From THE DEPARTMENT OF MEDICAL
EPIDEMIOLOGY AND BIOSTATISTICS
Karolinska Institutet, Stockholm, Sweden

PHYSICAL ACTIVITY, BODY MASS INDEX AND PROSTATE CANCER
- STUDIES OF RISK, PROGRESSION AND MORTALITY

Stephanie Bonn

Karolinska Institutet

Stockholm 2015

Front cover illustration by Nils Bonn (1924-2006)

Published by Karolinska Institutet.
Printed by AJ E-print AB

ISBN 978-91-7549-866-9

Physical Activity, Body Mass Index and Prostate Cancer - Studies of risk, progression and mortality

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Stephanie Bonn

Principal Supervisor:
Associate prof. Katarina Bälter
Karolinska Institutet
Department of Medical Epidemiology and Biostatistics

Co-supervisor(s):
Associate prof. Ylva Trolle Lagerros
Karolinska Institutet
Department of Medicine, Unit of clinical epidemiology

Associate prof. Fredrik Wiklund
Karolinska Institutet
Department of Medical Epidemiology and Biostatistics

Prof. Henrik Grönberg
Karolinska Institutet
Department of Medical Epidemiology and Biostatistics

Opponent:
Dr. Charles E. Matthews
National Cancer Institute, USA
Division of Cancer epidemiology and genetics, Nutritional epidemiology branch

Examination Board:
Associate Prof. Nicola Orsini
Karolinska Institutet
Institute of Environmental Medicine
Division of Nutritional epidemiology

Prof emer. Björn Ekblom
The Swedish School of Sport and Health Sciences
Department of Performance and Training

Associate Prof. Per Sjögren
Uppsala University
Department of Public Health and Care Sciences
Division of Clinical Nutrition and Metabolism

ABSTRACT

Prostate cancer is the most common cancer among men in developed countries, but it is still unclear what causes the disease. Body mass index (BMI) and physical activity are modifiable lifestyle factors with the potential to influence the development and progression of prostate tumors and may provide alternative strategies for reducing both prostate cancer incidence and mortality.

This thesis includes studies of the importance of body weight and physical activity on prostate cancer as well as methodological studies of how to assess physical activity in epidemiological studies. In **Study I** and **II** we aim to clarify the effect of BMI, weight change and physical activity on prostate cancer progression and mortality, while we in **Study V** aim to investigate the associations between BMI, serum prostate specific antigen (PSA) and the risk of prostate cancer. In **Study III** and **IV** we aim to assess the validity of the new web-based physical activity questionnaire Active-Q against three different reference methods.

In **Study I** and **II**, we found that high BMI was associated with increased rates of overall mortality, but not progression or prostate cancer specific mortality, in men diagnosed with localized prostate cancer. An increase in body weight by >5% after diagnosis was associated with a higher prostate cancer specific mortality, while a weight reduction by >5% after diagnosis was associated with higher overall mortality. Frequent walking/bicycling and exercise were associated with lower prostate cancer specific and overall mortality, compared to a less active lifestyle. Moreover, high levels of total recreational activity and household work were associated with lower overall mortality. **Study V** showed that men with high BMI had lower serum PSA-levels, compared to men with normal BMI. Although BMI was not associated with overall prostate cancer risk, there was a suggested association between high BMI and high-grade prostate cancer.

Active-Q was validated with regards to energy expenditure and total MET-hours against doubly labelled water and pedometers in **Study III** and with regards to time spent in different intensity levels of activity against accelerometers in **Study IV**. Active-Q showed moderate validity compared to the reference methods and good absolute agreement for energy expenditure while a somewhat lower agreement for time at different intensity levels was seen. When comparing repeated Active-Q assessments, the questionnaire showed high reproducibility.

In conclusion, a physically active lifestyle after prostate cancer diagnosis is beneficial and associated with lower levels of both overall and prostate cancer specific mortality. Our results also showed that a large increase in body weight after diagnosis was associated with higher prostate cancer specific mortality, whereas weight reduction was associated increased higher overall mortality. Although we did not find a clear effect of BMI on overall prostate cancer risk, progression or prostate cancer specific mortality, we found that men with high BMI had lower levels of serum PSA, potentially hampering early detection of prostate cancer. Weight maintenance and a physically active lifestyle after diagnosis may complement prostate cancer treatment to improve survival. Also, Active-Q is a valid method for assessing energy expenditure and time spent at different intensity levels in future epidemiological studies.

POPULÄRVETENSKAPLIG SAMMANFATTNING

Prostatacancer är den vanligaste cancerformen i Sverige och drabbar omkring 9000 män varje år. Överlevnaden är god och fler män dör av hjärt- och kärlsjukdomar än av sin prostatacancer. Vad som orsakar sjukdomen är ännu oklart men forskning visar att ålder, etnicitet och ärftliga faktorer spelar stor roll. Senare års forskning tyder också på att livsstilsfaktorer är betydelsefulla för risken att drabbas av prostatacancer samt för överlevnaden efter diagnos.

