediterranean Diet Score (MDS) developed by Trichopoulou *et al.* in 1995 <sup>(79)</sup> and updated in 2003 <sup>(80)</sup>. The MDS and modified versions of it have been used in numerous studies of diverse health outcomes <sup>(72,81)</sup>. However, its use in non-Mediterranean populations has been questioned since cut-offs for each score component is based on the study-specific median intake, which may differ largely between populations <sup>(64)</sup>. Although the MDS has been used in several non-

Mediterranean populations <sup>(81)</sup>, very few studies <sup>(82)</sup> have evaluated its usefulness outside the Mediterranean region.

### 2.2.2 Body size and prostate cancer

Obesity has in the last decades reached epidemic levels in Sweden, the US and many other Western societies. Today about 74 % of the US adult men are overweight or obese, and 35 % obese <sup>(3)</sup>. In Swedish men, prevalence of overweight and obesity is substantially lower but still at worrying levels, around 50 and 15 %, respectively <sup>(4)</sup>. This epidemic growth may play a role in the increased incidence of prostate cancer that has been observed for the same period.

Body size is closely linked to hormonal and metabolic pathways. For instance, fat mass has an important role in hormone metabolism <sup>(21)</sup> and exposure to growth factors and other hormones in childhood and adolescence determines attained height in adulthood <sup>(83)</sup>. Since prostate cancer is a hormone-related cancer, it is likely to be linked to anthropometric factors. The literature indeed suggests a potential relationship between body size and prostate cancer; however, it appears intriguingly complex. The disease is heterogeneous in terms of its likelihood to progress, and different disease subtypes seem to be differently associated with body size, sometimes in opposite directions. Moreover, body size seems to have shifting influences across the lifespan.

Since prostate cancer has a long latency period between tumor initiation and diagnosis, often several decades, exposure early in life has supposedly more influence. Few studies have examined the relationship between childhood body size and prostate cancer; three have suggested an inverse association with childhood overweight or obesity as assessed by self-perceived relative body size <sup>(84-86)</sup>, whereas others have shown no association <sup>(87-90)</sup>. Body size in early adulthood (18-30 years) has been incoherently associated with prostate cancer <sup>(86,91-97)</sup>. Furthermore, for obesity in middle-to-late adulthood studies have suggested a dual effect on prostate cancer; a positive association with more advanced-stage or aggressive disease <sup>(18,98,99)</sup>, and an inverse association with early-stage and less aggressive cancers <sup>(98)</sup>. As regards adult weight change, two studies have indicated an increased risk of prostate cancer for men who gain weight compared to those with stable weight <sup>(97,100)</sup>, although the evidence is conflicting. Tall height has been associated with an increased risk of prostate cancer in several but not all studies <sup>(83)</sup>.

Giovanucci *et al.* <sup>(85)</sup> has previously investigated childhood and adult body size in relation to prostate cancer risk in the Health Professionals Follow-up Study, one of the largest ongoing observational studies in men. One of the aims in this thesis was to update the earlier analysis, adding 16 more years of follow-up. Overall, there is a need to clarify the relationship between anthropometric factors and prostate cancer risk.

### **3 AIMS**

The overarching aim of this doctoral thesis was to elucidate the relationship between lifestyle factors and prostate cancer risk. The first part deals with diet quality and the second part with body size across the life course. In the long run, we aim to provide scientific evidence for future prostate cancer prevention strategies, including lifestyle recommendations for men and identification of high-risk groups of men.

More specifically, we aimed to:

#### **Study I**

- Investigate the association between adherence to the Nordic Nutrition Recommendations 2004 and prostate cancer risk.
- Examine whether this potential association was modified by genetic factors known to be related to prostate cancer.

#### **Study II**

- Investigate the association between the Mediterranean Diet and prostate cancer risk.
- Examine the usefulness of the Mediterranean Diet Score in a non-Mediterranean (Swedish) study population.

#### **Study III**

- Investigate the association between body size in childhood and throughout adulthood, including adult weight change, and prostate cancer risk.

#### **Study IV**

- Update a previous investigation of childhood and adult body size in relation to prostate cancer risk.

In **Study III** and **IV** we hypothesized that body size early in life has a larger influence on prostate cancer risk than body size later in life.

## 4 METHODS

### 4.1 EPIDEMIOLOGICAL STUDY DESIGN

In observational studies, the researcher observe disease occurrence in different exposure groups, in contrast to experimental studies where the main exposure of interest is controlled by the researcher. Two common study designs among observational studies are *cohort* and *case-control* studies.

A *cohort* is a group of people sharing some defined characteristics and being followed over a certain amount of time. During the follow-up period the incidence of disease is measured i.e. the number of events. A cohort study is characterized by the population being “at risk” of getting the disease; thus everyone must be free of the disease under study at the start of the follow-up. All members of the cohort contribute with individual *person-time* during the follow-up period. With a disease such as prostate cancer, any individual being diagnosed with prostate cancer is no longer at risk, i.e. no longer contributes with person-time at risk, and is therefore *censored* at time of diagnosis. Cohort members are also censored if they die from other causes or have been lost to follow-up. Typically, we talk about the *exposed* and *unexposed* cohort, and we compare the disease incidence between the two groups. Cohort studies are useful when the disease is common, or when the objective is to study several diseases and/or exposures.

A *case-control study* aims to do what the cohort study does, but in a more cost- and time-efficient way. Cases are identified from a hypothetical *target population*, and controls serve as a representative sample of the same population. The main purpose of the control group is to mirror the distribution of the exposure and other covariates in the target population. Therefore they need to be sampled independently of exposure status. In a *population-based* study controls are sampled directly from the same target population from which the cases were drawn i.e. through a population registry. Controls are often *matched* to cases by one or several factors to reduce confounding by these factors without losing power when sample size is small. Matching can be either *pairwise* i.e. individual-to-individual or *frequency-based* i.e. the distribution of the factor(s) among the controls reflects the distribution among the cases. Case-control studies are specific to one outcome, and are particularly useful when the outcome is rare.

In observational studies, information about exposure and other covariates can be collected either *prospectively* or *retrospectively*. Prospective data is collected *prior* to the disease, whereas retrospective data is collected *after* the disease has occurred. Prospective data is often preferred as it is less likely to be influenced by the disease. Case-control studies typically have retrospective data, although both types of data can occur in both cohort and case-control studies.

In this thesis, **Study I-III** are based on *retrospective* data from a *case-control study*, whereas **Study IV** is based on data from a *prospective cohort study*. Below is an overview of the study populations and methods used for analysis.

## 4.2 STUDY POPULATIONS

### 4.2.1 The Cancer of the Prostate in Sweden (CAPS)

The Cancer of the Prostate in Sweden (CAPS) study is a large population-based case-control study. In the period from January 2001 to September 2002, incident prostate cancer cases were identified from four of the six regional cancer registries, covering the health care regions of northern, central, Stockholm and southeastern Sweden; these regions included about 67 % of Sweden's entire population at the time. Cases with a histologically confirmed prostate cancer were informed about the study and invited to participate through their treating physician. The age span of the cases was 35-79 years at enrolment.

Controls were randomly selected from the Swedish Population Registry using the unique personal identification number of all Swedish citizens. Controls were frequency-matched to the expected age distribution (5-year intervals) and geographical residence of the cases; selection was performed every 6 months and invitations to participate in the study were sent out about once a month, except July and August, to reflect the continuous enrolment of cases. The controls received an invitation letter by mail with the same information about the study as the cases.

Cases and controls were mailed a self-administered questionnaire with questions on lifestyle and health as described in detail in section 4.3. They were also sent a blood draw kit for genetic analysis. Cases received the questionnaire and blood draw kit on average 5 months after diagnosis, and controls about 3-4 weeks after they had been invited to the study. To obtain a higher response rate, cases and controls that did not respond to the initial invitation were recontacted three times: by a follow-up letter after 3-4 weeks, a new questionnaire and blood draw kit after 6-8 weeks, and a phone call after 12 weeks. In total 1895 cases and 1694 controls were eligible for the study; 1499 (79%) of the cases and 1130 (67%) of the controls completed the questionnaire, and the corresponding numbers for both completing the questionnaire and donating blood was 1352 (71%) cases and 858 (51%) controls.

A more detailed description of the recruitment process in CAPS has been published previously <sup>(101)</sup>. The study was approved by the ethics committees at Karolinska Institutet and Umeå University. Written informed consent was obtained from all participants at study enrolment.

An overview of all exclusions in the CAPS study is presented in **Figure 4**. Participants were excluded if they had incomplete questionnaire data ( $n=67$ ). The remaining 1,499 cases and 1,118 controls were included in analyses of **Study III**. In **Study I-II**, participants with unreasonably high ( $>21,000$  kJ/d) or low ( $<3300$  kJ/d) energy intakes were excluded ( $n=27$ ), leaving 1,482 cases and 1,108 controls in final analyses of **Study II**. In **Study I**, we further excluded participants with partly missing data for physical activity ( $n=264$ ), leaving in total 1,386 cases and 940 controls for analyses. Furthermore, some cases lacked clinical information and were excluded from analyses of disease subtypes ( $n=83$  in **Study I**,  $n=87$  in **Study II**,  $n=80$  in **Study III**).

## Cancer of the Prostate in Sweden (CAPS)

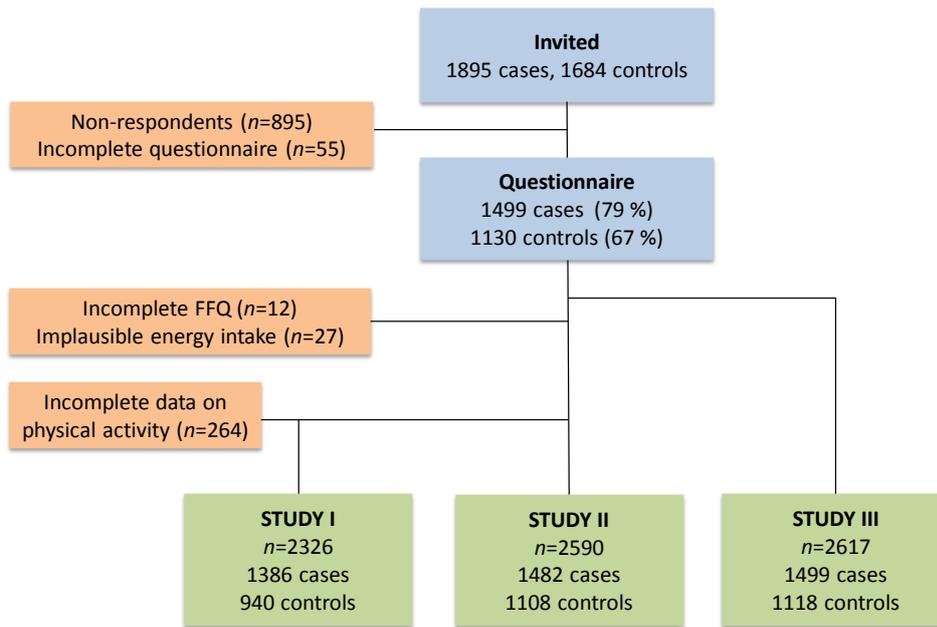


Figure 4. Flow chart of subjects and exclusions in the CAPS study (Study I-III).

## Health Professionals Follow-up Study (HPFS)

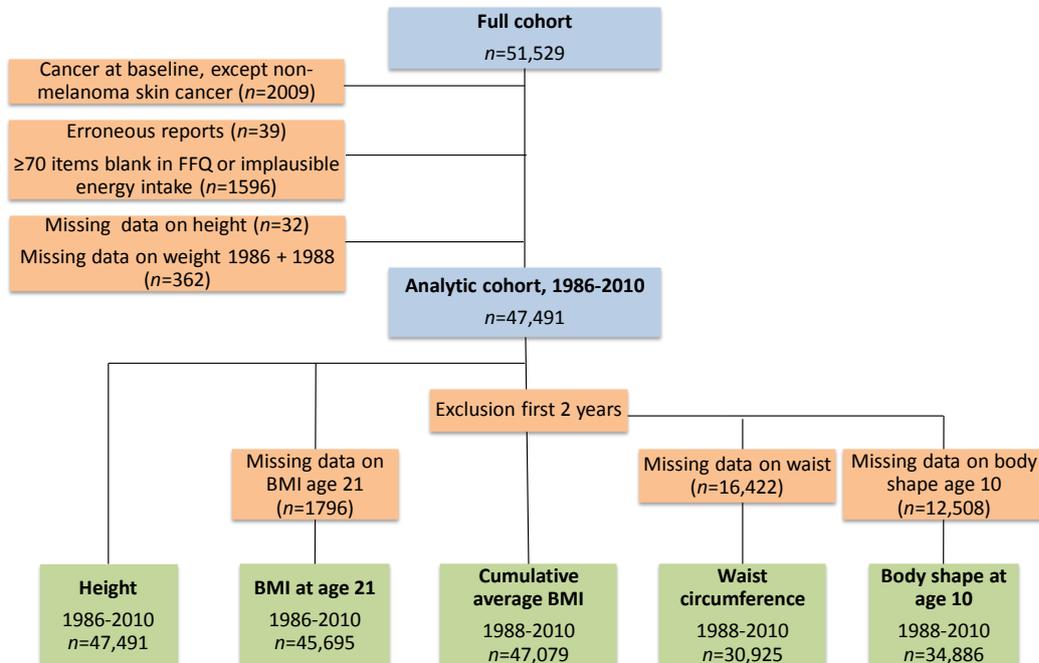


Figure 5. Flow chart of subjects and exclusions/missing values in the HPFS study (Study IV).

## 4.2.2 The Health Professionals Follow-up Study (HPFS)

The Health Professionals Follow-up Study (HPFS) is an ongoing prospective cohort study that started in 1986, with the overall purpose of investigating the relationship between nutritional factors and chronic diseases such as cancer and cardiovascular disease. The study design has been described in detail elsewhere <sup>(102)</sup>. At baseline, 51,529 US men in health occupations aged 40-75 years completed a self-administered questionnaire on demographic, lifestyle, and health-related factors, including medical diagnoses. Participants have been sent follow-up questionnaires every two years. The average response rate for the follow-up questionnaires was above 94 %. The HPFS study and use of the data for analysis is continually approved by the Institutional Review Board of the Harvard School of Public Health.

As illustrated in **Figure 5**, exclusions of participants in **Study IV** were based on the following criteria: erroneous reports ( $n=39$ );  $\geq 70$  items blank in the 1986 dietary questionnaire or with unreasonably high ( $>17,600$  kJ/d) or low ( $<3350$  kJ/d) energy intakes ( $n=1596$ ) <sup>(103)</sup>; cancer other than non-melanoma skin cancer at baseline ( $n=2009$ ); missing information on height ( $n=32$ ); or missing information on weight in both 1986 and 1988 ( $n=362$ ). After these exclusions, 47,491 men remained for analyses. Childhood body size data was collected in 1988, therefore the 1988 questionnaire was used as baseline. We excluded the first two years of follow-up in analyses on cumulative average BMI and waist circumference to reduce reverse causality due to disease-related weight loss. Because of missing information on some exposure variables, the number of men included in analyses was further reduced.

## 4.3 ASSESSMENT OF EXPOSURES AND COVARIATES

### 4.3.1 Dietary intake

Dietary intake in both the CAPS and the HPFS study was assessed by semi-quantitative Food Frequency Questionnaires (FFQs). Briefly, an *FFQ* consists of a list of foods and beverages, each with a number of frequency options so that respondents can report how often they have consumed each specific item during a specified time period. Thus, an FFQ measures the “usual” dietary intake. A *semi-quantitative* FFQ estimates portion size by using e.g. common units or pictures of portion sizes.

The FFQ used in the CAPS questionnaire assessed intake during the previous year of 106 foods and beverages, with eight categories of consumption frequency ranging from “never” to “three or more times per day”; it also included additional questions on dietary fat and supplements <sup>(104-107)</sup>. Portion sizes for the most commonly consumed items such as bread, milk, cheese, and coffee as well as for alcohol were assessed by commonly used units (e.g. glasses of milk, slices of cheese, cl of alcohol). Aggregated codes corresponding to 253 food and beverage items were used for calculation of energy and nutrient intakes. The calculation was performed by linking the reported dietary intake from the questionnaire to the energy and nutrient content of roughly 1500 foods, dishes, and beverages comprised in the Swedish National Food Administration database <sup>(108)</sup>. The questions on type of cooking fat and supplements were not included in the nutrient calculations.

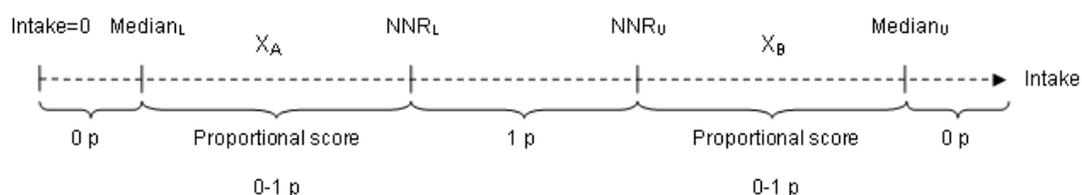
In the HPFS, dietary intake during the previous year was assessed at baseline and subsequently every four years in follow-up questionnaires. The FFQ includes 131 foods and beverages with nine categories of consumption frequency ranging from “never or less than once per month” to “six or more times per day”<sup>(109)</sup>. It also includes additional questions on supplements and open-ended questions for some items e.g. margarines, cooking/baking fat, breakfast cereals, and multivitamin supplements. Portion size was assessed by commonly used units (e.g. a slice of bread, ½ cup of beans) or portion sizes for some items. Daily energy and nutrient intakes were calculated based on a continuously updated food composition data base by multiplying the nutrient content for each serving by the reported frequency of consumption for that food and then summing across all foods and supplements<sup>(109)</sup>.

### 4.3.2 Diet quality scores

We used two different dietary scores to assess diet quality in **Study I** and **II**. Dietary scores or indexes are defined *a priori*, based on either dietary recommendations, current knowledge regarding chronic disease prevention, or a “healthy” dietary pattern such as the Mediterranean diet. The scores can be based on nutrients, food items, or a combination of both. Typically, individuals are ranked according to their intake levels for a certain number of score components, which together adds up to a total score. A high score normally implies a high-quality diet, and a low score a low-quality diet.

#### 4.3.2.1 The Nordic Nutrition Recommendations (NNR) score

To measure adherence to the NNR 2004 in **Study I** we created a score based on nine main variables: *fat* (sum of total, saturated, monounsaturated, and polyunsaturated fat), *carbohydrates*, *protein*, *fiber*, *vitamins*, *minerals*, *salt* (sodium), *alcohol* (ethanol), and *physical activity*. Intakes of vitamins, minerals, and fiber were energy-adjusted by the residual method, adding a constant equivalent to the predicted nutrient intake at an energy intake of 10,600 kJ. Intakes of macronutrients were in percentage of energy, as consistent with the NNR. Each individual dietary component of the score was graded on a continuous scale from 0 to 1 according to **Figure 6**: intake within the recommendation was accredited 1 point (perfect adherence); intake outside the extreme cut-points was accredited 0 points (non-adherence); for intermediate adherence we calculated a proportional score that approaches 1 when intake is close to the NNR and 0 when intake is far from the NNR.



**Figure 6.** Illustration of the calculation of adherence score for each dietary component of the NNR. The dashed line represents the intake range.  $NNR_L$  and  $NNR_U$  are the lower and upper recommendation cut-off points defined in the NNR; for intakes within these levels, 1 point was accredited (perfect adherence).  $Median_L$  and  $Median_U$  are the lower and upper extreme cut-off points, defined as the median among the ten lowest and ten highest intakes in the study population; for intakes outside the median cut-off points, 0 points were accredited (non-adherence). A proportional score between 0 and 1 was calculated for intakes between the NNR and the Median cut-off points (intermediate adherence) according to the formulas a) and b) below.  $X_A$  and  $X_B$  represent actual intake levels within the proportional score range.

For lower limits, the score varies from 0 to 1:  

$$\text{Proportional score} = (X_A - \text{Median}_L) / (\text{NNR}_L - \text{Median}_L) \quad (1)$$

For upper limits, the score varies from 1 to 0:  

$$\text{Proportional score} = 1 - (X_B - \text{NNR}_U) / (\text{Median}_U - \text{NNR}_U) \quad (2)$$

The NNR 2004 recommends at least 30 min/d of physical activity at least moderate intensity, and preferably >60 min/d. However, since activity levels were high in the study population, the cut-off points for adherence were set higher than the recommendation to obtain a sufficient number of subjects in the low adherence group. Perfect adherence (1 point) was set at  $\geq 60$  min/d and non-adherence (0 points) at  $\leq 30$  min/d; for intermediate adherence we calculated a proportional score by equation (1) in **Figure 6**, where  $\text{Median}_L=30$  and  $\text{NNR}_L=60$ .

To sum up individual recommendations into grouped variables (fat, carbohydrates, vitamins, and minerals), the individual scores were summed and divided by the number of individual recommendations in the variable. Finally, the nine main variables were summed to a total NNR score, 0-9 points, with each of the main variables having equal weight. The total score was categorized as low ( $\leq 6.7$  points), medium (6.7-7.6 points), and high adherence ( $> 7.6$  points); these cut-off points were chosen to obtain enough individuals in the extreme groups without too narrow intervals.

#### 4.3.2.2 The Mediterranean Diet Score (MDS)

To assess adherence to the Mediterranean diet in **Study II** we used a version of the Mediterranean Diet Score (MDS) adapted for use in non-Mediterranean populations<sup>(110,111)</sup>. The original score includes nine components: intake of *vegetables, fruits and nuts, legumes, cereals, fish, meat, dairy products, alcohol*, and the *ratio of monounsaturated to saturated fat*. The modified version includes both *mono- and polyunsaturated fat* in the numerator of the fat ratio due to the appreciably lower intake of monounsaturated fat outside the Mediterranean region.

As cut-off between low and high intake for each component, we used the median intake in g/d in the control group for our main score, denoted as *MDS-gram*. Questionnaire intake was converted to intakes in g/d using standard portion sizes<sup>(112)</sup>, and all intakes were energy-adjusted by dividing the intake of the food item by the individual's total energy intake and multiplying by 10,460 kJ (~2500 kcal)<sup>(79)</sup>. For beneficial components (vegetables, fruits and nuts, legumes, cereals, fish, and mono- and polyunsaturated to saturated (MP:S) fat ratio), 1 point was given to intakes at or above the median and 0 points otherwise. For meat and dairy products, 1 point was given for intakes below the median and 0 points otherwise. For alcohol 1 point was given for intake above zero and below the median, and 0 points otherwise. The scores of all nine components were summed up to a total score of 0-9 points, which we categorized into low (0-3 points), medium (4-5 points), and high (6-9 points) adherence to the Mediterranean diet based on approximate distribution of tertiles among the controls.

To evaluate the usefulness of the MDS we created four variants of our main score. An overview of all five score variants is given in **Table 1**. Three variants were based on the same components as *MDS-gram* but with other cut-off points between low and high intakes. *MDS-serv*, was based on study-specific median intakes in servings/week

instead of g/d. In MDS-cent, the study-specific 25<sup>th</sup> or 75<sup>th</sup> centiles of intake in g/d were used; the cut-off point for each component was chosen so as to approach the median intakes of a Greek reference population<sup>(80)</sup>, while maintaining enough subjects in the extreme groups. The 25<sup>th</sup> centile was used for intake of legumes, cereals, fish, milk, and meat, and the 75<sup>th</sup> centile for the MP:S fat ratio and intake of vegetables, fruits/nuts, and alcohol. In our fourth score variant, MDS-greek, we used the median intakes of the abovementioned Greek population as cut-off points, with the exception of vegetables and fruits/nuts for which the 90<sup>th</sup> centile among the controls was used since very few of the Swedish men reached the Greek intake levels. Finally, our fifth score variant MDS-alt was based on slightly alternative components, focusing on the most traditional and health-beneficial components of the Mediterranean diet. The fat ratio was replaced by olive oil use, cereals by whole grains, meat by red/processed meat, ethanol by red wine, and we separated fruits and nuts into two groups; thus the total score summed up to 10 points. Similar MDS variants have been proposed by others<sup>(113-116)</sup>. The study-specific median intakes in g/d were used as cut-off points for MDS-alt, similar to MDS-gram. Categorization of the score variants into low, medium, and high adherence were as follows: MDS-serv and MDS-cent were categorized as MDS-gram; MDS-greek 0-2 points, 3-4 points, and 5-9 points; MDS-alt 0-3 points, 4-5 points, and 6-10 points.

**Table 1.** Description of the Mediterranean Diet Score (MDS) variants

	MDS-gram	MDS-serv	MDS-cent	MDS-greek	MDS-alt
Cut-off values	Median in CAPS	Median in CAPS	25 <sup>th</sup> / 75 <sup>th</sup> centile <sup>a</sup> in CAPS	Median in Greek pop <sup>b</sup>	Median in CAPS
Unit	g/d	serv/w	g/d	g/d	g/d
MP:S fat ratio	X	X	X	X	Olive oil use
Vegetables	X	X	X	X	X
Fruits	+nuts/ seeds	+nuts/ seeds	+nuts/ seeds	+nuts/ seeds	X
Nuts	X	X	X	X	X
Legumes	X	X	X	X	X
Cereals	X	X	X	X	Whole grains
Fish	X	X	X	X	X
Dairy	X	X	X	X	X
Meat/meat products	X	X	X	X	Red/processed meat
Ethanol	>0,<median	>0,<median	>0,<75th centile	10-<50 g/d	Red wine: >0,<median <sup>c</sup>
<b>Total score (points)</b>	0-9	0-9	0-9	0-9	0-10

MP:S, mono- and polyunsaturated to saturated fat ratio. Vegetables also include tomato juice, ketchup and root vegetables, except potatoes. Fish also includes caviar and seafood. Meat also includes poultry.

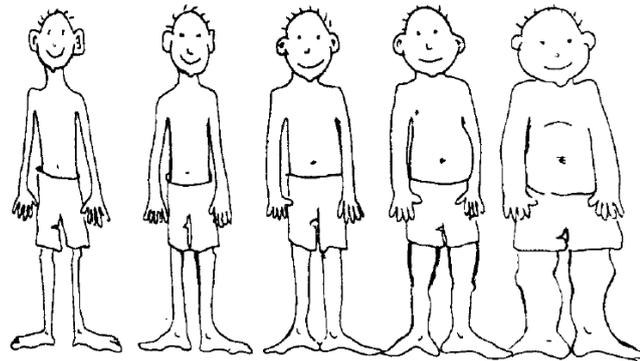
<sup>a</sup> The 25<sup>th</sup> centile was used for intake of legumes, cereals, fish, milk, and meat, and the 75<sup>th</sup> centile for the MP:S fat ratio and intake of vegetables, fruits/nuts, and ethanol.

<sup>b</sup> Trichopoulou et al.<sup>(80)</sup>

<sup>c</sup> The 75<sup>th</sup> centile was used as cut-off value since the median intake was zero.

### 4.3.3 Anthropometric measures

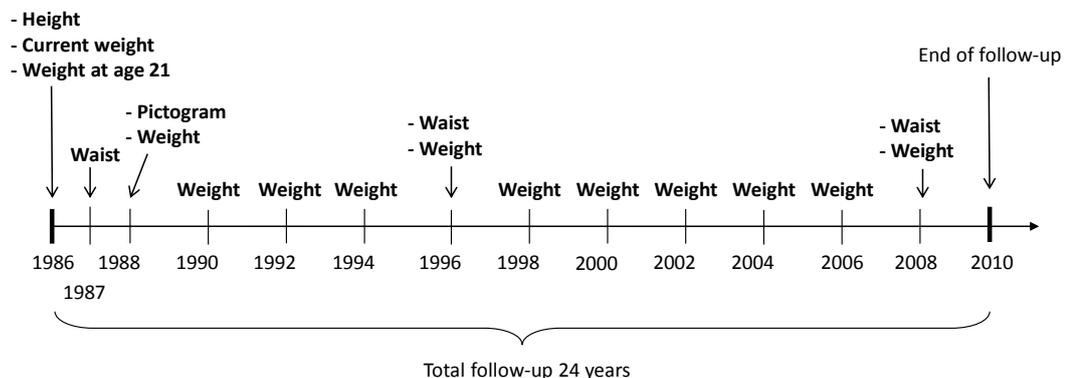
Participants in the CAPS study self-reported their current weight and height as well as their recalled weight at age 20, 30, 40, 50, 60, 65, and 70, or up to current age. In addition, they were asked which silhouette drawing best represented their body shape at age 10 according to the pictogram in **Figure 7**. Height was categorized based on the quartile distribution among controls. Body Mass Index (BMI) at each specific age and as the mean of age 20-70 was calculated by dividing weight by height squared ( $\text{kg}/\text{m}^2$ ). BMI was categorized in four groups:  $<22.5$  (reference), 22.5-25, 25-27.5, and  $\geq 27.5$ . Body shape at age 10 was categorized in four groups, combining silhouette 4 and 5 due to low power in the most obese group ( $n=29$ ) and using silhouette 3 as reference group.



**Figure 7.** Pictogram with silhouette drawings used for estimation of recalled body shape at age 10 in the Cancer of the Prostate in Sweden (CAPS) study.

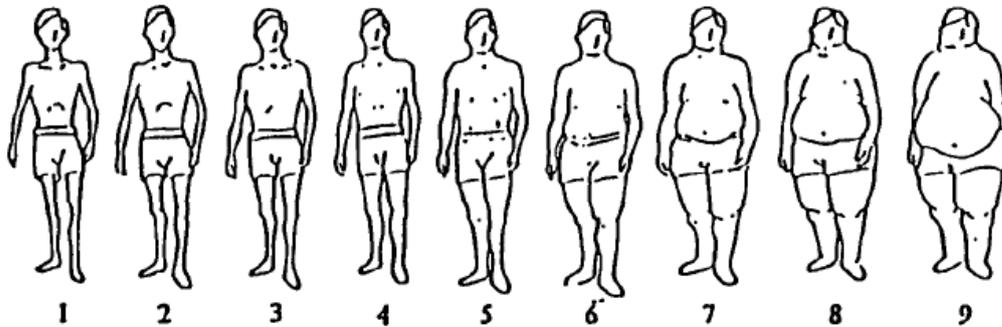
In the HPFS, current height and weight as well as recalled weight at age 21 was self-reported at baseline in 1986, and current weight has been updated in each biennial follow-up questionnaire. We calculated BMI at age 21 and the cumulative average BMI at each follow-up; if weight was missing at one follow-up we used data from the previous questionnaire cycle. Waist circumference was assessed in an additional self-administered questionnaire in 1987, where participants were provided a tape measure and were asked to measure their waist<sup>(117)</sup>. Measures of waist circumference were also collected in the 1996 and 2008 follow-up questionnaires; in the analyses we used the cumulative average of the measures in 1987 and 1996. **Figure 8** gives an overview of anthropometric measures assessed at baseline and in the follow-up questionnaires.

#### Health Professionals Follow-up Study (HPFS)



**Figure 8.** Assessment of anthropometric factors in the HPFS study.

The 1988 questionnaire additionally included a pictogram with silhouette drawings of nine sizes ranging from very thin to obese<sup>(118)</sup>, as shown in **Figure 9**. Participants were asked which pictogram best depicted their body shape at age 5, 10, 20, 30, 40, and current age, respectively. Only body shape at age 10 was included in analyses since the prior study showed strongest association with prostate cancer for this variable<sup>(85)</sup> and also to achieve comparability with the body shape measure in the CAPS study.



**Figure 9.** Silhouette drawings used in the Health Professionals Follow-up Study (HPFS) to assess body shape at age 5, 10, 20, 30, 40, and current age. Reproduced from Stunkard et al.<sup>(118)</sup> with permission from Wolters Kluwer/Lippincott Williams & Wilkins.

The height variable in HPFS was categorized based on approximate quintiles. BMI at age 21 was categorized in five groups: <20; 20-21.9 (reference); 22-23.9; 24-25.9;  $\geq 26$  kg/m<sup>2</sup>; and cumulative average BMI was categorized in six groups since the distribution differed from the young adult BMI: <21; 21-22.9 (reference); 23-24.9; 25-27.5; 27.5-29.9;  $\geq 30$  kg/m<sup>2</sup>. Waist circumference was categorized in quintiles. Body shape at age 10 was divided in six groups, combining silhouette 6-9 since few individuals were in these groups, and silhouette 2 as reference group.

#### 4.3.4 Other health-related factors

The CAPS questionnaire included questions on known and potential risk factors for prostate cancer such as education, occupation, marital status, smoking history, other tobacco use, physical activity, diagnosis of diabetes, family history of prostate cancer, or family history of other cancers. Participants reporting at least one family member with prostate cancer were recontacted for more detailed information, and prostate cancers in first-, second-, and if possible also third-degree relatives were verified through medical records or cancer registries.

Physical activity was assessed in CAPS as occupational activity, walking/bicycling, exercise, and household/leisure-time activities at age 15, 30, 50, and 65 and age at study entry, respectively, as described in detail elsewhere<sup>(119)</sup>. In **Study I**, physical activity was included as a component in the score measuring adherence to the NNR. Since the recommendation for activity is given in minutes per day, we calculated total minutes of daily activity of at least moderate intensity using the most recent age category that preceded current age at study inclusion, as further described in **Paper I**. In **Study II** and **III** physical activity was included as a potential confounder, and we calculated metabolic equivalents (METs) in hours per day by multiplying the reported

time for each activity by the assigned MET value <sup>(120)</sup>; we only included activities of moderate or vigorous activity (MET  $\geq 3$ ) <sup>(121)</sup>.

The HPFS baseline questionnaire included information on potential confounders such as age, ethnicity, marital status, work status, diabetes, smoking history, and physical activity. Information on diabetes, smoking, and physical activity were updated in each biennial follow-up questionnaire. For physical activity, we used only vigorous activity (MET  $\geq 6$ ), expressed as MET-hrs/week. History of prostate cancer among first-degree relatives was self-reported in the 1990, 1992, and 1996 questionnaires. In 1994, participants were asked whether they had had a PSA test, and subsequently PSA screening during the prior 2-year period was assessed in each follow-up questionnaire.

### **4.3.5 Genetic factors (Study I)**

All participants in the CAPS study were asked to draw blood samples at the nearest health clinic or hospital. A detailed description of the blood sampling procedure and subsequent genetic analyses has been given elsewhere <sup>(101)</sup>. To date, over 50 single-nucleotide polymorphisms (SNPs) have been associated with prostate cancer risk <sup>(15)</sup>. Most SNPs have two variants i.e. two alleles. An accumulation of disease risk has been shown with increasing number of risk alleles i.e. alleles associated with prostate cancer <sup>(17,122)</sup>. Therefore, we used a polygenic risk score to investigate if the association between the NNR and prostate cancer in **Study I** was modified by genetic factors. The score included 34 SNPs associated with prostate cancer. We calculated the genetic risk score as the number of risk alleles in each individual divided by the total number of alleles successfully analyzed in that individual. The score ranged from 0 to 1 and was categorized as low, medium, and high genetic risk based on approximate tertile distribution among the controls.

## **4.4 CLASSIFICATION OF OUTCOME**

### **4.4.1 Clinical data and follow-up**

#### *4.4.1.1 The CAPS study*

A criterion to be included as a case in CAPS was a pathologically or cytologically confirmed adenocarcinoma of the prostate (ICD-10 code: C61). Clinical information was retrieved through linkage to the National Prostate Cancer Registry for 95 % of the cases; these data included TNM (tumor-node-metastasis) stage, Gleason score, and PSA level at diagnosis. Prostate-cancer specific death was assessed through the Swedish Cause of Death Registry with follow-up through December 2010.

#### *4.4.1.2 The HPFS study*

In the HPFS study, incident prostate cancer cases were firstly identified through self-reports in the follow-up questionnaires or by contact with next-of-kin if the subject had died. After obtaining written permission from the patient to go through medical records and pathology reports, diagnosis was clinically confirmed in more than 90 % of the cases; the remaining self-reported diagnoses were included in the analysis of total prostate cancer as the accuracy of the self-reports was over 98 %. Clinical information at diagnosis (TNM stage, Gleason, PSA) was retrieved through questionnaires, medical

records, and pathology reports. Progression of diagnosed tumors was followed-up through biennial questionnaires starting in the year 2000. Deaths were identified from family reports and the National Death Index in the US, which in combination cover about 98 % of all deaths in the HPFS cohort. Cause of death was determined based on all available information. In our study, participants were followed-up for prostate cancer diagnosis, tumor progression, and mortality through January 2010.