Denna avhandling har två huvudsyften. Det första är att studera hur kroppsvikt uttryck som BMI (body mass index, kg/m^2), viktförändring och fysisk aktivitet är kopplat till prostatacancer. Det andra syftet är att validera den nya webbenkäten ”Active-Q” som mäter fysisk aktivitet. För att kunna studera hur fysisk aktivitet är kopplat till hälsa och sjukdom i framtida studier är det viktigt att använda pålitliga mätmetoder.

I avhandlingens första två delstudier (**I** och **II**) analyserade vi data från omkring 5000 svenska män som fått en prostatcancerdiagnos mellan åren 1997-2002. Detta är den största studien i sitt slag som följt en grupp män med prostatacancer och undersökt hur livsstilen påverkar sjukdomens utveckling och dödlighet. I den femte delstudien (**V**) analyserade vi data från drygt 15000 män som inte hade prostatacancer vid studiens start. I denna studie undersökte vi sambandet mellan BMI och prostatacancerrisk samt kopplingen mellan BMI och den bilogiska markören prostataspecifikt antigen (PSA). PSA är ett protein som bildas i prostatan och som normalt finns i mycket små mängder i blodet. Vid olika sjukdomar, inklusive prostatacancer, är nivåerna ofta förhöjda och PSA-tester används därför för att upptäcka prostatacancer.

I delstudie ett (**I**) undersökte vi kopplingen mellan BMI vid tiden för diagnos och risken för prostatacancerprogression (cancertumörens utveckling). Vi studerade även hur BMI vid diagnos, viktförändring efter diagnos och fysisk aktivitet efter diagnos påverkade prostatacancerspecifik dödlighet (död orsakad av cancern) och total dödlighet. BMI används ofta för att definiera vad som är normalvikt (BMI <25kg/m^2), övervikt (BMI 25<30kg/m^2) eller fetma (BMI >30kg/m^2). Vi fann inget samband mellan BMI och progression eller prostatacancerspecifik dödlighet. Däremot hade män med ett BMI över 30 kg/m^2 högre total dödlighet jämfört med normalviktiga män. Detta kan bero på den ökade risken för hjärt- och kärlsjukdom som är förknippad med ett högt BMI. När vi studerade viktförändring fann vi att män som ökade mycket i vikt efter diagnos hade högre prostatacancerspecifik dödlighet jämfört med män som höll en stabil vikt. Män som istället gick ner mycket i vikt hade högre total dödlighet. Detta kan delvis förklaras med att sjukdomen i sig kan leda till både viktnedgång och dödlighet. Det är alltså inte viktnedgången i sig som ökar dödligheten utan en mer svårartad sjukdom. Samantaget visar våra resultat att det efter en prostatcancerdiagnos kan vara till fördel att undvika viktuppgång och att ett högt BMI kan öka risken att dö i förtid.

I den andra delstudien (**II**) undersökte vi kopplingen mellan olika typer av fysisk aktivitet och dödlighet. Män som rapporterat att de promenerade eller cyklade mer än 20 minuter per dag eller utförde mer än 1 timmes hushållsarbete per dag eller tränade mer än 1 timme i veckan hade lägre total dödlighet jämfört med män som rapporterat att de utförde aktiviteterna mer sällan eller under kortare tid. Vi såg också en minskad dödlighet från prostatacancer hos de män som rapporterat att de promenerade eller cyklade mer än 20 minuter per dag eller tränade mer än 1 timme i veckan.

Våra resultat är bland de första i världen att visa på positiva effekter av fysisk aktivitet på både prostatacancerspecifik och total överlevnad och att en aktiv livsstil kan förlänga livet efter en prostatacancerdiagnos.

I delstudie fem (**V**) undersökte vi sambandet mellan BMI och prostatacancerrisk samt kopplingen mellan BMI och PSA i blod. Våra resultat visade inte på något samband mellan BMI och risken för prostatacancer men vi såg att män med högre BMI hade lägre PSA-koncentrationer. Eftersom PSA används för att tidigt upptäcka prostatacancer är det viktigt att veta vilka faktorer som kan påverka koncentrationen av PSA och därmed tolkningen av provresultat.

I avhandlingens andra del (delstudie **III** och **IV**) undersökte vi validiteten och reproducerbarheten hos den webbaserade enkäten Active-Q. I delstudie tre (**III**) studerade vi hur väl Active-Q mätte total energiförbrukning och fysisk aktivitet hos vuxna. Energiförbrukning skattad med enkäten jämfördes mot resultat från dubbelmärkt vatten (DLW). DLW är en biomarkör och den bästa metod som finns tillgänglig för att mäta total energiförbrukning. Vi utvärderade också hur bra enkäten var på att skatta den totala aktivitetsnivån genom att jämföra resultat mot totalt antal dagliga steg. I delstudie fyra (**IV**) utvärderade vi hur väl Active-Q skattade tid spenderad på olika aktivitetsnivåer (stillasittande, måttlig och hög nivå) jämfört med accelerometermätningar. En accelerometer mäter acceleration, det vill säga rörelse, mycket noggrant.