#### 4.4.2 Definition of prostate cancer subtypes

In addition to studying risk of total prostate cancer as outcome, we analyzed different prognostic subtypes of prostate cancer. A prostatic tumor is characterized in terms of stage and grade at diagnosis. According to the TNM classification system for tumor stage, T1/T2 tumors are confined within the prostate; T3/T4 tumors have invaded the surrounding tissue; N+ tumors have formed lymph node metastases; and M+ tumors have formed bone metastases. Tumor differentiation grade or aggressiveness is defined by the Gleason score: low-grade tumors have Gleason score 2-6; intermediate-grade tumors have Gleason score 7; and high-grade tumors have Gleason score 8-10. PSA levels at diagnosis are often used together with stage and grade to get a more comprehensive picture of the severity of the tumor.

In **Study I**, *advanced* cases were defined as those meeting any of the following criteria at diagnosis: T3/T4, N+, M+, Gleason score 8-10, or PSA  $\geq$ 100 ng/ml; *localized* cases did not meet any of the above criteria. In **Study II**, the same definition was used for advanced cases, and localized cases were defined as T1/T2, N0/X, M0/X, Gleason score 2-6, and PSA  $<$ 20 ng/ml at diagnosis. Cases with Gleason score 7 were excluded due to the varying progression patterns seen for Gleason 3+4 versus 4+3<sup>(123)</sup>, and only cases with PSA levels  $<$ 20 ng/ml were included due to the uncertainty in using PSA values as a prognostic definition factor. In **Study III** we used a similar definition as above but with the terms *low-intermediate-risk* (T1/T2, N0/X, M0/X, Gleason score 2-7, and PSA  $<$ 20 ng/ml at diagnosis) and *high-risk* (T3/T4, N+, M+, Gleason score 8-10, or PSA  $\geq$ 20 ng/ml at diagnosis) cases instead, referring to the risk of tumor progression. These definitions are in accordance with the guidelines of the European Association of Urology<sup>(124)</sup>. In sub-group analyses, we further separated *low-risk* (Gleason score 2-6, PSA  $<$ 10 ng/ml) and *intermediate-risk* (Gleason score 7, PSA 10- $<$ 20 ng/ml) cases. In Study III, an additional outcome was fatal prostate cancer, defined as cases who died from prostate cancer during follow-up. The slightly different definitions of disease subtypes across **Study I-III** partly reflect overall changes in the definitions and practices during the last decade. The term localized/advanced has commonly been used also when differentiation grade and PSA is included in the definition, even though clinical *stage* in fact only involves the TNM classification.

In **Study IV**, we classified prostate cancer subtypes by stage and grade separately, as well as by metastases and/or mortality. T1a cases were excluded from all analyses since they tend to be benign and are prone to detection bias. *Lethal* cases included those who died of prostate cancer or had distant metastases during follow-up. *Fatal* cases, as a subgroup of lethal, were defined by death due to prostate cancer. *Advanced* cases were those with stage T3b/T4, N+, or M+ at diagnosis, or were lethal during follow-up. *Non-advanced* (localized) cases included stage T1/T2, N0/X, and M0/X at diagnosis, and

were not lethal during follow-up. We further defined cases by aggressiveness as either *low-grade* (Gleason score 2-6), *intermediate-grade* (Gleason score 7), or *high-grade* (Gleason score 8-10).

## 4.5 STATISTICAL ANALYSIS

In epidemiological studies we typically want to estimate the *effect* of a specific exposure on an outcome. A point estimate quantifies the strength and direction of an association, whereas the confidence interval (CI) provides a measure of the reliability of the point estimate. A 95 % CI means that if the same study was repeated many times, and assuming that variation is only random, the “true” value would be within this interval 95 % of the times. The *p* value tests the null hypothesis that there is no difference between exposure groups e.g. no association between exposure and outcome, based on an arbitrary level of significance being commonly set at  $p < 0.05$ . However, a statistical test showing a significant association at any arbitrary level of significance is obviously not enough to claim that there is a “true” association. The *power* of a statistical test is the probability to find a statistically significant difference when there is a true difference, and power is mainly affected by sample size. However, the estimates may also be biased by e.g. confounding. The use of statistical models is an efficient way not only to obtain estimates, but also to assess the variability of the data and control for multiple confounding factors simultaneously.

### 4.5.1 Descriptive analyses

Characteristics of cases and controls in **Study I-III** were compared by the Wilcoxon-Mann-Whitney test for continuous variables and the  $\chi^2$  test for categorical variables. In **Study I-II**, we estimated correlation coefficients between each dietary score and its components as well as between score components, and in **Study III-IV** we estimated the correlation between all anthropometric measures.

### 4.5.2 Measures of effect

In a cohort study we can estimate the *incidence rate* of a disease (or other outcome). The rate is the number of new cases per unit of person-time at risk i.e. the total time at risk for all individuals being followed. For example, in Sweden the age-adjusted incidence rate of prostate cancer is 104 new cases per 100,000 person-years. The *incidence rate ratio* is obtained by taking the ratio of the incidence rates in the exposed and unexposed group. The *hazard ratio (HR)* is another term for the incidence rate ratio in time-to-event analyses, as further described in Section 4.5.5. The rate/hazard ratio is a measure of the *relative risk (RR)*.

$$RR = \frac{\text{incidence rate among exposed}}{\text{incidence rate among unexposed}}$$

In a case-control study, we cannot estimate the incidence rate since we cannot measure person-time. Instead we can estimate the *odds* of the outcome in relation to exposure, since the odds of being exposed if having the disease are the same as the odds of having the disease if exposed. By taking the odds of being a case among the

exposed divided by the odds of being a case among the unexposed we obtain the *odds ratio (OR)*.

$$OR = \frac{\text{odds of being a case among exposed}}{\text{odds of being a case among unexposed}}$$

An OR in a case-control study can be interpreted in different ways depending on how the controls were sampled. In the CAPS study, controls were selected randomly from the same target population from which the cases were drawn and continuously during the period that the cases occurred. Under the rare disease assumption (prevalence of prostate cancer in Sweden is about 2 % <sup>(7)</sup>), we can then interpret the OR as an approximation of the RR.

Henceforth, the term *risk* will be used to refer to the relative risk in this thesis.

### 4.5.3 Modeling exposure-disease associations

*Regression analysis* is a general statistical tool for estimating the relationship between a dependent variable (outcome) and one or more independent variables (exposures). The fundamental principle is that based on the observed data points, a regression line is drawn representing the average value of the dependent variable given the values of the independent variable(s). The model is often used to predict the probability of the outcome *conditional* on the values of the independent variables based on some specified function.

The simplest form of regression is the *linear regression*, in which a linear function is used to predict estimates of a linear relationship between a continuous dependent variable and some independent variables, which can be either continuous or categorical. However, with a binary outcome (case vs. non-case) the risk estimates in a regression model can take on values that are not meaningful, e.g. negative rates. Therefore the dependent variable needs to be transformed on some scale to produce meaningful estimates. A common type is the *logistic* transformation, which uses the natural logarithm of the dependent variable, the *logit*, to fit in a linear regression. A *logistic regression* model estimates the logarithm of the odds ratio i.e. the log-odds of being a case among the exposed compared to the log-odds of being a case among the unexposed. *Multivariate* regression models include several independent variables, a major advantage being that they enable control for multiple confounding variables simultaneously.

### 4.5.4 Unconditional logistic regression (Study I-III)

Frequency-matching in case-control studies may introduce selection bias. The logistic regression model is then *unconditional* on the matching factors, therefore we need to adjust for them to remove any selection bias that may have been introduced in the matching process.

In **Study I-III** we used unconditional logistic regression to estimate ORs with 95 % CIs. The matching factors age and region were included in all models (simple models included only these variables). Multivariate-adjusted models in **Study I** and **II** included

education, smoking, BMI, total energy intake, and family history of prostate cancer. In **Study II** we additionally adjusted for physical activity and diabetes. In **Study III** we adjusted for family history of prostate cancer (with height and weight change as exposures), physical activity and age at the first reported weight (weight change as exposure), and time span between the first and last recalled weight (mean adult BMI and weight change as exposures).

We modeled the exposures as categorical variables as defined in Section 4.3. To test for dose-response trends we also modeled them continuously by assessing the linear effect of a 1-point increment in the dietary scores in **Study I** and **II**, and a 5-unit increment of adult height, BMI, and weight change in **Study III**. Statistical significance was set at  $p < 0.05$  (two-sided) in all analyses.

#### 4.5.5 Cox proportional hazards regression (Study IV)

Logistic regression models can only be used when all individuals are followed for the same amount of time. In a longitudinal study where individuals contribute with different amounts of person-time, we therefore need other modeling options that take the time aspect into account.

*Time-to-event analyses* (or *survival analyses*) are useful to assess the effect of an exposure on the outcome per time unit i.e. event rates. In analyses of risk, as in the current thesis work, the measure of interest is the incidence rate, i.e. the *hazard rate*. The *hazard ratio* compares the hazard rates among the exposed to the unexposed. A common model in time-to-event analyses is the *Cox proportional hazards regression*, which allows the rates to vary over time. The underlying time scale is a central concept and is often defined as age or time since study entry. The basic assumption in Cox models is that hazard rates are *proportional* to the baseline hazard i.e. the ratio between two hazards is constant over the time scale. In other words, the effect of the exposure is assumed to be constant over time. This assumption always needs to be tested. With *time-varying effects* i.e. when the ratio is not constant, the proportional assumption is violated, in which case we need to take the interaction with time into account in the regression models. Similar to the logistic regression, the effect in time-to-event analyses is estimated on the logarithmic scale.

In **Study IV** we used Cox proportional hazards regression to estimate hazard ratios as a measure of the relative risk with 95 % CIs. Time at risk was calculated in person-years and the underlying time scale was calendar time in 2-year intervals. Person-time was calculated from the month of return of the baseline questionnaire until the month of prostate cancer diagnosis, month of death from any cause, or end of follow-up (January 31, 2010), whichever came first. To reduce the risk of reverse causality due to disease-related weight loss, we excluded the first two years of follow-up in analyses on cumulative average BMI and waist circumference.

The assumption of proportional hazards over time and age was tested by the likelihood ratio test. The effect with cumulative average BMI was non-proportional against age, therefore we stratified the analysis by age ( $\leq 65$ ,  $> 65$ ). In additional analysis, we stratified all exposures by this age variable.

All models were adjusted for age in months at baseline. Multivariate models additionally included ethnicity, vigorous activity, energy intake, smoking, diabetes, family history of prostate cancer, PSA test, and PSA intensity. We modeled the exposures both as categorical variables, as defined in Section 4.3.3, and continuously as a 2-inch increment in height, a 5 kg/m<sup>2</sup> increment in BMI, and a 1-inch increment in waist circumference. Statistical significance was set at  $p < 0.05$  (two-sided).

#### **4.5.6 Selection of confounders**

Selection of covariates to include in the multivariate-adjusted models was based on prior knowledge about known or potential confounders in the association between diet or body size and prostate cancer. Directed Acyclic Graphs (DAGs) guided the process of confounder selection. After identifying sets of potential confounders, we ran regression models on the exposure and outcome with and without potential confounders in the models to explore if there was a substantial change in the estimates. Covariates were included both one-by-one and as sets of covariates, taking into account potential combined covariate effects.

#### **4.5.7 Interaction**

Interaction occurs when the measure of an effect between exposure and disease changes between different values of a third factor, an effect modifier. In **Study I** we tested whether the association between the NNR score and prostate cancer risk was modified by the genetic risk score, family history of prostate cancer, BMI at inclusion, smoking, and dietary supplement use. In **Study II** we tested interaction with age, family history of prostate cancer, history of diabetes and BMI at inclusion. In **Study III** we explored interaction with age, family history of prostate cancer, physical activity, total energy, and diabetes. Potential interaction was explored by including multiplicative interaction terms in logistic regression models as well as by use of interaction indicator variables to obtain a stratified effect. In **Study IV** we explored potential effect modification by age and family history of prostate cancer using formal interaction tests and stratified analyses.

## 5 RESULTS

### 5.1 CHARACTERISTICS OF THE STUDY PARTICIPANTS

#### 5.1.1 The CAPS study population (Study I-III)

Selected characteristics of cases and controls in CAPS are displayed in **Table 2**. Figures are shown for the subjects included in **Study III**, without the additional exclusions made in **Study I** and **II**. The mean age was 66.8 years in cases and 67.7 years in controls. Cases were more likely to live in Northern Sweden, to be employed, and to have a family history of prostate cancer compared to controls. The difference in region of residence, which the controls were matched for, could best be explained by a lower participation rate among the controls than among cases. The groups did not differ substantially with regards to education level, marital status, employment status, history of diabetes, smoking, physical activity, energy intake, or BMI at inclusion. The study population was ethnically homogenous with most of the men being born in Sweden. The level of PSA-detected prostate cancers was low (29 %). Subjects excluded from analyses due to incomplete data were to a higher extent controls than cases.

**Table 2.** Selected characteristics of cases and controls in the CAPS study

	Cases (n=1499)	Controls (n=1118)
<b>Age, mean (years)</b>	66.8	67.7
<b>Region of residence, n (%)</b>		
	Northern Sweden	459 (31)
	Central Sweden	198 (18)
<b>Country of birth Sweden, n (%)</b>	1040 (69)	920 (82)
<b>Education level, n (%)</b>		
	0-9 years	1427 (95)
	10-12 years	209 (14)
	≥13 years	127 (11)
<b>Employment status, n (%)</b>		
	Employed	601 (40)
	Unemployed	472 (42)
	Retired/disability pension	512 (46)
<b>History of diabetes, n (%)</b>	462 (31)	267 (24)
<b>Family history of prostate cancer, n (%)</b>	37 (2)	26 (2)
<b>PSA-detected prostate cancer, n (%)</b>	997 (67)	820 (74)
<b>Smoking status, n (%)</b>		
	Never smoker	174 (12)
	Former smoker	137 (12)
	Current smoker	277 (18)
<b>BMI at inclusion, mean (kg/m<sup>2</sup>)</b>	-	437 (29)
<b>Physical activity, mean (MET-hrs/d)<sup>a</sup></b>	584 (39)	427 (38)
<b>Total energy intake, mean (kJ/d)</b>	738 (49)	541 (48)
<b>Alcohol intake, mean (g/d)<sup>b</sup></b>	159 (11)	135 (12)
	26.2	26.3
	12.7	12.9
	9586	9362
	8.8	8.2

<sup>a</sup> The average of activity levels at age 15, 30, 50, and 65. Only includes activities of at least moderate intensity (metabolic equivalents, METs ≥3).

<sup>b</sup> Adjusted to a total energy intake of 10,460 kJ (2,500 kcal).

### 5.1.2 The HPFS study population (Study IV)

The cohort of 47,491 men in the HPFS were followed for a total period of 24 years. During this time, 6183 incident prostate cancer cases were identified. Of these, 618 were fatal, 785 lethal, 1016 advanced, 3990 non-advanced, 707 high-grade, 1776 grade-7, and 2476 low-grade cases.

For descriptive characteristics across exposure categories of the men in the HPFS we refer to Table 1 in **Paper IV**. Tall compared to short men were to a larger extent Caucasian and had higher intakes of energy, alcohol and calcium. These characteristics did not differ substantially between categories of the other exposures. Obesity as defined by BMI and waist circumference was related to diabetes and less healthy lifestyle characteristics, as well as higher intakes of coffee and red/processed meat. Men who were overweight or obese in childhood were more likely to be past/current smokers and had a higher coffee intake than men who were lean in childhood. Family history of prostate cancer did not differ considerably between any exposure groups. The frequency of PSA testing fluctuated across categories of adiposity: men with a high BMI were less likely to have taken a PSA test in 1994 compared to men with a healthy weight, whereas men with a large waist circumference were more likely to have taken the test compared to men with a thin waist.

## 5.2 STUDY I

### 5.2.1 Descriptive results

The individual components of the NNR score and the recommendation levels are presented in **Table 3**, together with mean intakes and percentage of adherence among cases and controls in the CAPS study population. For adherence cut-off points for each score component we refer to Table 1 in **Paper I**. Less than 7 % of the participants met the recommendations for saturated fat, sugar, and salt, and around 20 % for polyunsaturated fat, vitamin D and E, and selenium. In contrast, over 90 % of the participants reached the recommendations for protein, vitamins A, B<sub>1</sub>, B<sub>2</sub>, B<sub>6</sub>, and B<sub>12</sub>, calcium, magnesium, iron, zinc, and alcohol. Overall, the cases had slightly better adherence to recommended nutrient levels than the controls, with a few exceptions.

The mean total NNR score was 7.2 points (range 4.1-8.6 points) with a distribution of 22 % for low adherence, 55 % for medium adherence, and 24 % for high adherence to the NNR. The score differed little between cases and controls. Spearman correlation coefficients between the score and its main components are presented in **Table 4**; all correlations were below 0.40 except for fiber and physical activity. Inter-correlation between the components ranged from  $r=0.46$  (fiber versus vitamins) to  $r=0.50$  (fat versus carbohydrates). Both the score and its components were unrelated to total energy intake ( $r<0.20$ ).

**Table 3.** Individual components of the Nordic Nutrition Recommendations (NNR) score: recommendation levels, mean intakes, and percentage of adherence among cases and controls in the CAPS study

Components of the NNR score	Recommended levels according to the NNR	Cases (n 1386)		Controls (n 940)	
		Mean intake	% within adherence	Mean intake	% within adherence
<b>Fat (%E)<sup>a</sup></b>					
Total fat	25-35	32.8	63	32.9	61
Saturated fat	≤10	14.4	6	14.6	7
Monounsaturated fat	10-15	11.4	76	11.5	77
Polyunsaturated fat	5-10	4.5	21	4.3	18
<b>Protein (%E)<sup>a</sup></b>	10-20	16.1	93	16.3	93
<b>Carbohydrates (%E)<sup>a</sup></b>					
Carbohydrates	50-60	51.1	54	50.8	52
Sugar	≤10	21.6	0.5	21.4	1
<b>Vitamins<sup>b</sup></b>					
Vitamin A (μg/d) <sup>c</sup>	900-3000	1704	93	1733.4	94
Vitamin B1 (mg/d)	≥1.3	1.7	92	1.7	92
Vitamin B2 (mg/d)	≥1.5	2.4	97	2.4	97
Vitamin B3 (mg/d)	≥17	19.6	76	19.7	75
Vitamin B6 (mg/d)	≥1.6	2.4	97	2.4	97
Folate (μg/d)	≥300	336.2	65	334.9	63
Vitamin B12 (μg/d)	≥2.0	8.9	100	9.5	100
Vitamin C (mg/d)	≥75	128.3	81	123.3	80
Vitamin D (μg/d)	10-50	8.1	19	8.3	22
Vitamin E (mg/d) <sup>d</sup>	≥10	9.1	24	8.9	23
<b>Minerals<sup>b</sup></b>					
Calcium (mg/d)	800-2500	1394	94	1396.9	94
Phosphorus (mg/d)	600-4000	1843	100	1852.3	100
Magnesium (mg/d)	≥350	436.5	92	433.8	92
Potassium (mg/d)	≥3500	4160	84	4133.9	83
Iron (mg/d)	9-25	14.4	97	14.5	98
Zinc (mg/d)	9-25	13.2	98	13.4	99
Selenium (μg/d)	50-300	43.9	22	44.5	24
<b>Fiber (g/d)<sup>b</sup></b>	≥25-35	27.3	59	27.1	60
<b>Salt/sodium (g/d)<sup>b</sup></b>	≤2.8	3.8	4	3.8	4
<b>Alcohol intake (%E)<sup>a</sup></b>	≤5	2.4	90	2.4	91
<b>Physical activity (min/d)<sup>e</sup></b>	≥30	125.4	69	128.0	68

<sup>a</sup> Calculated as percentage of total energy intake (not including energy from alcohol).

<sup>b</sup> Vitamins, minerals, fiber, and sodium were energy-adjusted by the residual method.

<sup>c</sup> Vitamin A: the sum of retinol, β-carotene and other carotenoids.

<sup>d</sup> Vitamin E: α-tocopherol i.e. the most active form of tocopherols.

<sup>e</sup> Cut-off points for physical activity were set higher (≥60 min/d) than the recommendation due to high activity levels in the study population.

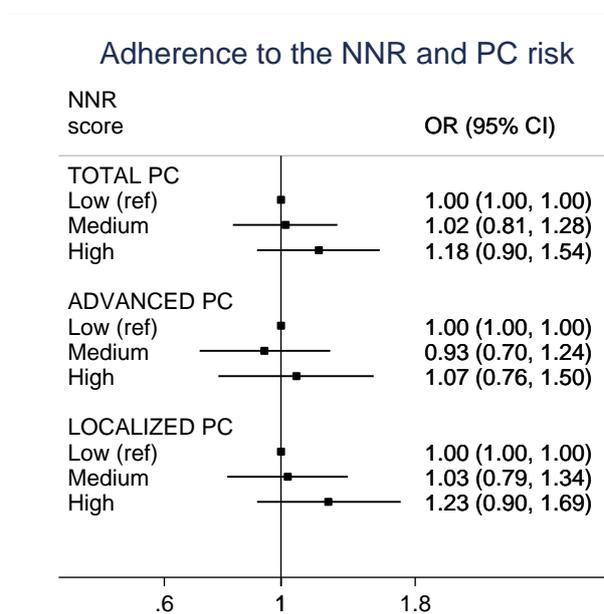
**Table 4.** Correlation between the NNR score and its main components

	Total NNR score
<b>Fat</b>	0.39
<b>Protein</b>	0.18
<b>Carbohydrates</b>	0.33
<b>Vitamins</b>	0.36
<b>Minerals</b>	0.15
<b>Fiber</b>	0.49
<b>Salt</b>	-0.01
<b>Alcohol</b>	0.29
<b>Physical activity</b>	0.64

*Spearman correlation coefficients between continuous variables.*

### 5.2.2 Exposure-disease associations

Adherence to the NNR was not associated with prostate cancer risk in our study, as shown in **Figure 10**. Results were overall similar between simple and multivariate-adjusted models. When we analyzed the NNR score components individually, we found a high intake of polyunsaturated fat (>6 E% i.e. within the recommendation), to be associated with an increased risk of localized disease (OR 1.65, 95 % CI 1.01-2.69) compared to low intake (<3.5 E%); however, the trend across intake categories was not significant ( $P_{\text{trend}}=0.08$ ). No associations were seen with the other score components.



**Figure 10.** Multivariate-adjusted odds ratios (OR) with 95 % confidence intervals (CI; shown by horizontal bars) for total, advanced and localized prostate cancer (PC) according to adherence to the NNR score: low adherence (reference group)  $\leq 6.7$  points; medium adherence 6.7-7.6 points; high adherence  $> 7.6$  points. Results are derived from unconditional logistic regression models adjusted for age, region of residence, education, smoking, BMI at inclusion, energy intake, and family history of prostate cancer.  $P_{\text{trend}}$  was not statistically significant ( $p > 0.05$ ) in any subgroup analysis.

## Interaction

We did not observe any statistically significant interaction with the genetic risk score ( $P_{\text{interaction}}=0.51$ ). However, in stratified analyses men with a high genetic risk score and high NNR adherence had an increased risk of prostate cancer (OR 1.91, 95 % CI 1.15-3.19) (**Table 5**). Similar estimates were seen for advanced and localized disease. Family history of prostate cancer, BMI at study inclusion, smoking, or use of dietary supplements were not found to modify the association between NNR adherence and prostate cancer risk.

**Table 5.** Odds ratios (OR) with 95 % confidence intervals (CI) for total prostate cancer according to adherence to the NNR, stratified by the genetic risk score

		Genetic risk score (tertiles)					
		Low risk ( $\leq 0.40$ )		Intermediate risk (0.40-0.46)		High risk ( $>0.46$ )	
Adherence to the NNR	Cases/ controls	OR (95 % CI)	Cases/ controls	OR (95 % CI)	Cases/ controls	OR (95 % CI)	
Low adherence	52/50	1.00 (ref)	107/48	1.00 (ref)	100/53	1.00 (ref)	
Medium adherence	116/125	1.00 (0.61-1.61)	231/148	0.76 (0.51-1.15)	299/123	1.39 (0.92-2.08)	
High adherence	52/58	1.04 (0.59-1.84)	100/61	0.80 (0.50-1.30)	124/37	1.91 (1.15-3.19)	

*Derived from unconditional logistic regression models adjusted for age, region of residence, education, energy intake, BMI at inclusion, smoking, and family history of prostate cancer. ( $P_{\text{interaction}}=0.51$ .)*

## 5.3 STUDY II

### 5.3.1 Descriptive results

**Table 6** presents a summary of the intake levels of the MDS components, as well as intake levels of total energy, fatty acids, and selected food items, in both our Swedish study population and the Greek reference population. The comparison with the Greek men is made for the CAPS controls only, since their intake levels theoretically reflect the “background” level of dietary intake in the target population. The major differences were seen for vegetable and fruit intakes being 3-5 times higher in the Greek population, while the intake of dairy products and legumes were almost 3-fold higher in the Swedish population. Fish and cereal intakes were also slightly higher among the Swedish men. As previously explained, the M:S fat ratio in the original MDS was modified in our score by adding polyunsaturated fat to the numerator. Unsurprisingly, the MP:S fat ratio in the CAPS population was lower than the M:S fat ratio among the Greek men, which is explained by considerably lower intakes of both mono- and polyunsaturated fat among the former. The intake of saturated fat and meat products

**Table 6.** Intake levels of the components of the Mediterranean Diet Score (MDS) variants and the intake of energy, fatty acids and selected food items among the controls in the CAPS study and in the male study population in the European Prospective Investigation into Cancer and Nutrition (EPIC) in Greece

	CAPS (n 1108 controls)			EPIC – Greece <sup>a</sup> (n 8895 men)	
	25 <sup>th</sup> centile	Median	75 <sup>th</sup> centile		Median
<b>Components of MDS-gram, MDS-serv, MDS-cent and MDS-greek</b>			<b>Components of the original MDS</b>		
MUFA+PUFA:SFA (MP:S) <sup>b</sup>	1.0	1.3	1.7	MUFA:SFA (M:S) <sup>b</sup>	1.7
Vegetables (g/d)	80.3	118.2	176.6	Vegetables (g/d)	549.9
Fruits, nuts & seeds (g/d)	70.1	116.0	176.7	Fruits & nuts (g/d)	362.5
Legumes (g/d)	15.8	26.2	41.4	Legumes (g/d)	9.1
Cereals (g/d)	219.0	278.8	377.2	Cereals (g/d)	266.4
Fish (g/d)	25.6	36.5	51.5	Fish (g/d)	23.7
Dairy products (g/d)	344.8	551.8	820.4	Dairy products (g/d)	196.7
Meat/meat products (g/d)	90.2	120.1	156.3	Meat/meat products (g/d)	120.8
Ethanol (g/d)	1.4	4.1	8.6	Ethanol <sup>c</sup>	-
<b>Components of MDS-alt</b>					
Olive oil use (yes/no)	-	-	-	Olive oil (g/d)	45.5
Fruits	68.8	115.2	175.0	-	-
Nuts & seeds	0	0	1.8	-	-
Whole grains (g/d)	74.5	121.7	190.0	-	-
Red/processed meat (g/d)	78.5	107.5	141.4	-	-
Red wine (g/d)	0	0	41.8	-	-
<b>Energy, fatty acids, and selected food items</b>					
Total energy (kJ/d)	7543	9183	10991	Total energy (kJ/d)	9851
Saturated fat (g/d)	25.7	33.2	43.9	Saturated fat (g/d)	33.1
Monounsaturated fat (g/d)	21.0	26.2	33.3	Monounsaturated fat (g/d)	55.9
Polyunsaturated fat (g/d)	8.0	9.9	12.7	Polyunsaturated fat (g/d)	15.0
Potatoes (g/d)	62.5	108.2	146.9	Potatoes (g/d)	88.7
Sweet foods (g/d) <sup>d</sup>	21.8	37.8	59.4	Sweets (g/d)	22.8
Non-alcoholic beverages (g/d) <sup>e</sup>	0	133.9	294.8	Non-alcoholic beverages (g/d)	337.5

Intakes in the CAPS study are adjusted to a daily energy intake of 10,460 kJ (equivalent to 2,500 kcal).

<sup>a</sup> Trichopoulou et al<sup>(80)</sup>

<sup>b</sup> The ratio of monounsaturated to saturated fat (MUFA:SFA) in the original score was replaced by the ratio of monounsaturated + polyunsaturated to saturated fat (MUFA+PUFA:SFA) in our study.

<sup>c</sup> Categorization of ethanol (<10 g/d; 10 to <30 g/d; ≥30 g/d) was independent of the median intake in the study population.

<sup>d</sup> Sweet foods includes confectionery, sweet bakery products and ice cream.

<sup>e</sup> Non-alcoholic beverages includes juices and soft drinks.

was similar in both populations, whereas total energy intake was higher in the Greek men. Potatoes are generally consumed in large amounts in the Nordic population but less so in Mediterranean countries, as shown in the table. It was not included in the MDS variants of our study, which is consistent with the original score.

The mean values of the MDS variants and the distributions between adherence groups were similar between cases and controls, although the cases had overall slightly better adherence than the controls (see Table 3 in **Paper II**). The main score, MDS-gram, had a mean of 4.4 points, with 32 % of the participants having low adherence, 41 % medium adherence, and 27 % high adherence to a Mediterranean diet.

Correlation between the five MDS variants were in the range  $r=0.43-0.79$  (**Table 7**). Furthermore, correlation coefficients between the continuous main score, MDS-gram, and the nine individual score components were in the range  $r=0.07-0.58$  as shown in **Table 8**; individual components correlated weakly with each other (range of  $r=0.02-0.40$ ). Correlations between the alternative score, MDS-alt, and its ten components were similar, ranging from  $r=0.05$  (meat) to  $r=0.58$  (vegetables); inter-correlations between components were in the range  $r=0.01-0.40$ . The MDS-gram as well as the other MDS variants showed weak correlations with energy intake ( $r \leq 0.33$ ); similarly, all individual score components were weakly correlated with energy intake ( $r \leq 0.31$ ) except the MP:S fat ratio that showed a strong correlation of  $r=-0.84$ .

**Table 7.** Correlation between the MDS variants.

	MDS-gram	MDS-serv	MDS-cent	MDS-greek	MDS-alt
MDS-gram	1.00	0.79	0.67	0.55	0.79
MDS-serv		1.00	0.59	0.43	0.67
MDS-cent			1.00	0.52	0.57
MDS-greek				1.00	0.49
MDS-alt					1.00

*Spearman correlation coefficients between continuous variables.*

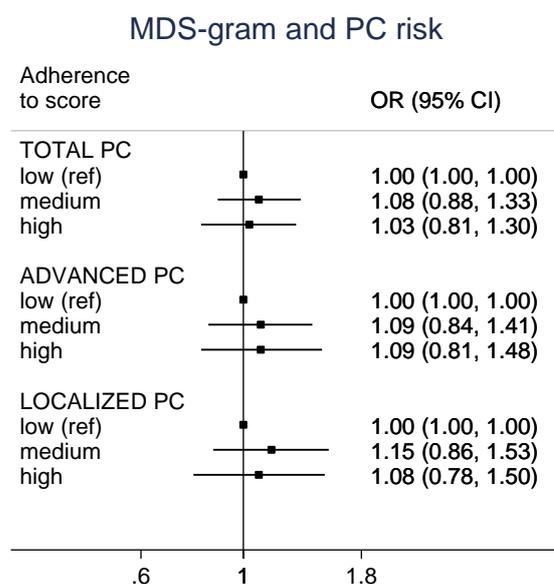
**Table 8.** Correlation between the main score (MDS-gram) and its components

	MP: S	Vegetables	Fruits /nuts	Legumes	Cereals	Fish	Dairy	Meat	Ethanol
MDS-gram	0.49	0.58	0.50	0.46	0.35	0.52	-0.34	0.09	0.07
MP:S	1.00	0.35	0.24	0.21	0.17	0.35	-0.22	0.36	0.15
Vegetables		1.00	0.40	0.39	0.08	0.36	-0.15	0.28	0.23
Fruits/nuts			1.00	0.22	0.11	0.23	-0.05	0.13	0.07
Legumes				1.00	0.05	0.25	-0.09	0.20	0.09
Cereals					1.00	0.05	-0.02	0.07	-0.14
Fish						1.00	-0.16	0.23	0.21
Dairy							1.00	-0.15	-0.26
Meat								1.00	0.12
Ethanol									1.00

*Spearman correlation coefficients between continuous variables.*

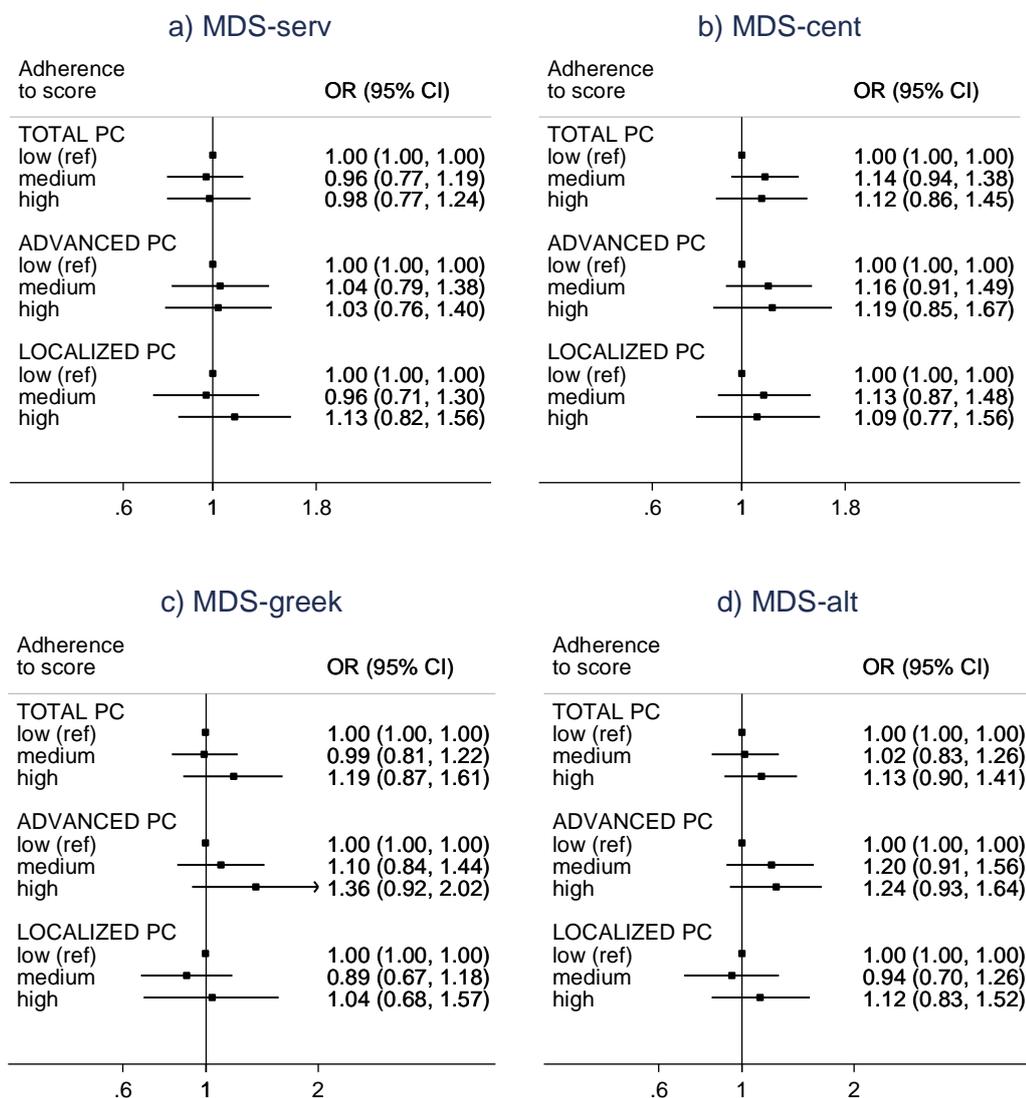
### 5.3.2 Exposure-disease associations

**Figure 11** shows the relative risk of prostate cancer in relation to our main score, MDS-gram, and no association was observed. The relationship with the other MDS variants is presented in **Figure 12**, and overall we did not find any statistically significant associations. However, among men with high adherence to a Mediterranean-like diet as assessed by the MDS-cent, MDS-greek, and MDS-alt, the estimates showed tendencies of an increased risk of disease, especially advanced subtype, although the CIs were wide and did not show statistical significance. Additionally we looked at the risk of prostate cancer characterized by Gleason score 7, a disease subtype that has been shown to be largely unpredictable in relation to prognosis. No statistically significant associations were found for any of the MDS variants.