I delstudie tre (**III**) visade Active-Q medelgod validitet med avseende på total energiförbrukning. I genomsnitt överskattade enkäten den totala energiförbrukningen något. Jämförelsen mellan total aktivitetsnivå och dagliga steg visade på låg överenstämmelse mellan metoderna. Detta kan dock bero på att det totala antalet steg per dag inte är ett bra mått på total aktivitet. I delstudie fyra (**IV**) visade jämförelser av tid spenderad på olika aktivitetsnivåer på medelgod validitet när resultat från Active-Q jämfördes med accelerometermätningar. Enkäten överskattade tid spenderade på måttlig och hög aktivitetsnivå medan stillasittande underskattades. Reproducerbarheten av upprepade skattningar med enkäten var god i båda studierna. Sammantaget visar våra resultat på god validitet hos Active-Q för mätningar av total energiförbrukning och tid spenderad på olika aktivitetsnivåer.

Resultaten i denna avhandling bidrar med ny kunskap om hur BMI, viktförändring och fysisk aktivitet är kopplat till prostatacancer. Vi visar även att BMI påverkar koncentrationen av PSA i blodet. BMI bör därför vägas in i tolkningen av PSA vid diagnosticering av prostatacancer. Med tanke på de 85000 män som idag har eller har haft prostatacancer är våra resultat mycket lovande och erbjuder möjligheter för män att själva välja en aktiv livsstil som inte bara har positiva effekter på den allmänna hälsan utan också förbättrar överlevnaden efter en prostatacancerdiagnos. Vi visar också att den webbaserade enkäten Active-Q kan användas i framtida studier för att mäta fysisk aktivitet.

LIST OF PUBLICATIONS

I. **Bonn SE**, Wiklund F, Sjölander A, Szulkin R. Stattin P, Holmberg E, Grönberg H, Bälter K. Body Mass Index and Weight Change in Men with Prostate Cancer: Progression and Mortality.
Cancer Causes & Control. 2014 Aug;25(8):933-43.

II. **Bonn SE,** Sjölander A, Trolle Lagerros Y, Wiklund F, Stattin P, Holmberg E, Grönberg H, Bälter K. Physical Activity and Survival among Men Diagnosed with Prostate Cancer.
Cancer Epidemiology, Biomarkers & Prevention. 2015 Jan;24(1):57-64.

III. **Bonn SE**, Trolle Lagerros Y, Christensen SE, Möller E, Wright A, Sjölander A, Bälter K. Active-Q: Validation of the Web-Based Physical Activity Questionnaire Using Doubly Labeled Water.
Journal of Medical Internet Research. 2012 Feb 15;14(1):e29.

IV. **Bonn SE**, Bergman P, Trolle Lagerros Y, Sjölander A, Bälter K. A validation study of the web-based physical activity questionnaire Active-Q against the GENEA accelerometer.
Manuscript

V. **Bonn SE**, Tillander A, Sjölander A, Wiklund F, Grönberg H, Bälter K. Body mass index in relation to PSA-levels and Prostate Cancer Risk.
Manuscript

RELATED PUBLICATIONS

(Not included in thesis)

I. Sjörs C, **Bonn SE**, Trolle Lagerros Y, Bälter K. Perceived Reasons, Incentives, and Barriers to Physical Activity in Swedish Elderly Men *Interactive Journal of Medical Research* 01/2014; DOI: 10.2196/ijmr.3191

II. Christensen SE, Möller E, **Bonn SE**, Ploner A, Bälter O, Lissner L, Bälter K. Relative validity of micronutrient and fiber intake assessed with two new interactive meal- and web-based food frequency questionnaires. *Journal of Medical Internet Research*. 2014 Feb 21; 16(2):e59.

III. Christensen SE, Möller E, **Bonn SE**, Ploner A, Wright A, Sjölander A, Bälter O, Lissner L, Bälter K. Two New Meal- and Web-Based Interactive Food Frequency Questionnaires: Validation of Energy and Macronutrient Intake. *Journal of Medical Internet Research*. 2013 Jun 5; 15(6):e109.

IV. **Bonn SE**, Trolle Lagerros Y, Bälter K. How valid are Web-based self-reports of weight? *Journal of Medical Internet Research*. 2013 Apr 9;15(4):e52.

V. **Bonn SE,** Surkan PJ, Lagerros YT, Bälter K. Feasibility of a novel web-based physical activity questionnaire for young children. *Pediatric Reports*. 2012 Dec 6; 4(4):e37.

VI. Jan M, **Bonn SE**, Sjölander A, Wiklund F, Stattin P, Holmberg E, Grönberg H, Bälter K. The effects of stress and social support on prostate cancer prognosis. *Submitted manuscript*

VII. Trinh T, Eriksson M, Darabi H, **Bonn SE**, Brand JS, Cuzick J, Czene K, Sjölander A, Bälter K, Hall P. Background risk of breast cancer and the association between physical activity and mammographic density. *Submitted manuscript*

VIII. Cantarutti A, **Bonn SE**, Adami HO, Grönberg H, Bellocco R, Bälter K. Body Mass Index and Mortality in men with prostate cancer. *Submitted manuscript*

IX. Henriksson H, **Bonn SE**, Bergström A, Bälter K, Bälter O, Delisle C, Forsum E, Löf M. A new tool using cell phones for assessing intakes if energy and certain foods in young children – a validation study. *Submitted manuscript*

X. Christensen SE, Fondell E, Ström P, Bälter O, **Bonn SE**, Nyrén O, Plymoth A, Bälter K. Intake of vitamin C, vitamin E, slenium, zinc and polyunsaturated fatty acids and upper respiratory tract infection – a prospective cohort study. *Submitted manuscript*

CONTENTS

LIST OF ABBREVIATIONS

BMI	Body Mass Index (kg/m^2)
BMR	Basal Metabolic Rate
CDR	Cause of Death Register
DAG	Directed Acyclic Graph
DLW	Doubly Labeled Water
EE	Energy Expenditure
GENEA	Gravity Estimator of Normal Everyday Activity
GPAQ	Global Physical Activity Questionnaire
HR	Hazard Ratio
Hz	Hertz
ICC	Intraclass correlation
IPAQ	International Physical Activity Questionnaire
IQR	Interquartile Range
kcal	kilogram calories
kJ	kilojoule
MET	Metabolic Equivalent
NCR	National Cancer Register
NPCR	National Prostate Cancer Register
PAEE	Physical Activity Energy Expenditure
PAL	Physical Activity Level
PSA	Prostate Specific Antigen
RQ	Respiratory Quotient
SCR	Swedish Cancer Register
SD	Standard Deviation
SVM_{gs}	Signal Vector Magnitude – gravity subtracted
TEE	Total Energy Expenditure
WHO	World Health Organisation
95% CI	95% Cofidence Interval

1 INTRODUCTION

"Walking is man's best medicine"
Hippocrates c. *460 - 377 B.C.*

Already in ancient Greece, physical activity was known to have positive effects on health. However, even with more knowledge than ever before, we are adopting more and more sedentary lifestyles and have never been less active than we are today. Physical inactivity has been identified as the fourth leading risk factor for global mortality by the World Health Organization (WHO).[2]

Concomitant to being increasingly inactive, or perhaps because of, the number of overweight or obese individuals worldwide has increased dramatically during the past decades.[3] Nevertheless, overweight and obesity are preventable and as physical inactivity, modifiable. This gives us great possibilities to influence our own health by changing our lifestyle. It is also important to remember that other lifestyle factors, including for example diet, plays an important role in our health. Physical activity contributes to our energy expenditure (energy output) and diet contributes to our energy intake (energy input). Our body weight represents the result of the balance between output and input and reflects our energy storage. While all factors in this triad are important for our health, this thesis will focus on body weight and physical activity.

To better understand what a healthy weight and a sufficient level of activity are, we can study the associations between these behaviors and different health outcomes in epidemiological studies. Our results may guide policy makers and prevention strategies for different outcomes of specific interest. However, assessing physical activity is not trivial. Most large epidemiological studies rely on self-reported questionnaires to assess this complex behavior as this is a cost-efficient method with a low participant burden. To make sure that you are actually measuring what you think you are measuring, it is important to use a validated questionnaire.

Prostate cancer is the second most common cancer in men globally and the most common among men in developed countries.[4] What causes or may prevent the disease is still unclear but lifestyle factors, including body weight and physical activity, may be of importance for both the development and progression of tumors. Finding ways to reduce the incidence and mortality of prostate cancer is of great public health concern. As overweight and obesity and physical activity or inactivity are modifiable factors, they are of particular interest to study in relation to the disease.

This thesis has two parts. The first part concerns how body weight and physical activity affects progression of tumors and survival after prostate cancer diagnosis **(Study I** and **II**) as well as levels of prostate specific antigen (PSA) and the risk of developing prostate cancer (**Study V**). The second, more methodological part, concerns the development and validation of a new web-based physical activity questionnaire, Active-Q, designed for use in large epidemiological studies (**Study III** and **IV**).

2 BACKGROUND

2.1 EPIDEMIOLOGY

In epidemiology, we study the causes and spread of health and disease in a population. With the aim of drawing conclusions regarding the causality of associations between different exposures and outcomes we develop methods for better assessment of such, keep detailed registries, design our studies and model our data as best we can. However, although we aim to find out how the real world works, we can only study what we are able to observe and measure. While descriptive epidemiology will give us information regarding the occurrence of an outcome in the population, the associations between exposures and outcomes are described using analytical epidemiology where information from observational or experimental studies is analyzed. To make interpretations with a public health implication, information from both descriptive and analytical studies are needed. Even if there is a strong association between a risk factor and an outcome, the implications on public health may be small if the occurrence of the exposure or outcome is rare.