**Figure 11.** Multivariate-adjusted odds ratios (OR) with 95 % confidence intervals (CI; shown as horizontal bars) for total, advanced, and localized prostate cancer (PC) according to the Mediterranean Diet Score (MDS-gram). Results are derived from unconditional logistic regression models adjusted for age, region of residence, education, smoking, BMI at inclusion, energy intake, physical activity, history of diabetes, and family history of prostate cancer.

## Adherence to MDS variants and PC risk



**Figure 12.** Multivariate-adjusted odds ratios (OR) with 95 % confidence intervals (CI; shown as horizontal bars) for total, advanced, and localized prostate cancer (PC) according to the MDS variants: a) MDS-serv; b) MDS-cent; c) MDS-greek; and d) MDS-alt. Results are derived from unconditional logistic regression models adjusted for age, region of residence, education, smoking, BMI at inclusion, energy intake, physical activity, history of diabetes, and family history of prostate cancer.

### Score components

We further investigated the association between individual MDS components and prostate cancer risk, using intakes below the median as reference groups. Surprisingly, we found a high vegetable intake to be positively associated with 25 % increased risk of total and localized prostate cancer, and 37 % increased risk of advanced disease (**Table 9**), although the estimates were statistically significant for total and advanced disease. High intake of ethanol was associated with a 25 % increased risk of advanced prostate cancer ( $p=0.06$ ) (**Table 9**). A high red wine intake was associated with a 33 %

increased risk of advanced disease (not shown in table). Age- and region-adjusted models showed inverse associations with a high MP:S fat ratio and high meat intake; however, the associations did not remain after adjusting for multiple confounders. We did not observe any associations with the other components.

**Table 9.** Odds ratios (OR) of prostate cancer by vegetable and ethanol intake

	Total prostate cancer (n 2590)		Advanced prostate cancer (n 1696)		Localized prostate cancer (n 1915)	
	Cases/ controls	OR (95 % CI)	Cases/ controls	OR (95 % CI)	Cases/ controls	OR (95 % CI)
<b>Vegetables</b>						
Low intake (<118 g/d)	603/471	1.00	239/471	1.00	204/471	1.00
High intake (≥118 g/d)	782/480	1.25 (1.05-1.50)	304/480	1.37 (1.09-1.72)	286/480	1.25 (0.98-1.60)
P value		0.01		0.006		0.07
<b>Ethanol</b>						
Low intake (<4.1 g/d)	466/353	1.00	178/353	1.00	165/353	1.00
High intake (≥4.1 g/d)	919/598	1.12 (0.93-1.34)	365/598	1.25 (0.99-1.58)	325/598	1.00 (0.78-1.28)
P value		0.24		0.06		0.99

*Median intake among controls was used as cut-off point between high and low intake. Estimates are derived from unconditional logistic regression models adjusted for age, region of residence, education, smoking, BMI at inclusion, energy intake, physical activity, history of diabetes, and family history of prostate cancer.*

### Interaction

Formal interaction tests showed no statistical evidence that the association between our main score, MDS-gram, and prostate cancer risk was modified by family history of prostate cancer, age at inclusion, BMI at inclusion, or history of diabetes.

## 5.4 STUDY III

### 5.4.1 Descriptive results

The mean height was 176.8 cm among cases and 176.0 cm among controls. Both groups had a mean adult BMI of 24.2 kg/m<sup>2</sup>, a mean total weight change of +11.7 kg, and a mean linear change in BMI of 0.1 kg/m<sup>2</sup>/year. Among the cases, 12 % reported being very thin in childhood (silhouette 1), 31 % being thin (silhouette 2), 40 % being normal weight (silhouette 3), and 11 % being overweight or obese (silhouette 4-5). Equivalent numbers for the controls were 10 %, 32 %, 37 %, and 9 %.

As displayed in **Table 10**, adult height was unrelated to the other measures of body size, and childhood body shape correlated weakly with adult BMI ( $r=0.16-0.23$ ). The correlation between adult BMI at varying ages ranged from  $r=0.30$  to  $r=0.87$  and as expected the correlation was stronger for ages closer to one another and weaker for ages further apart; mean adult BMI correlated well with all age-specific BMI measures ( $r=0.70-0.89$ ). Both variables of weight change tended to be more strongly correlated with BMI in late adulthood than in early adulthood, and were weakly correlated with mean adult BMI ( $r=0.19-0.25$ ).

**Table 10.** Correlation between anthropometric measures in the CAPS study

	Adult height	Body shape age 10	BMI at varying ages							Total weight change in kg	Linear change in BMI over age
			Age 20	Age 30	Age 40	Age 50	Age 60	Age 70	Mean age 20-70		
Adult height	1.00	-0.05	-0.17	-0.14	-0.11	-0.06	-0.04	-0.08	-0.11	0.14	0.10
Body shape at age 10 <sup>a</sup>		1.00	0.21	0.20	0.21	0.20	0.16	0.18	0.23	-0.04	-0.04
BMI age 20			1.00	0.80	0.64	0.50	0.38	0.30	0.70	-0.37	-0.33
BMI age 30				1.00	0.84	0.70	0.56	0.45	0.83	-0.08	-0.09
BMI age 40					1.00	0.87	0.71	0.57	0.89	0.18	0.21
BMI age 50						1.00	0.87	0.69	0.88	0.39	0.46
BMI age 60							1.00	0.82	0.89	0.52	0.59
BMI age 70								1.00	0.77	0.58	0.64
Mean BMI age 20-70									1.00	0.19	0.25
Total weight change in kg										1.00	0.91
Linear change in BMI over age											1.00

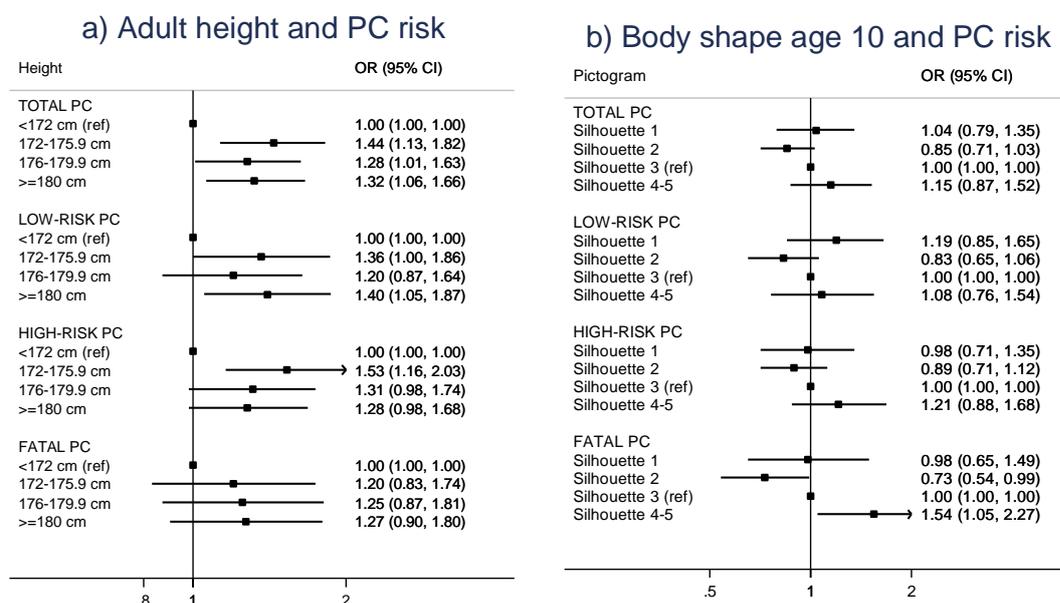
<sup>a</sup> Correlations with body shape at age 10 (categorical) was based on Kendall Tau rank correlation coefficients. Correlations between all other variables (continuous) were based on Spearman correlation coefficients.

## 5.4.2 Exposure-disease associations

### Height

**Figure 13 a)** shows that men in the three highest quartiles of height had a statistically significantly higher risk of total prostate cancer compared to men in the lowest quartile (<172 cm). No dose-response was observed across categories ( $P_{\text{trend}}=0.07$ ), but a linear increase of 5 cm was associated with a 6 % higher risk of total prostate cancer (95 %

1.00-1.13). Similar patterns of association were observed for all disease subtypes, although with varying levels of statistical significance as seen by the wider CIs.



**Figure 13.** Odds ratios (OR) with 95 % confidence intervals (CIs) of total, low-intermediate-risk, high-risk, and fatal prostate cancer (PC) according to a) adult height and b) body shape at age 10, in the CAPS study. Estimates were derived from unconditional logistic regression models adjusted for age and region of residence; models of height were additionally adjusted for family history of prostate cancer. Tests for trend showed statistical significance for childhood body shape and fatal disease ( $P_{trend}=0.01$ ).

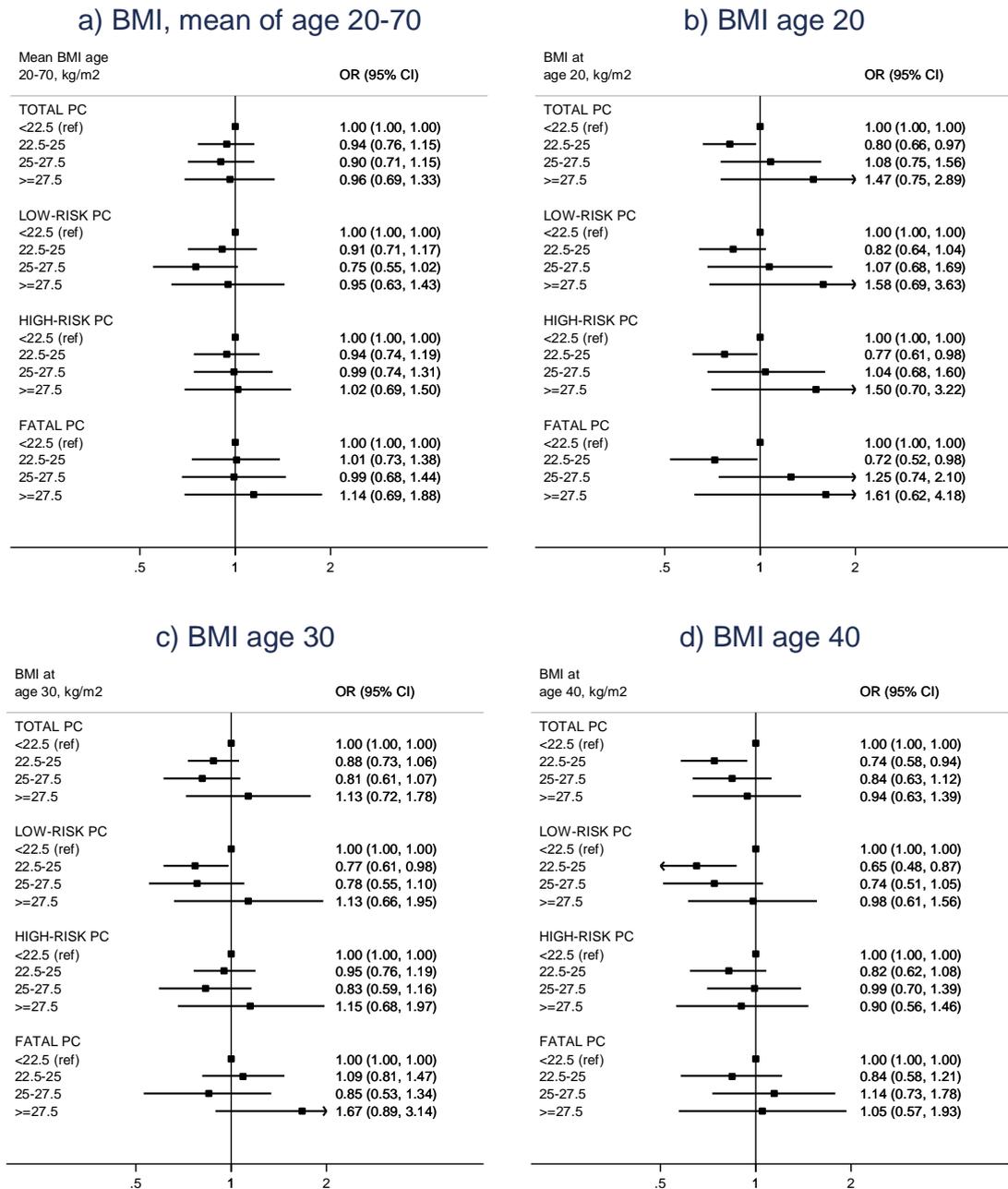
### Childhood body shape

Men who reported being moderately thin in childhood, as represented by silhouette 2 in **Figure 13 b**), had a lower risk of prostate cancer overall compared to men of normal weight (silhouette 3). However, the association was statistically significant only for fatal disease with a risk reduction in the magnitude of 27 %. Overweight or obesity in childhood (silhouette 4-5) was associated with a 54 % increased risk of prostate cancer with fatal consequence, with a statistically significant dose-response trend ( $P_{trend}=0.01$ ).

### Adult BMI

The relative risk of prostate cancer in relation to BMI at different ages is presented in **Figure 14**. Men who were slightly overweight throughout adulthood (mean BMI 25-<27.5), had a 25 % lower risk of low-intermediate-risk prostate cancer compared to BMI <22.5, though only borderline significant. A healthy BMI of 22.5-<25 at age 20 was associated with approximately 20-30 % lower risk of all disease subtypes compared to BMI <22.5. Similar risk reductions were seen for a healthy BMI at age 30 and 40, especially for low-intermediate-risk disease (OR 0.77 and 0.65, respectively;  $p<0.05$ ). We observed no associations with overweight or obesity in age 20-40, but these analyses had limited power as can be seen from the wide CIs, because few of the men were obese in early adulthood. Moreover, BMI at age 50 or 60 was not associated with prostate cancer risk.

## BMI at varying ages and PC risk



**Figure 14.** Odds ratios (OR) with 95 % confidence intervals (CIs) of total, low-intermediate-risk, high-risk, and fatal prostate cancer (PC) according to BMI at varying ages in the CAPS study. Estimates were derived from unconditional logistic regression models adjusted for age and region of residence; models of mean BMI was additionally adjusted for time span between the first and last reported weight. Tests for trend showed statistical significance for BMI at age 20 and total and fatal disease ( $P_{trend}=0.05$  and  $0.06$ ).

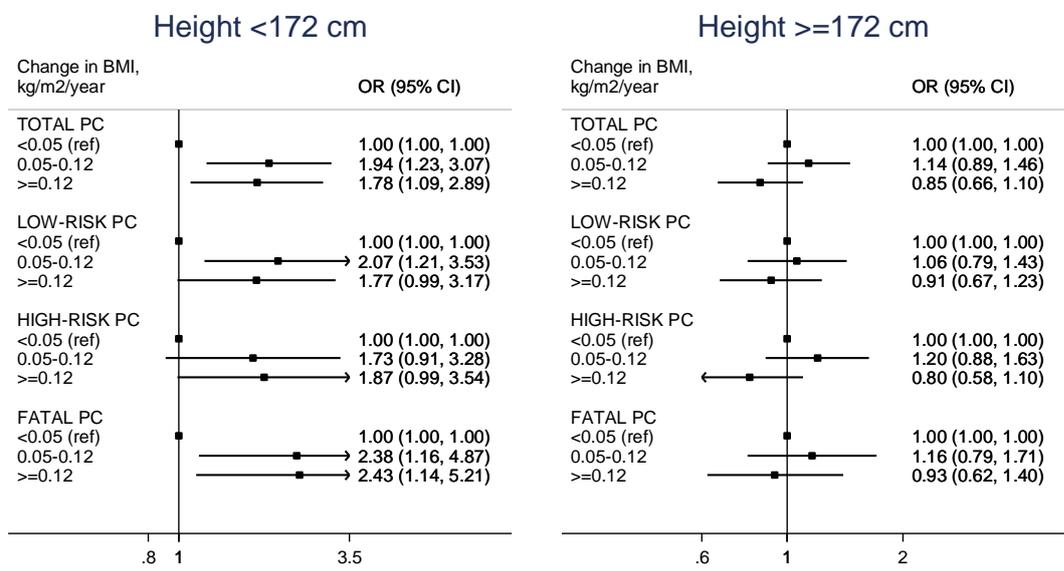
The estimates for height, childhood body shape, and adult BMI were stable between simple and multivariate-adjusted models; moreover, they were not substantially affected by additional adjustment for energy intake, physical activity, education, history of diabetes, and family history of prostate cancer. The inverse associations with a healthy BMI at age 20-40 were stable when adjusted for childhood body size. The

inverse association between adult overweight and low-intermediate-risk disease became stronger and statistically significant after adjustment for childhood body shape. The inverse associations with a healthy BMI at age 30 and 40 were attenuated when we adjusted for previous adult BMI.

### Adult weight change

The association between linear change in BMI and prostate cancer was modified by height ( $P_{\text{interaction}}=0.02$ ), as can be seen in **Figure 15**. Short men (<172 cm) with an average linear increase in BMI  $\geq 0.05$  units per year had a strongly increased risk of all disease subtypes compared to the reference group, with magnitudes of effect approaching 2-fold increases in risk. No association was seen among taller men.

Average linear change in BMI per year and PC risk



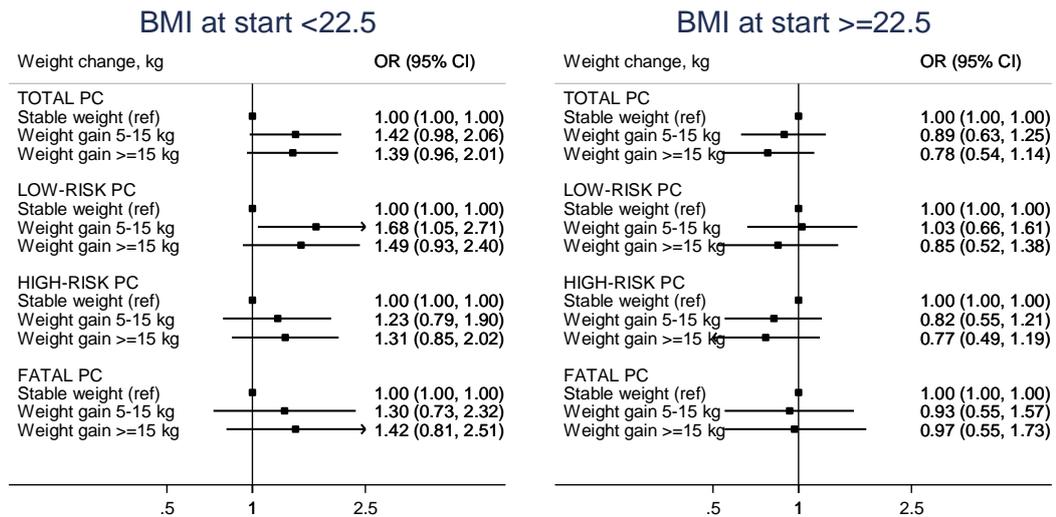
**Figure 15.** Odds ratios (OR) with 95 % confidence intervals (CIs) of total, low-intermediate-risk, high-risk, and fatal prostate cancer (PC) according to the average linear change in BMI per year, stratified by height in the CAPS study. Estimates were derived from unconditional logistic regression models adjusted for age, region of residence, family history of prostate cancer, lifetime physical activity, age at the first reported weight, and time span between first and last reported weight.