2.1.1.1 Epidemiological study design

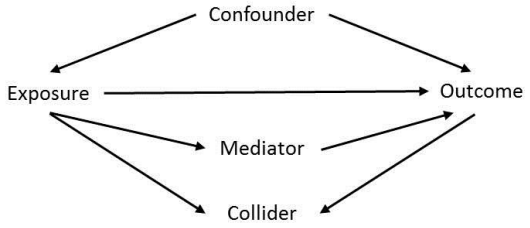
The three association studies (**Study I, II and V**) included in this thesis are based on data from two *cohort studies*. A cohort is a group of people at risk for the outcome of interest, i.e. not having experienced the outcome at the start of the cohort, followed over a specific amount of time. During the follow-up time, outcome events and exposures are assessed either prospectively or retrospectively. The incidence of the outcome is then compared among the exposed and unexposed to determine if it differs between the two groups. Cohort studies are useful when studying common outcomes or multiple outcomes or exposures. When studying a rare outcome, a case-control design may be more efficient and worth mentioning although this type of design is not included within this thesis work. In a *case-control study*, cases (individuals having developed the outcome) and controls (individuals that have not developed the outcome) are sampled from a source population (which can be thought of as a cohort). The exposure status is thereafter assessed among cases and controls. Results from association studies may guide *intervention studies* and *clinical trials* where exposure (or no exposure) is assigned to individuals who are thereafter followed-up. A r*andomized trial* is a study where the exposure is randomly assigned to participants, a study design that aims to remove the influence of confounding from other factors by creating an equal distribution of such factors among both exposed and unexposed individuals.

2.1.1.2 Confounding

Confounding is caused by a third factor affecting the association between an exposure and an outcome. If confounding is present and not controlled for, the observed association may be biased. This can lead us to see associations where there are no or to true associations being masked. A *confounder* is a factor that is associated with and causes both the exposure and the outcome. Confounding can be addressed directly in the study design (e.g. by randomization or matching) or at the analysis stage, by controlling for known and measured confounders in statistical models. Even if confounding is controlled for to the best of our ability, there may always be unknown, unmeasured or residual confounding affecting the results. Other factors which are

associated with both the exposure and outcome but that are not confounders are mediators and colliders. A *mediator* is a factor that lies in the causal pathway between an exposure and an outcome, i.e. it is an effect of the exposure and a cause of the outcome. A *collider* is an effect of both the exposure and the outcome. Controlling for mediators and colliders may cause bias similar to not controlling for confounders. Directed Acyclical Graphs[5] can be used to visually display associations between an exposure and an outcome and other factors affecting the association, **Figure 1**.

Figure 1. Example of a Directed Acyclic Graph (DAG) illustrating the relationship between an exposure and an outcome. The arrows indicate associations and the direction of such



2.1.1.3 E-epidemiology

Using the Internet for epidemiological research (e-epidemiology) has during the recent decade changed the prerequisites for large scale data collection.[6] The use of web-based questionnaires to collect data is more rapid and cost effective than traditional modes of data collection, including use of paper-based questionnaires, and offers additional advantages such as increased data quality due to implementation of automatic checks for errors or missing answers.[7] Internet access in Sweden is high, with more than 90% of all adults having access at home.[8] The validity of web-based self-reports of lifestyle factors is generally reported to be high.[7] The newly developed web-based physical activity questionnaire Active-Q is validated in **Study III** and **IV** in this thesis and used in the large scale data collection in **Study V**.

2.2 BODY MASS INDEX

Our body weight reflects our body's storage of energy which is a result of the balance between the energy intake from the food we eat and our energy expenditure from being alive, breathing, digesting food and being physically active. An imbalance between the intake and the expenditure will lead to weight loss if the intake is less than the expenditure and a weight gain if the intake is greater than the expenditure. Our body weight, however, also depends on other factors including our height and body composition (e.g. muscle mass, bone mass, fat mass and total body water).

Body mass index (BMI) is used in most large epidemiological studies as a proxy measure for body fat as it is easy to assess in large study populations. Other methods for assessing body composition in detail include bioelectrical impedance analysis, dual energy x-ray absorptiometry, and dilution techniques, among others.[9] BMI is body weight in kilograms divided by height in meters squared (kg/m^2). Adults with a BMI <18.5, $18.5<25$, $25<30$ and ≥ 30 kg/m^2 are usually defined as being underweight, normal weight, overweight or obese, respectively.[10] However, the fact that BMI does not differentiate between fat free mass and fat mass is a major limitation and subjects with high muscle mass and low fat mass may be incorrectly classified as overweight or obese by BMI.[11, 12] Nevertheless, BMI has been shown to perform similar to waist circumference as an indicator of body fat.[13]

There is a clear trend between a high BMI and negative health consequences including increased risk of mortality from hypertension, dyslipidemia, type-2-diabetes, coronary heart disease and some types of cancer as well as overall-mortality.[10] The prevalence of overweight has increased dramatically during the last decades and the prevalence of obesity has nearly doubled since1980.[14] In 2014, 49% of all adult men in the world and 57% of men ages 16-84 years in Sweden were overweight or obese.[14, 15] The prevalence was even higher among Swedish men in the age groups 45-64 and 65-84 years, where 69 and 67%, respectively, were overweight or obese, respectively. The high and increasing prevalence of overweight and obesity makes it important to determine any potential effects a high BMI may have on our health.