The association between total weight change and prostate cancer risk was modified by BMI at the first reported age ( $P_{\text{interaction}}=0.04$ ), and the stratified results are shown in **Figure 16**. The estimates for weight loss were underpowered and are therefore not included. Among men who were thin (BMI <22.5) at the start of the reported weight change period, those who gained 5-15 kg during that period had a 68 % increased risk of low-intermediate-risk prostate cancer. The estimates were in the same direction but non-significant for larger weight gain as well as for total, high-risk, and fatal disease.

Likewise, a positive association with prostate cancer was seen also for a modest linear increase in BMI among men with a low BMI at start (not shown in table). An average

linear increase of 0.05-0.12 BMI units per year resulted in ORs of 1.49 (95 % CI 1.10-2.0) for total prostate cancer and 1.62 (95 % CI 1.10-2.37) for low-intermediate-risk disease, compared to the reference group. This is equivalent to a modest increase of 0.5-1.2 BMI units per 10-year period. However, we observed no dose response relationship, and the *p* for interaction did not show statistical significance.

## Total weight change in kg and PC risk



**Figure 16.** Odds ratios (OR) with 95 % confidence intervals (CIs) of total, low-intermediate-risk, high-risk, and fatal prostate cancer (PC) according to total adult weight change, stratified by BMI at the first reported age, in the CAPS study. Estimates were derived from unconditional logistic regression models adjusted for age, region of residence, family history of prostate cancer, lifetime physical activity, age at the first reported weight, and time span between first and last reported weight.

In contrast, among men with a start BMI of  $\geq 22.5$  we observed no associations with neither of the two weight change variables. However, we observed statistically significant inverse dose response relationships with total and low-intermediate-risk prostate cancer; for every 5 kg total weight gain disease risk was reduced by 7-9 %, and for every 1 kg/m<sup>2</sup> increment in BMI per 10 years, it was reduced by 15-17 %.

It is worth noting that these subgroup analyses were limited in precision due to small reference groups, especially for the lower strata of BMI at start and of height (numbers can be retrieved from Table 3 and 4 in **Paper III**).

### Additional analyses

Age at inclusion, family history of prostate cancer, history of diabetes, energy intake, and physical activity did not modify the association between any anthropometric measure and prostate cancer. Furthermore, we separated the effects of low-risk and intermediate-risk disease, and the associations were overall similar between the two.

## 5.5 STUDY IV

### 5.5.1 Descriptive results

Correlations between the anthropometric measures are presented in **Table 11**. Height was unrelated to the other variables. The two BMI measures were moderately correlated with each other ( $r=0.47$ ), and waist circumference correlated strongly with cumulative average BMI ( $r=0.70$ ) but not with BMI at age 21 ( $r=0.27$ ). Body size in childhood correlated weakly with BMI in early adulthood ( $r=0.38$ ), and unrelated to body size in middle-to-late adulthood.

**Table 11.** Correlation between anthropometric measures in the HPFS

	Height	BMI age 21	BMI cum avg	Waist circumference	Body shape age 10
Height	1.00	-0.007	-0.002	0.22	-0.02
BMI age 21		1.00	0.47	0.27	0.38
BMI cum avg			1.00	0.70	0.18
Waist circumference				1.00	0.09
Body shape age 10					1.00

*Spearman correlation coefficients between categorical variables.*

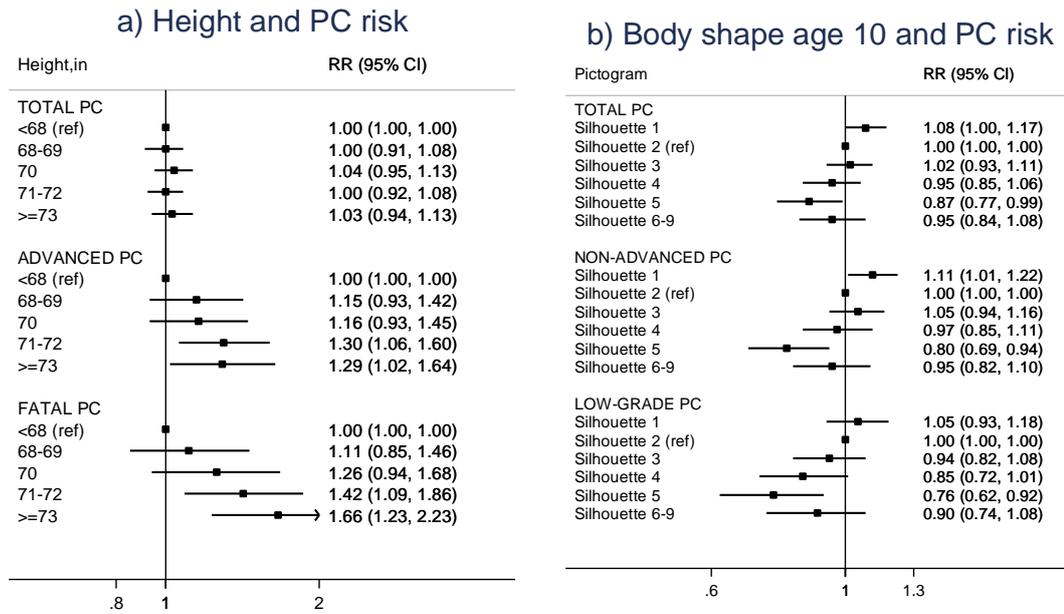
### 5.5.2 Exposure-disease associations

#### Height

As can be seen in **Figure 17a**), height was not associated with total prostate cancer. However, taller men had an increased risk of advanced, lethal, fatal and grade-7 disease; the association was strongest for prostate cancer with fatal consequence, similar in magnitude between lethal (not shown in figure) and advanced disease, and somewhat weaker for prostate cancer classified as Gleason score 7 (not shown). There was statistically significant evidence of a dose-response relationship with all of these disease subtypes ( $P_{\text{trend}} < 0.05$ ). For every 2 inch (~5 cm) increment in height, the risk of advanced and fatal disease increased by 8 and 15 %, respectively. Unexpectedly, we observed an inverse association with low-grade disease, the RR being 0.83 (95 % CI 0.72-0.97) comparing the highest quintile of height to the lowest.

#### Childhood body shape

**Figure 17b**) shows that men who selected the middle-size category of the pictogram (silhouette 5) as best depicting their body shape at age 10 had a lower risk of total, non-advanced, and low-grade prostate cancer, compared to men that conceived themselves as thin in childhood (silhouette 2). However, the middle-size men were at increased risk of disease with fatal outcome (RR 1.46, 95% CI 1.01-2.11). The thinnest category of body shape was associated with a slightly higher risk of total, non-advanced, and grade-7 (not shown in figure) disease compared to the reference group. We observed no associations with the overweight/obese group (silhouette 6-9).



**Figure 17.** Relative risks (RRs) with 95 % confidence intervals of a) total, advanced, and fatal prostate cancer (PC) in relation to adult height and b) total, non-advanced, and low-grade PC in relation to body shape at age 10 in the HPPFS. Estimates were derived from Cox proportional hazards regression models, adjusted for age in months, calendar time, ethnicity, vigorous activity, energy intake, smoking, diabetes, family history of prostate cancer, prostate-specific antigen (PSA) test, and PSA intensity.

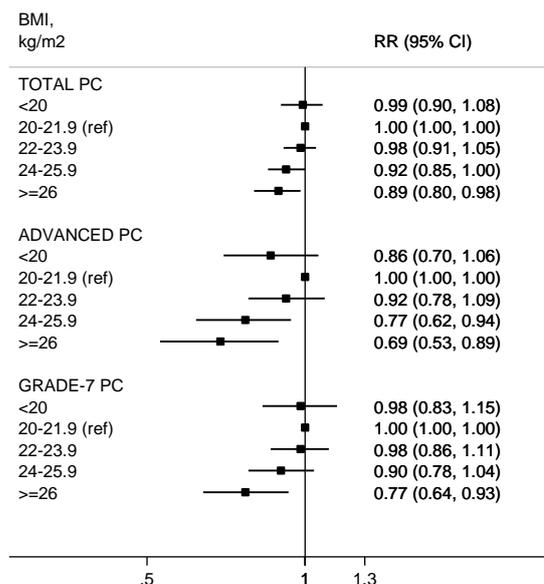
### BMI in early adulthood

A high BMI at age 21 was associated with a slightly lower risk of total prostate cancer as shown in **Figure 18** ( $P_{\text{trend}}=0.01$ ). An even stronger risk reduction was seen for more advanced-stage cancers (lethal, fatal, and advanced) and grade-7 disease, with RRs in the range 0.69-0.77 for BMI  $\geq 26$  compared to BMI 20-21.9. The effect estimates for lethal and fatal disease (not shown in figure) were similar as for advanced prostate cancer. A continuous increment of 5 kg/m<sup>2</sup> was associated with 12-15 % lower risk of all advanced-stage disease subtypes.

### BMI in middle-to-late adulthood

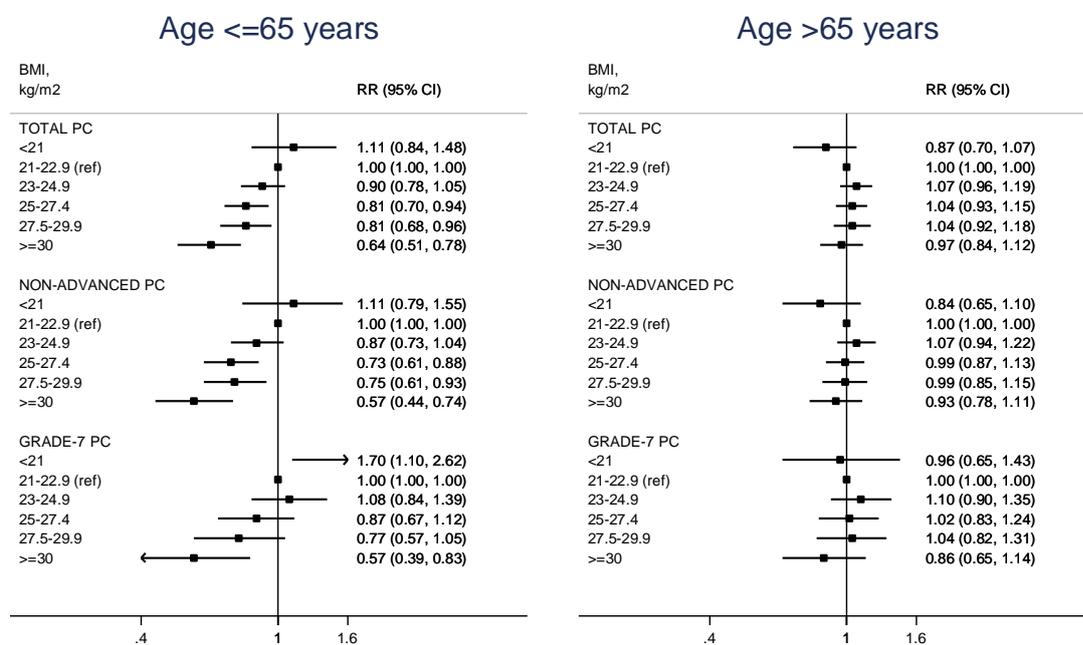
Since the association with cumulative average BMI since baseline was not constant over age ( $P_{\text{interaction}}<0.001$ ), we stratified the effect by men  $\leq 65$  and  $>65$  years at diagnosis, as displayed in **Figure 19**. No associations were seen in men  $>65$  years; however, in the young age group we saw that both overweight and obese men had a lower risk of total prostate cancer as well as of non-advanced, low-grade, and grade-7 disease compared to men with a healthy weight (BMI 21-22.9). The strongest associations were seen in the obese group (BMI  $\geq 30$ ), with RRs in the range 0.57-0.64. The magnitude of effect was similar between low-grade and grade-7 disease. For each of the abovementioned disease subtypes, including total prostate cancer, there was a significant dose-response trend ( $P_{\text{trend}}<0.001$ ), and a continuous 5 kg/m<sup>2</sup> increment was associated with a 17-28 % statistically significantly lower risk.

## BMI at age 21 and PC risk



**Figure 18.** Relative risks (RRs) with 95 % confidence intervals of total, advanced, and grade-7 prostate cancer (PC) in relation to BMI at age 21 in the HPFS. Estimates were derived from Cox proportional hazards regression models, adjusted for age in months, calendar time, ethnicity, vigorous activity, energy intake, smoking, diabetes, family history of prostate cancer, prostate-specific antigen (PSA) test, and PSA intensity.

## Cumulative average BMI and PC risk



**Figure 19.** Relative risks (RRs) with 95 % confidence intervals of total, non-advanced, and grade-7 prostate cancer (PC) in relation to cumulative average BMI since baseline, stratified by age at diagnosis, in the HPFS. Estimates were derived from Cox proportional hazards regression models, adjusted for age in months, calendar time, ethnicity, vigorous activity, energy intake, smoking, diabetes, family history of prostate cancer, prostate-specific antigen (PSA) test, and PSA intensity.

## Waist

Waist circumference was not associated with total prostate cancer. An inverse association with low-grade and grade-7 disease was seen in men in the highest quintile ( $\geq 40$  in,  $\sim 102$  cm) compared to the lowest, with multivariate-adjusted RRs 0.88 (95% CI 0.75-1.02) and 0.84 (95% CI 0.70-1.00), respectively. There was a significant dose-response for both disease subtypes ( $P_{\text{trend}}$  0.01-0.02).

## Additional analyses

Overall, age-adjusted and multivariate-adjusted models showed similar results. In additional analyses we mutually adjusted for body size in different ages. Adjusting for childhood body shape slightly attenuated the associations with adult BMI and waist circumference. On the contrary, the association between the middle-size body build in childhood and fatal disease was strengthened when adjusting for BMI at age 21, but adjusting for BMI or waist in middle-to-late adulthood did not affect the results. Mutual adjustment for BMI in early versus middle-to-late adulthood somewhat attenuated the associations with prostate cancer.

In analyses stratified by age, the observed associations with height was more pronounced among men  $\leq 65$  years (RRs for every 2 inch increment were 1.11, 1.12, and 1.27 for advanced, lethal, and fatal disease, respectively). Similarly, the observed inverse associations with BMI at age 21 were more pronounced among men  $\leq 65$  years; this was especially apparent for grade-7 disease (RR 0.61, 95 % CI 0.45-0.83 comparing BMI  $\geq 26$  to a healthy BMI), but also for non-advanced and low-grade disease although the associations were still non-significant. The association between waist circumference and grade-7 disease was stronger in the young age group, but inversely it was stronger in men  $> 65$  years for low-grade disease.

## 6 DISCUSSION

### 6.1 METHODOLOGICAL CONSIDERATIONS

*In all science, error precedes the truth, and it is better it should go first than last.*  
- Hugh Walpole

The main objective of an epidemiologic study is to obtain estimates of exposure-disease associations that are accurate, i.e. as close to reality as possible. Factors that threaten accuracy are random and systematic errors. *Random errors* affect the *precision* of the estimates, whereas *systematic errors*, commonly called *biases*, affect the *validity* of the study. Below are potential random and systematic errors that need to be considered when interpreting the findings in this thesis.

#### 6.1.1 Precision

Epidemiologic investigations are performed in a sample of the target population that we aim to study. In an ideal world, the sample reflects that target population perfectly. In reality however, we need to deal with random sampling variability, which causes uncertainty in the estimates. Precision refers to the spread of the data; precision is high when the random variability around the “true” value (i.e. random error) is low. Random error can never be ruled out in an epidemiological study.

Increasing the sample size is a way of reducing random error and thereby improving precision and power. The amount of random error of a relative risk estimate is given by the confidence intervals (CI). With increasing sample size the CIs become narrower i.e. precision is improved. In general, a case-control study has less precision than a cohort study performed in the same study population, although precision can be efficiently improved by increasing the number of controls per case. Both the CAPS study and the HPFS study have large sample sizes for their respective study design, though obviously the latter had much higher precision as reflected by the narrower CIs in **Study IV** compared to **Study I-III**. Precision was lower in some sub-group analyses in all four studies, as reflected by wider CIs. The low number of controls in the CAPS study is a potential limitation. Furthermore, matching on potential confounders in case-control studies, as was done in the CAPS study, is a way to improve precision when sample size is low by ensuring enough cases and controls within all strata of the confounder.

#### 6.1.2 Validity

*Systematic errors* occur when the observed value in the sample differ from the true value of the target population due to reasons other than random variability. Validity in contrast to precision does not depend on sample size since the error will be systematically repeated every time the same method is used. The *internal validity* of a study, i.e. validity of the findings within the study population, is influenced by selection bias, information bias, and confounding. The *external validity* deals with generalizability of the findings to other populations. Internal validity is required for external validity.

### 6.1.2.1 Selection bias

Non-random sampling from the target population may lead to *selection bias*, which occurs if the likelihood of being included in a study is related to exposure and disease status, so that the exposure-disease association will differ between those who participate in the study and those who do not. This may be due to factors influencing eligibility and/or willingness to participate.

The CAPS study was population-based i.e. controls were randomly sampled from the same population that the cases were retrieved from, thus the eligibility criteria were the same for cases and controls. Although the response rate was overall high, the lower participation rate among controls than among cases may have introduced selection bias. In general, cases are more prone to participate in a study than controls, which may lead to selection of healthy controls as men that are more health-conscious are more likely to participate in a health-related study. Since health-consciousness tends to be related to lifestyle factors such as the exposures in this thesis, our results may be biased. If the controls are healthier than the cases, then the association with a potentially protective factor such as high diet quality would likely be underestimated. This may in part explain the lack of association seen with overall diet in **Study I** and **II**.