2.3 PHYSICAL ACTIVITY

Physical activity is a multidimensional behavior defined as "Any bodily movement produced by skeletal muscles resulting in energy expenditure".[1] According to this definition, any activity, however sedentary, light, moderate or vigorous, as long as it results in contractions of skeletal muscles producing energy expenditure, is physical activity. Nevertheless, many of us think about exercise when we hear physical activity, but to be clear, exercise has been defined as "Physical activity that is planned, structured and repetitive, and results in the improvement or maintenance of one or more facets of physical fitness".[1] Physical fitness is in turn the resulting physical outcome from being physically active or exercising and has been defined as "A set of out-comes or traits that relate to the ability to perform physical activity".[1] The relationships between the different physical activity behaviors are shown in **Figure 2**.

Our physical activity behavior is closely related to our total energy expenditure which is composed of three main parts. The most modifiable part is the result of our physical activity and is dependent on the frequency, duration and intensity of the physical activities we perform. This part can vary greatly between individuals but is usually in the range of 15-30% of our total energy expenditure, although both lower and higher percentages may occur in very sedentary and very active individuals respectively. The largest part of our total energy expenditure, approximately 60-75%, is our basal metabolic rate (BMR), i.e. the energy we need to expend to stay alive.[16] BMR is a function of body size and body composition, which are mainly affected by sex, age, weight and height, as well as other factors including physical fitness and explains much of the variation seen in total energy expenditure between subjects. Standard equations for estimating BMR take sex, age, weight and height into account.[17] Lastly, an additional 10% of our total energy expenditure is the energy we need to digest food and absorb nutrients, i.e. diet induced thermogenesis. Our body weight is stable when our total energy expenditure and our energy intake are in balance. **Figure 2** describes the relationship between components of our total physical activity behavior and energy expenditure. Our total energy expenditure can also be expressed as multiples of BMR. The resulting physical activity (PAL) value is comparable between individuals as it by definition controls for factors which influence BMR, i.e. sex, age, weight and height.

Physical activity epidemiology can be divided into a two part process.[18] In the first part, the association between physical activity behavior and disease or health outcomes, potential determinants for the physical activity behavior and possible interrelationships between physical activity and other behaviors are studied. Secondly, the knowledge gained in the first part is applied to health promotion and prevention and control of

disease.[18] However, the process is dependent on valid and reproducible methods for assessing physical activity.

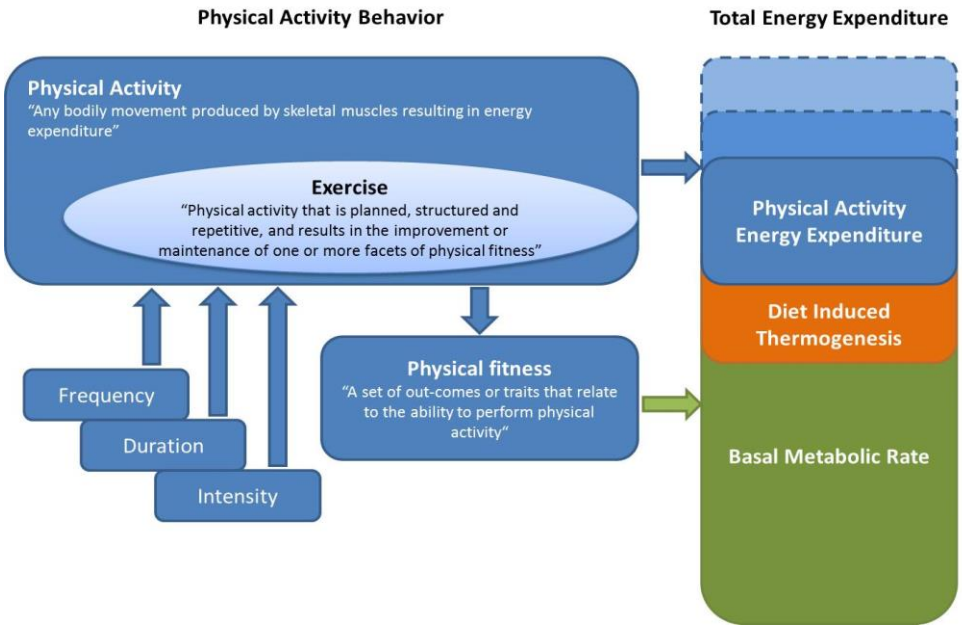


Figure 2. Constitutes and definitions of physical activity behavior[1] and the relationship to total energy expenditure of which the physical activity energy expenditure is modifiable.

2.3.1.1 The concept of metabolic equivalents (METs)

An important concept within physical activity research is metabolic equivalents (MET), a multiple of BMR representing the intensity of a specific activity.[19] For example, an activity with a MET=1 (e.g. lying down or sitting quietly), does not increase the energy expenditure at all compared to our BMR (BMR*1) whereas an activity with a MET=3 (e.g. walking), raises our energy expenditure by three times (BMR*3) during the time of performing the activity. The higher the MET, the more intense the activity and the more energy is expended during performance. BMR in a healthy, normal weight adults can be approximated to equal an energy expenditure of 1 kcal·kg^{-1} body weight·h^{-1}. This corresponds to an oxygen consumption of 3.5 ml O_2·kg^{-1} body weight·minute^{-1}. Performing an activity with an intensity of 3 MET will therefore result in an energy expenditure of 3*1 kcal·kg^{-1} body weight·h^{-1}, i.e. the total energy expended depends on the individuals body weight and the duration of the performed activity. Examples of using MET-values to calculate the energy expenditure during four different activities are shown in **Table 1**.

Table 1. Examples of the energy expenditure for one individual having a body weight of 60 kg when performing activities with different MET-values for 1 hour.

Activity	**MET-value**[1]	**Activity level**	**Calculation** MET ·kg^{-1} body weight·h^{-1}	**Estimated Energy Expenditure** (kcal)
Sitting	1.0	Sedentary	1.0 (MET) · 60kg · 1 h	60
Standing	2.5	Light	2.5 (MET) · 60kg · 1 h	150
Walking	3.0	Moderate	3.0 (MET) · 60kg · 1 h	180
Running	7.0	Vigorous	7.0 (MET) · 60kg · 1 h	420

[1]Ainsworth et al. 2011 Compendium of Physical Activities: A Second Update of Codes and METvalues

Activities are often categorized by intensity as sedentary (MET <1.5), light (MET 1.5<3), moderate (MET 3<6) or vigorous (MET >6) depending on the MET-value for each activity. Ainsworth et al.[19-21] has published comprehensive lists of MET-values for various activities. Although the use of METs to estimate individuals' energy expenditure from, for example, physical activity questionnaires is widespread, it is not without limitations. Factors including age, sex, body weight and body composition, as well as physical fitness affect the energy cost of activities.[22, 23] The underlying assumptions for MET-values in adults do not hold for all individuals. In for example obese persons, the oxygen consumption per kg-body weight may be lower than that of normal weight persons.

2.3.1.2 Physical inactivity

For a long time, epidemiological research has been focused on physical *activity* but more recently, attention has been given to our increasingly sedentary behaviors and *inactivity.* Together with light intensity activities, sedentary time comprises most of our daily activity. Sedentary behaviors are usually defined by a posture of sitting or lying down and their low energy expenditure corresponding to a MET-value below 1.5. During the past decades, declines in work-related activity and active transportation have led to the accumulation of increased amounts of sedentary time.[24] In Sweden, time spent sedentary has increased by almost half-an-hour per day in only six years between 2002 and 2008.[25] Now recognized as an important lifestyle factor, sedentary behavior has been suggested as an independent risk factor for both metabolic diseases and all-cause mortality[26, 27], and WHO has listed inactivity as the fourth leading risk factor for mortality worldwide.[28] When talking about physical activity and the benefits of being active, we also need to remember the negative impact that inactivity has on our health.

2.3.1.3 Physical activity recommendations

To maintain health, Swedish adults are recommended to engage in at least 150 min per week of activity on a moderate level or 75 min per week on a vigorous level.[29] Activities should be performed in bouts of 10 min and to achieve additional health benefits the amount of activity should be increased. The newest addition to the Nordic recommendations on physical activity is an additional point encouraging sedentary time to be decreased.[29] Similar recommendations are issued by the American College of Sports Medicine and the American Heart Association[30], as well as by the WHO.[2]

2.3.2 Measuring physical activity

Accurate exposure assessment is critical in epidemiological studies of for example physical activity. Valid and reliable methods for measuring this complex behavior are therefore a key issue when aiming to study the associations between physical activity and any outcome. There are many different methods available today and the choice of a method for any specific study should be considered carefully. Both scientific as well as logistic considerations need to be made depending on the dimension of the physical activity of interest and the type of study conducted. While research has had to rely on self-reported measures such as questionnaires in the past, the development of new technologies, such as accelerometers, has made it possible to measure physical activity objectively in large-scale studies as well. Common methods of physical activity assessment in adults used in epidemiological studies are summarized in **Figure 3**.