Study participation in the HPFS was unrelated to disease status as no one had prostate cancer at study start. However, selection bias may occur in a cohort if loss to follow-up is differential between exposed and unexposed individuals and is related to the outcome. An important example is the presence of *competing risks*, i.e. when the event under study, such as a prostate cancer diagnosis, is prevented to occur by another competing event. Overweight and obesity are strongly related to cardiovascular risk factors, and death from cardiovascular disease is the leading cause of death in the US<sup>(125)</sup>. Accordingly, it is possible that some overweight/obese men in the HPFS may have died from cardiovascular disease before getting diagnosed with prostate cancer, resulting in an elimination of the sickest individuals from the overweight/obese group being at risk of prostate cancer. Those who remain alive may be the healthiest fraction of the overweight/obese men. Competing risks may have affected the observed risk associations for cumulative average BMI and waist circumference in **Study IV**.

### 6.1.2.2 Information bias

Any type of measurement error in the data that is not completely random will result in *information bias*. Another term for systematic measurement error is *misclassification*, which can be either differential or non-differential and can affect either the exposure, the outcome, or confounder variables.

#### **Misclassification of exposure**

*Differential misclassification of exposure* occurs when information bias is influenced by disease status. A common type of such misclassification in case-control studies with retrospective exposure assessment is *recall bias*. A cancer diagnosis may affect the overall awareness of one's lifestyle or increase the motivation to fill in a long study questionnaire appropriately; or it may be that controls are more health-conscious and therefore better able to report lifestyle factors in the past, thus influencing the quality of

the exposure assessment. In the CAPS study, case status may have affected the participants' ability or motivation to recall dietary intake and/or body size in the past. In **Study III**, the amount of missing exposure data was higher among controls than among cases, which may reflect potential recall bias. However, in **Study III** it is unlikely that cases would consciously relate their cancer diagnosis to their body size since it is not common knowledge that there may be an association. Recall bias or any other misclassification that is differential may influence the effect estimates in any direction.

In **Study IV**, most anthropometric variables were assessed prospectively. However, the retrospective recall of body size in childhood and at age 21 entails more possibilities for measurement error. Since exposure was assessed before the outcome occurred, any exposure misclassification will be *non-differential* between men with and without prostate cancer. A common misapprehension is that non-differential misclassification will attenuate the results; however, this is only true if the exposure is binary i.e. has only two levels. With three or more categories the bias can sometimes be biased away from the null <sup>(126)</sup>. The exposures in **Study IV** are all polytomous i.e. categorical with more than two levels; thus we cannot assess the direction of potential non-differential misclassification of exposure.

Furthermore, arbitrary categorizations of the exposure may lead to measurement error. Categorization is often a delicate balance between having meaningful cut-offs that can discriminate difference between groups, and achieving groups that are of approximately equal size to ensure statistical power in each group.

### **Measurement error in dietary data**

Measures of dietary data contain large variability due to both random and systematic errors. Dietary intake in **Study I-IV** was assessed by self-administered semi-quantitative FFQs. An FFQ measures habitual intake and is prone to measurement error as it relies on memory, has limited ability to capture the whole diet, and is also affected by social desirability that may lead to over-reporting of healthy foods and underreporting of unhealthy foods. Nevertheless, FFQs are useful tools for ranking of individuals, which is the main objective in our studies. Furthermore, we used energy-adjusted dietary intake to obtain more valid measures.

It is fundamental to investigate both the validity and the reproducibility of an FFQ. Energy and nutrient intake from an 88-item FFQ almost identical to the one used in CAPS has been validated against fourteen repeated 24-h recall interviews in a sample of 248 Swedish men <sup>(127)</sup>. Comparison of intakes assessed with the FFQ and the 24-h recalls was based on Spearman correlation coefficients; for macronutrients they ranged from 0.44 (protein) to 0.81 (ethanol) with a mean of 0.65, and for micronutrients they ranged from 0.25 (iron) 0.77 (calcium) with a mean of 0.49. Energy intake estimated by the questionnaire was within 8% of the intake assessed by the 24-h recalls. Reproducibility for two FFQs distributed 1-year apart was examined by intraclass correlation coefficients ranging from 0.61 (PUFA) to 0.85 (ethanol) for macronutrients and from 0.56 (vitamin C) to 0.70 (calcium) for micronutrients, and 0.69 for total energy intake <sup>(127)</sup>.

Food intake from a shorter version (60 items) of the FFQ in CAPS has been validated against four 7-day weighed food records in a random sample of 111 Swedish women<sup>(128)</sup>. Spearman correlation coefficients between intakes assessed with the questionnaire and the food records ranged from 0.16 (refined grains) to 0.82 (wine), with a mean correlation of 0.46. An analysis of reproducibility of two FFQs 1-year apart ( $n=197$ ) yielded correlation coefficients between 0.44 (egg) to 0.82 (wine), with a mean of 0.61.

The FFQ in the HPFS has been validated against two 1-week food records with six months in between in a sub-sample of 127 men in the HPFS cohort<sup>(109,129)</sup>. For food intake the correlation was in the range 0.17-0.95, with a mean correlation of 0.63<sup>(129)</sup>, and for energy-adjusted nutrient intake it was in the range 0.28-0.86, with a mean correlation of 0.59<sup>(109)</sup>.

The validation studies showed moderate to strong correlation for most food items or nutrients. In nutritional epidemiology however, correlation coefficients for dietary factors are rarely above 0.80. Moreover, FFQs frequently underestimate total energy intake, especially among obese individuals<sup>(103)</sup>. In the CAPS population, reported energy intake was lower among overweight and obese men than among normal weight men, indicating a potential underreporting among these individuals. This may have influenced our results in **Study I** and **II**.

The FFQs asked about usual intake during the previous year. This is a potential limitation in **Study I-II** as intake was measured only once and shortly after diagnosis in cases, and because current dietary intake may differ from intake that occurred earlier in life before the tumor was initiated, i.e. prior to the latency period of the disease.

### **Measurement error in diet quality scores**

The way a diet quality score is constructed will highly affect its validity. Critical aspects include the choice of components, grouping of foods/nutrients within the components, choice of cut-off values, scoring method, adjustment for energy intake, and the relative contribution of individual components to the total score<sup>(64)</sup>. An inappropriate scoring method may lead to misclassification of exposure or may be too blunt to detect potentially weak diet-disease associations<sup>(64,65)</sup>.

The NNR score aims to evaluate adherence to dietary guidelines, which guided the choice of components to include. Although each of the nine main components included different number of individual nutrients, they were weighted so that all contributed equally to the score. Cut-off values were externally defined, which may be problematic if the intake in the study population is much lower or higher than these cut-off points. However, we used a proportional scoring system to assess the relative adherence to each nutrient recommendation, as it is less likely to be subject to misclassification than a strictly categorical score. Several NNR scoring models have been tested in a population of Swedish men and women, and no major differences were seen<sup>(54)</sup>.

The MDS aims to assess adherence to the Mediterranean dietary pattern, and is based on nine food components as defined by the original score. Cut-off values were study-specific i.e. based on the median intake in the CAPS population, which has the

advantage of ensuring statistical power in each intake group. However, such cut-off points may not represent a true distinction between beneficial and non-beneficial intake levels. Comparing the median intake levels of each score component between our Swedish study population and the Greek reference population we found significant differences mainly for vegetables, fruits, and dairy products; this may indicate limited discriminating power for these components in assessing adherence to a Mediterranean diet in the CAPS population. The reliability of the MDS and other scores assessing adherence to the Mediterranean diet has been evaluated previously; 30 % of the variability between the different scores was attributed to measurement error, but the MDS performed well <sup>(130)</sup>.

Furthermore, correlations between the score and its individual components as well as inter-correlations between the components may affect the validity of the score in terms of the relative contribution of each component. In both **Study I** and **II**, correlations were low to moderate ( $r < 0.60$ ) with exception of the physical activity component of the NNR score ( $r = 0.64$ ). However, since no associations were seen between any of the NNR score components and prostate cancer risk, except for polyunsaturated fat, we do not consider our results to be substantially influenced by the dominance of the physical activity component.

Another potential issue in studies using diet quality scores is adjustment for energy intake. Individual dietary intakes were energy-adjusted prior to creating the scores, and we also adjusted for total energy intake in multivariate regression models. It has been argued that including energy in the regression model leads to over-controlling for a factor that in itself contributes to the score. However, the scores and the individual components were weakly correlated with energy intake ( $r < 0.20$  in Study I;  $r < 0.35$  in Study II), and no major changes were observed in main effect models adjusted and unadjusted for energy intake.

### **Measurement error in anthropometric data**

Height and weight are easy and precise measures that are highly valid also when self-reported; strong correlations ( $r \geq 0.94$ ) have been shown between questionnaire data and objectively measured values <sup>(117,131)</sup>. Systematic tendencies of overreporting of height and underreporting of weight have been shown, resulting in BMI being biased downward <sup>(132)</sup>. The tendency of underreporting weight is more common among overweight/obese than among normal weight individuals <sup>(133,134)</sup>, which may lead to an attenuation of potential associations between overweight/obesity and prostate cancer.

BMI is the standard surrogate measure for adiposity in large-scale observational studies. However, it does not directly measure body composition and does not distinguish between fat and lean body mass <sup>(135)</sup>. Measures of body fat distribution such as waist circumference have been suggested to better reflect body adiposity <sup>(136)</sup>. Waist circumference measures contain larger variability compared to height and weight <sup>(103)</sup>, nevertheless self-reported values have shown to be highly valid ( $r = 0.95$ ) in a sub-sample of the HPFS cohort members <sup>(117)</sup>. In addition, BMI and waist circumference have shown similar performance in terms of categorizing percentage of body fat <sup>(137)</sup>. BMI can be considered a valid measure of adiposity in young to middle-age adults ( $< 65$

years), but less so in older adults due to changes in body mass distribution with increasing age<sup>(103)</sup>. This may explain why the observed association between cumulative average BMI and prostate cancer in Study IV was stronger in men  $\leq 65$  years.

As regards recall of weight from earlier ages, error due to reliance on memory increases. In a study on elderly individuals aged 71-76 years, the correlation between self-reported and measured values of weight at age 18 was  $r=0.64$ <sup>(138)</sup>. Other studies have shown correlations in the range  $r=0.71-0.95$  for recall of body weight at age 18-40 in men older than 50 years<sup>(139-141)</sup>. Overweight individuals tended to underestimate their weight in the past<sup>(141)</sup>.

The 9-size pictogram used in **Study IV** has been validated for assessment of both childhood and adult body shape. Recall of body shape at age 10 in a group of elderly individuals was strongly correlated with weight measured in childhood ( $r=0.66$ )<sup>(138)</sup>. In adults, silhouettes 1-4 were shown to be valid for identifying thin individuals and silhouettes 6-9 for obese individuals<sup>(131)</sup>. The 5-size pictogram used in **Study III** has not been validated, which is a potential limitation.

### **Misclassification of disease**

Prostate cancer cases in the CAPS study were retrieved from the regional cancer registries, covering 100 % of all cancer diagnoses in those regions. Prostate cancer was further verified by biopsies or cytological methods. For definition of disease subtypes, we obtained information on clinical characteristics and prostate cancer-specific deaths through registries with nearly complete coverage. Men in the control group that had prostate cancer at diagnosis were excluded from the study ( $n=13$ ). However, some of the controls included in the study may have been diagnosed with prostate cancer after enrolment; they were still counted as controls in all analyses.

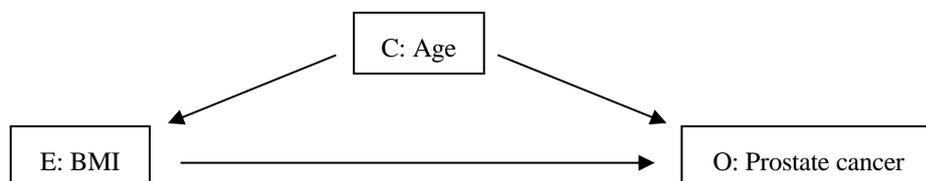
As described in section 4.4.1, identification of cases in the HPFS study and retrieval of clinical information and death reports was thorough and highly complete, although less reliable compared to the coverage of the Swedish registries.

The PSA test has high sensitivity but low specificity, which leads to many false positives and over-diagnosis of non-clinically relevant cases. In the CAPS study, a low fraction of the cases (29 %) were PSA-detected, thus most cases had clinically relevant cancers. Among the HPFS participants, the frequency of having had a PSA test in the prior two years was  $\sim 75$  % in the year 2000, but it did not differ across categories of BMI and waist circumference.

Disease status in **Study I-II** is assumed to be independent of the exposure. However, in **Study III-IV**, overweight and obesity may influence the likelihood of being diagnosed at an early stage, since these men have lower levels of PSA and because the diagnostic tests are more difficult to perform in overweight/obese individuals<sup>(18)</sup>. This could lead to *detection bias*; a larger proportion of undetected tumors among overweight/obese men could result in an apparent “protective” effect and potentially mask a true positive association.

### 6.1.2.3 Confounding

Confounding is bias due to mixing of the main effect between exposure and outcome by the effect of a third factor, a *confounder*. A confounder is defined as a common cause of the exposure and the outcome and not being an intermediate step in the causal pathway. It can weaken or strengthen the true association, or even produce a false effect. The relationship can be depicted in a directed acyclic graph (DAG) as shown in **Figure 20**.



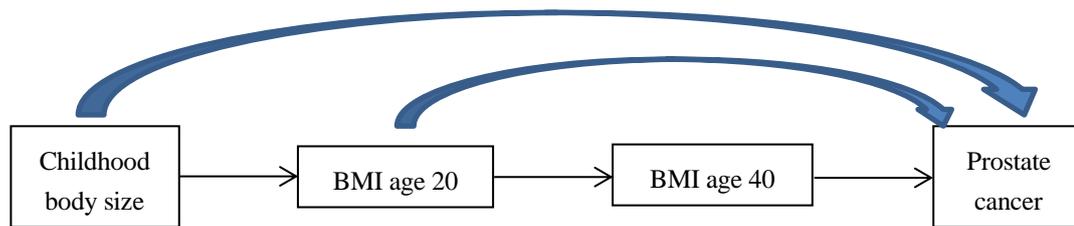
**Figure 20.** An example of a DAG illustrating the causal relationship between an exposure (E: BMI), an outcome (O: prostate cancer), and a confounder (C: age).

Potential confounding needs to be controlled for to obtain unbiased estimates. Randomization (in experimental studies) is the most efficient way of removing confounding; however, this is not feasible in observational studies. In case-control studies, matching on known confounders removes the variability of these factors between cases and controls without the loss in power that would otherwise occur when stratifying on the confounder(s). Matching in the CAPS study was described in section 4.2.1.

Stratifying on potential confounders removes their effect in the analysis phase. This is where regression models come in handy, allowing for adjustment of multiple covariates simultaneously. However, even after adjustment there may be *residual confounding* of the effect estimates as a result of either the confounder strata being too wide, measurement error in the assessment of the confounder, or unmeasured confounding i.e. the presence of confounders that were not measured or not considered in the analysis. With the extensive datasets available in **Study I-IV**, we were able to consider and adjust for numerous potential confounders, as described previously. Nonetheless, the possibility of residual confounding cannot be ruled out.

A covariate that is an intermediate step in the causal pathway between the exposure and the outcome is called a *mediator*. Distinguishing between confounders and mediators can sometimes be a complicated matter. In **Study III-IV** we mutually adjusted for body size in different ages in additional analyses, as we wanted to filter out the main effect of the exposure in question. A simplified picture of the potential relationships is presented in **Figure 21**. We hypothesized that early-life body size has a role in prostate cancer development independent of body size later in life (although they are probably related in some way) as depicted by the two upper arrows. Under this hypothesis, body size earlier in life can be considered a confounder of the relationship between body size later in life and prostate cancer. When investigating the main effect of childhood body size on prostate cancer risk, adult BMI is likely a mediator; however, it may also be a proxy for unmeasured confounders such as genetic or socio-demographic factors in

childhood. As described in sections 5.4.2 and 5.5.2, adjusting for previous or later BMI produced some changes in the effect estimates, but not in the direction of the effects.



**Figure 21.** Causal diagram illustrating the potential relationship between body size at different ages and prostate cancer (for simplicity we do not take other potential confounders into account).

#### 6.1.2.4 Generalizability

The underlying goal in most epidemiologic studies is to have a *representative* sample of the target population, so that inference can be made to the larger perspective. This refers to the *external validity* of a study, the *generalizability*. However, in etiological studies where we want to establish causal relationships, it is more crucial to reduce the effect of potential confounding and keep the internal validity high, than to aim primarily for a representative sample. Given that the study is of good quality and internally valid, inference can be drawn to the population that it targets as well as to other populations, as long as caution is taken to how the study population was defined.

The CAPS study was population-based, with random sampling based on national registries with nearly complete coverage. Therefore, given internal validity the findings of **Study I-III** are generalizable to the whole Swedish population. Self-selection of healthy subjects is likely to occur to some extent in any sampling process since participation is voluntary. This may lower the generalizability of the study, but on the other hand it will likely result in a more motivated study population. The HPFS was restricted to male health professionals; higher response rate and more complete follow-up are expected in this well-educated and assumingly health-conscious population, thus improving internal validity so that the results in **Study IV** can be generalized also to other populations.

## 6.2 MAIN FINDINGS AND INTERPRETATION

### 6.2.1 Diet quality and prostate cancer

To our knowledge, **Study I** and **II** were the first two studies to evaluate adherence to dietary recommendations in the Nordic countries and to a Mediterranean-like diet, respectively, in relation to prostate cancer risk. Overall, we found no associations.

Our null findings for overall diet and prostate cancer are in line with several prospective cohort studies <sup>(40-42,70,71,78)</sup>. However, three case-control studies have reported increased risk of prostate cancer for empirically derived “Western” or

“processed” dietary patterns, characterized by high intakes of e.g. refined grains and red/processed meat, but no associations with “healthy” patterns<sup>(37-39)</sup>.

Similar to **Study I**, the association between dietary recommendations and prostate cancer has been investigated in two recently published studies<sup>(70,71)</sup>. In the large prospective NIH-AARP study, including about 293,000 American men, a reduced risk of total prostate cancer was seen among men who followed the DGA-2005 compared to men who did not<sup>(71)</sup>. A lower disease risk was seen also in men with a high AHEI score, based on foods and nutrients related to lower risk of chronic disease. However, the associations were only seen in men who had taken a recent PSA test, and neither of the scores were associated with advanced or fatal disease. In the European Prospective Investigation into Cancer and Nutrition (EPIC) study, no association with prostate cancer risk was observed for adherence to the WCRF/AICR cancer prevention guidelines<sup>(70)</sup>.

Furthermore, two studies on overall cancer risk have shown beneficial effects of adherence to the DGA<sup>(142)</sup> and the AICR cancer prevention recommendations<sup>(59)</sup>, though only in women. Other studies in both men and women have reported no association between adherence to dietary guidelines and total cancer risk<sup>(61,66-69,143,144)</sup>. These null findings were confirmed in a meta-analysis that we previously performed<sup>(62)</sup>; moreover, we found a 22 % lower mortality from cancer in a meta-analysis of eight cohort studies<sup>(62)</sup>, including a study evaluating the ACS cancer prevention guidelines<sup>(58)</sup>. Inverse risk associations with adherence to dietary guidelines have been seen for several site-specific cancers, primarily colorectal<sup>(70,142,145-148)</sup> and breast cancer<sup>(70,113,115,142)</sup>.

Moreover, in **Study II** the lack of an association between a Mediterranean diet and prostate cancer is supported by recently published null findings for total, advanced and fatal prostate cancer in two large prospective cohorts of US men<sup>(71,78)</sup>. A protective effect has been seen for overall cancer risk<sup>(110,149,150)</sup> as well as for specific cancer sites, notably breast, colorectal, and gastric cancer<sup>(113,145,147,151-153)</sup>. Results for cancer-specific mortality are inconsistent<sup>(110,154,155)</sup>. A recent meta-analysis based on seven cohort studies yielded a pooled RR of 0.94 (95 % CI 0.92-0.96) for a 2-point increment in the MDS in relation to total cancer incidence or mortality<sup>(72)</sup>. Additionally, a review based on twelve studies concluded that the Mediterranean diet has a “probable” protective role for cancer in general<sup>(156)</sup>.

Wirt *et al.*<sup>(65)</sup> performed an extensive review of diet quality scores assessing adherence to dietary guidelines as well as the Mediterranean diet in relation to health outcomes. In general, moderate inverse effects were seen for total cancer risk (7-35 %) and cancer-specific mortality (13-30 %). Score components are often chosen based on epidemiological findings of associations with chronic diseases, mainly cardiovascular disease<sup>(65)</sup>. As can be expected, the scores have shown to better predict risk for cardiovascular outcomes or all-cause mortality than for cancer<sup>(65,157)</sup>. Also, many of the scores are designed to measure diet quality and adherence to guidelines and not to predict disease risk<sup>(65,157)</sup>. Consequently, they may lack sensitivity to discriminate differences in dietary behavior that are large enough to predict cancer risk<sup>(64)</sup>, due to methodological issues discussed in section 6.1.2.2.

The CAPS study population was well-nourished with generally good adherence to the NNR, resulting in narrow intervals of the NNR score and limited discriminating difference between low and high adherence. This may in part explain the lack of association seen in **Study I**.

An interaction with the genetic risk score was suggested, though non-significant, for the association between NNR adherence and prostate cancer. However, the finding does not appear biologically plausible and was limited by low power. This was an explorative analysis that needs to be clarified in further studies.

### **Usefulness of the MDS**

In **Study II**, we further evaluated the usefulness of the MDS in a non-Mediterranean population by comparing several score variants that differed with regards to the included components and cut-off values. The MDS variants were moderately to strongly correlated, with the highest correlations seen for MDS-gram, and no association with prostate cancer was observed for any of them. In an Australian study the MDS showed similar performance in predicting mortality among Greek-Australians and Anglo-Celts <sup>(82)</sup>. Furthermore, the EPIC study showed similar estimates of total cancer risk reduction for adherence to the MDS among men in the Northern and Southern European countries <sup>(158)</sup>.

Moreover, a recent study described the changes in adherence to the Mediterranean diet from the 1960s to the 2000s in 41 countries worldwide <sup>(159)</sup>. Interestingly, a marked decrease was seen in the European Mediterranean countries, whereas the Nordic countries (Sweden, Norway, and Denmark) had actually adopted a more Mediterranean-like diet comparing the two time periods. In other words, the differences between the dietary habits of Mediterranean and non-Mediterranean regions are shrinking, which argues for the usefulness of the MDS in our Nordic study population.

We suggest that the MDS with study-specific median intakes as cut-off values is appropriate for use also in non-Mediterranean populations. However, it is important to bear in mind that the MDS assesses adherence to a *Mediterranean-like* diet in the population under study rather than the “true” Mediterranean diet.

### **6.2.2 Body size and prostate cancer**

In **Study III** and **IV**, we investigated similar hypotheses on the potential associations between several anthropometric factors and prostate cancer risk in two study populations with different study designs.

#### **Height**

In both **Study III** and **IV** we found tall height to be associated with an increased risk of prostate cancer, though the findings deviated in terms of disease subtypes. No dose-response trend was seen in **Study III**, while there was a strong linear association in

**Study IV.** Based on the latter, height seems to be more strongly related to advanced-stage cancer forms, including those with fatal outcomes.

Our results on height confirm the previous findings in the HPFS<sup>(85,160)</sup>, and are further supported by a meta-analysis showing 9 % and 12 % increased risk of total and advanced/aggressive/fatal disease, respectively, for every 10 cm increment in height<sup>(83)</sup>.

Adult height can be seen as a marker of early-life factors as it is largely influenced by levels of growth hormones in childhood and adolescence, notably IGF-I. High levels of free IGF-I have been associated with higher prostate cancer risk and mortality<sup>(161-163)</sup>, thus suggesting a plausible biological explanation for the observed positive association with height.

### **Childhood body size**

The results for body shape in childhood were inconsistent in **Study III** and **IV**. A lower risk of total, non-advanced, and non-aggressive disease was seen in men that reported being in the middle-size group in **Study IV**. A higher risk of fatal disease was seen in the same group of men, as well as in the overweight/obese group in **Study III**. Men in the moderately thin group (silhouette 2) in **Study III** had a lower overall disease risk. Overweight/obesity in childhood was unrelated to overall prostate cancer in both studies; however, few individuals reported being obese in childhood, which limits the statistical power in this group.

**Study IV** was an update of a previous investigation in the HPFS, but we did not confirm the prior findings of a reduced risk of total and advanced/metastatic disease in the most overweight group<sup>(85)</sup>. Few other studies have investigated childhood body size in relation to prostate cancer. Robinson *et al.*<sup>(86)</sup> reported a non-significant reduced risk of advanced disease comparing silhouette 6-9 with 1-4 at age 10, using the same pictogram as in **Study IV**. Another study found a significant 62 % lower risk of total prostate cancer in men that reported being “heavier than their peers” at age 10-13<sup>(84)</sup>. Other studies show no associations with body size at age 8-9<sup>(89)</sup> or in adolescence<sup>(87,88,90)</sup>. Furthermore, obesity in childhood as assessed by a pictogram has been associated with lower risk of breast cancer<sup>(164-166)</sup> but increased risk of colorectal cancer<sup>(167)</sup>.

The hormonal environment in childhood and adolescence is closely related to body size. However, there is no clear biologic explanation for the findings in **Study III** and **IV**. There is large uncertainty in these data due to difficulties in recalling body size from the distant past, and the findings should be cautiously interpreted.

### **Adult adiposity**

The results in **Study III** suggest a beneficial effect of a healthy weight in early adulthood, whereas BMI in late adulthood was unrelated to prostate cancer risk. Additionally, a non-significant inverse association with low-intermediate-risk disease was observed in men being slightly overweight throughout adulthood. The analyses on obesity were limited by few individuals in the obese group. **Study IV** showed a high

BMI both in early and late adulthood to be beneficial in prostate cancer development, at least among men  $\leq 65$  years at diagnosis. Lower risk of total, advanced-stage, and fatal tumors was seen for BMI at age 21 and lower risk of total, non-advanced, and less aggressive disease for BMI in middle-to-late adulthood. Similarly, high waist circumference was inversely associated with less aggressive disease subtypes. Obesity in middle-to-late adulthood was associated with the largest risk reduction. Overall, the reported findings in **Study IV** showed strong dose-response relationships.

Previous studies on overweight or obesity in early adulthood (18-30 years) and prostate cancer risk show inconsistent results. A lower risk of advanced and fatal disease has been seen previously in the HPFS <sup>(85,93)</sup> as well as in other studies <sup>(86,91)</sup>, which is in line with our observations for BMI at age 21 in **Study IV**. However, null findings with advanced/aggressive disease have also been reported <sup>(91,92,94,96,97)</sup>, and a review on total prostate cancer concluded that there is likely no or weak associations <sup>(95)</sup>; this is consistent with our null findings for high BMI at age 20-30 in **Study III**. Results for non-advanced and less aggressive disease have been mixed <sup>(91,94,96,97)</sup>.

Overweight or obesity in middle-to-late adulthood seems to be associated with an increased risk of advanced and aggressive prostate cancer <sup>(18,98,99)</sup>, but a reduced risk of non-advanced and less aggressive disease <sup>(98)</sup>. The observed inverse association with non-advanced/less aggressive disease in **Study III** and **IV** is consistent with a meta-analysis on localized prostate cancer showing a significant 6 % lower risk for every 5 kg/m<sup>2</sup> increase in BMI <sup>(98)</sup>. We observed no association with advanced-stage or aggressive disease, which is in line with previous null findings <sup>(91,94,96,97,168-170)</sup>. The inverse association with total prostate cancer seen in **Study IV** was mainly explained by the strong inverse association with non-advanced and less aggressive cancer forms. No or weak positive associations with total prostate cancer have been suggested in earlier studies <sup>(99,171)</sup>. Importantly, a recent extensive meta-analysis showed a 15 % higher risk of dying from prostate cancer for every 5 kg/m<sup>2</sup> increment in BMI <sup>(168)</sup>.

The lack of an association between waist circumference and total prostate cancer in **Study IV** is consistent with two meta-analyses <sup>(99,172)</sup>. However, we observed an inverse association with less aggressive disease, which is supported by similar findings in the Prostate Cancer Prevention Trial <sup>(173)</sup>.

Biologically plausible mechanisms for the association between adiposity and prostate cancer likely involve sex hormones, insulin, IGF-I, and adipokines <sup>(18,174)</sup>. Overweight and obese men have lower levels of testosterone, and higher circulating levels of insulin and IGF-I <sup>(175)</sup>, which may impose higher risk of prostate cancer <sup>(18,19,161-163,176-178)</sup>. However, prolonged obesity is related to insulin resistance and diabetes, which have been shown to reduce the risk of prostate cancer <sup>(20,23)</sup>. This could be an explanation of the inverse associations observed for BMI and waist circumference in middle-to-late adulthood. Furthermore, pre-pubertal obesity may delay puberty <sup>(179)</sup> and thereby limit the exposure to IGF-I at a critical time point of prostatic growth. Obesity in adolescence often persists up to early adulthood <sup>(180)</sup>, thus reduced levels of IGF-I could be part of the explanation for the observed inverse association with high BMI at age 21 in **Study IV**.

The apparent “protective” effect of overweight/obesity in middle-to-late adulthood may have non-causal explanations. As discussed in section 6.1.2, detection bias and competing risks may have biased our results in **Study IV**. Additionally, disease-related weight loss may give rise to reverse causality in the association with cumulative average BMI and waist circumference. However, this is not likely to have affected our results markedly since this would mainly have influenced the association with late-stage tumors, and because we excluded the first two years of follow-up.

The results in **Study III** are consistent with our hypothesis that body size in early adulthood has higher importance for disease development than in later ages. Also, in both **Study III** and **IV** adjusting for BMI in early adulthood attenuated the results for adiposity later in life, which implies that the early adult BMI measure is more strongly related to prostate cancer.

### **Adult weight change**

In **Study III** we found that a modest total weight gain of  $\geq 5$  kg during adulthood, or an increase in BMI by on average  $0.5\text{-}1$   $\text{kg}/\text{m}^2$  per 10 years, increased the risk of prostate cancer, especially in short men and in men being thin (BMI  $<22.5$ ) at the start of the weight change period. However, these findings need to be interpreted with caution as there was no apparent dose-response relationship, although the similarity between associations with both weight change variables strengthens the credibility of our results. An interesting observation was that among men with a BMI  $\geq 22.5$  at start, an inverse dose-response association was observed between weight gain and total and low-intermediate-risk disease.

Two large prospective cohort studies showed 12-33 % increased risk of total and localized/non-aggressive prostate cancer for weight gain in the range 5-20 kg between age 18 to middle age <sup>(97,100)</sup>, which supports our findings. However, other studies show conflicting results <sup>(94,181,182)</sup>. In a prior investigation of the HPFS data, adult weight gain from age 18 to baseline was not associated with prostate cancer risk <sup>(85)</sup>, which is in line with other null findings <sup>(89,96,183-185)</sup>.

### **6.2.3 Final reflections**

The findings in **Study I** and **II** suggest that overall diet quality has less relevance for prostate cancer development compared to what has been seen previously for individual dietary factors. This is in contradiction to our hypothesis that overall diet is more informative to study in relation to health rather than individual dietary factors. However, strong diet-cancer associations are rarely achieved in epidemiological studies, and our findings may be biased so that a true association with diet could not be observed. Consequently, we cannot make recommendations on dietary intake for prostate cancer prevention based on the results in this thesis. However, we would not argue against following dietary guidelines as they are still likely beneficial for health. Also, the Mediterranean diet is likely to confer beneficial health effects in many aspects as previously mentioned, even if unrelated to prostate cancer.

Our findings in **Study III** and **IV** may have implications for prostate cancer prevention. Tumors with an early onset and/or a worse prognosis is the most critical concern, and screening or intervention programs may be specifically targeted at these susceptible groups of men. Although height is not a modifiable risk factor, our findings are relevant as we identified tall men, especially those of age 65 or younger, as a high-risk group for more severe disease subtypes. Our results further suggest that body size in early adulthood may have larger influence on prostate cancer development than body size later in life. We did observe an apparent “protective” effect on early-stage and less aggressive prostate cancer in overweight or obese men; however, these results may be non-causal. Besides, overweight and obesity are related to numerous unfavorable effects on health, and significantly higher mortality from prostate cancer has been shown in this group. Our results in **Study III** further suggest that even a moderate weight gain during adulthood, particularly among thin or short men, may increase the risk of prostate cancer. This clearly argues for recommendations on maintaining a healthy weight throughout adulthood. The importance of weight maintenance has been highlighted in the current ACS guidelines for overall cancer prevention <sup>(51)</sup>.

Based on current evidence, the ACS recommends the following for prostate cancer prevention <sup>(51)</sup>: “Eat a substantial portion of fruit and vegetables every day, limit the intake of calcium from foods and dietary supplements, be physically active, and maintain a healthy weight.”

# CONCLUSIONS

## Study I and II:

In a large population-based sample of Swedish men:

- adherence to the Nordic Nutrition Recommendations 2004 was not associated with prostate cancer risk;
- adherence to a Mediterranean-like diet was not associated with prostate cancer risk;
- the Mediterranean Diet Score with study-specific intake cut-offs appeared useful for assessment of a Mediterranean-like diet in a non-Mediterranean, Nordic population.

## Study III and IV:

In a large population-based Swedish case-control study and a large American cohort study:

- the influence of body size on prostate cancer risk varied largely by tumor stage and aggressiveness, and body size in early adulthood appeared to have stronger influence than body size later in life;
- tall height increased the risk of advanced-stage and fatal prostate cancer;
- a healthy weight in young adulthood reduced the risk of prostate cancer overall, whereas overweight in young adulthood reduced the risk of total, advanced-stage, and fatal prostate cancer;
- overweight or obesity in middle-to-late adulthood reduced the risk of non-advanced and less aggressive prostate cancer;
- associations between adult body size and prostate cancer were suggested to be stronger among men  $\leq 65$  years at diagnosis;
- moderate weight gain in adulthood increased the risk of prostate cancer in men who were short or thin;
- childhood body size was incoherently associated with prostate cancer risk.

## 7 FUTURE PERSPECTIVE

The relationship between diet, body size and prostate cancer is indeed complex, and many knowledge gaps still remain to be filled. Also, I strongly encourage that dietary and lifestyle recommendations are evaluated in terms of their potential to reduce incidence of cancer and other major health outcomes.

The evaluation in **Study I** was based on the NNR 2004. A brand new edition of the NNR was released in October 2013 <sup>(53)</sup>. The new version emphasizes the whole diet perspective and quality of food sources in addition to quantitative nutrient intake, and also highlights the role of dietary patterns in prevention of major diet-related chronic diseases. The NNR 2012 suggests a healthy dietary pattern with a high intake of vegetables, fruits and berries, legumes, fish, vegetable oils, wholegrain, low-fat dairy products and meat, and low consumption of red and processed meat, sugar, salt, and alcohol. This appears very similar to the traditional Mediterranean dietary pattern that we investigated in this thesis. It would be a natural step to evaluate adherence to the new NNR, as well as the suggested dietary pattern, in relation to prostate cancer and other chronic diseases. In fact, in the last few years there has been a growing interest in the potential health benefits of a traditional Nordic diet <sup>(186-189)</sup>. Beneficial effects on cardiovascular risk factors and mortality have been shown <sup>(186,189)</sup>, similar to what has been seen for the Mediterranean diet. The Nordic diet also has environmentally friendly and regional aspects and is more easily applied to the Nordic population <sup>(187,188)</sup>. Are we perhaps facing a new era with the Nordic diet as the up-and-coming “replacement” for the Mediterranean diet? More studies will for sure follow.

The inconsistent findings across studies on body size and prostate cancer reflect not only methodological flaws but also the complexity in the potential relationship. A crucial issue is to define the most critical time point when obesity potentially has the greatest impact on prostate cancer development. Future studies should therefore include childhood, adolescence, and early adulthood in the time window of exposure. For example, in Sweden we have good opportunities for high-quality anthropometric data through e.g. records of school children’s weight and registries of military enlistment.

Moreover, the potential interplay between genes and both diet and body size open up for opportunities to study genetic interactions. This may be relevant for future genetic screening to guide individualized strategies for prostate cancer prevention.

This thesis has focused on disease risk. However, lifestyle factors after diagnosis are also motivated to study, since some factors may affect the progression of the tumor and survival even if not associated with the risk of disease. This is especially relevant since the prognosis varies largely between prostate cancer subtypes and it is possible that men could modify their chances of survival by making lifestyle changes. Future lifestyle recommendations for prostate cancer should therefore take into account both prevention and progression of the disease.

*The real voyage of discovery  
consists not in seeking new landscapes  
but in having new eyes.*

*- Marcel Proust*

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