Figure 3. An overview of commonly used methods to assess physical activity among adults in epidemiological studies

	Self-reports		Objective methods				
	Questionnaire	Diary/record	Pedometer	Accelerometer	Heart rate monitors	Doubly Labelled water	Calorimetry
Measure	Duration and frequency	Duration and frequency	Steps	Acceleration	Heart rate	CO_2-production	O_2-consumption and CO_2-production
Outcome	Time MET-hours[1] EE[1]	Time MET-hours[1] EE[1] Bouts and patterns	No. of steps taken	Acceleration, output of different intensity identified	Intensity, frequency and duration of heart rate	TEE/PAEE/BMR	REE (~BMR)
Prospective measure	No	Yes	Yes	Yes	Yes	Yes	Yes
Participant burden	Low	High	Low	Low/Moderate	Moderate	Low	High
Researcher burden	Low	Moderate	Low	Moderate	Moderate	Moderate	High
Qualitative information	Yes	Yes	No	No	No	No	No
Low cost →							→ High cost
Low validity →							→ High validity

[1]By the use of MET-values. Abbreviations: Energy Expenditure (EE), Total Energy Expenditure (TEE), Physical Activity Energy Expenditure (PAEE), Basal Metabolic Rate (BMR) ~Resting Energy Expenditure (REE)

2.3.3 Self-reported methods

Much of what we know today regarding associations between physical activity and different health outcomes is based on self-reported measures of physical activity which have been used in research during the past century.[31] The most common methods for collecting self-reported physical activity data are through questionnaires or by diaries/records. Although self-reported instruments are widely used, they are not without limitations such as social desirability bias, cognitive demands on recall and difficulties capturing all physical activities performed.[32] Central to this thesis work are physical activity questionnaires.

2.3.3.1 Physical activity questionnaires

Self-reported physical activity questionnaires are cost effective and convenient to use. They generate both quantitative (frequency and duration) and qualitative (settings and domains of activity) information, the latter is not captured by objective methods. However, we must not forget the limitations of physical activity questionnaires which are prone to bias and measurement errors, which need to be addressed.[32, 33] A limited number of included activities and pre-defined response intervals may have an effect on the results and must be carefully considered at the design stage of a questionnaire. Physical activity is many times over-estimated while time spent sedentary is under-estimated .[34] Intentional or unintentional misreporting may differ between subgroups. Women have been seen to over-report more than men, and a high BMI has also been associated with high levels of self-reported physical activity when compared to direct measures.[34, 35]

It is important to assess validity and reliability of any questionnaire within the specific population in which it is intended to be used. The time frame that the questionnaire aims to measure, the types of activities included, the length of the questionnaire, and frequencies used for assessment of activities must also be carefully considered. These factors are important for the questionnaire's performance and interpretation of the

results.[33] Structured questionnaires can provide information on physical activity within different domains as well as the frequency and duration of different activities.

There are many different physical activity questionnaires available and even more validation studies published. These have been summarized in several extensive reviews.[36-38] Physical activity questionnaires have previously been focused on activity and usually capture recreational activities and activities performed during leisure time. Today most questionnaires also assess physical activity within additional domains, such as occupation and the majority of newly developed questionnaires also include sedentary activities. The time frame measured in a questionnaire can vary from a period of one day to the past months or year. A very common time frame is the "last 7 days" or during "a typical week".[36] Over-reporting of physical activity is common due to misreporting of frequency, intensity and/or duration of activities and can be caused by for example social desirability and memory bias.[39] In particular older individuals may have cognitive difficulties in recalling activities.[40]

In an extensive review by Helmerhorst et al.[36], most physical activity questionnaires reported a good to high reliability but poor to moderate validity. While the absolute validity was limited, the questionnaires appeared valid for ranking subjects. Sedentary behavior was reportedly a difficult domain of activity to measure and correlations with objective measures were poor. However, as the authors argue, objective methods themselves are limited in measuring sedentary behavior, which may contribute to poorer agreement. Interestingly, despite the many new questionnaires being developed, no substantial difference was seen between newer and already existing questionnaires.[36] In an attempt to develop a standardized questionnaire assessing overall physical activity, the international physical activity questionnaire (IPAQ)[41] and the global physical activity questionnaire (GPAQ)[42] assessing physical activity during the past seven days have been developed.

2.3.4 Objective methods

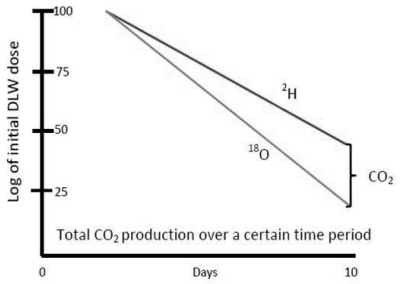
Technology development during the past decades has added to the field of physical activity research and although still more expensive, new objective methods are much more available and feasible to use in large-scale studies today than ever before. Objective methods include doubly labelled water (DLW), accelerometers (motion sensors), pedometers and heart rate monitors. While good at capturing the overall physical activity measured as energy expenditure, acceleration, steps or heart rate, these objective methods do not capture qualitative information regarding activities performed or the context in which they were performed.[43] Central to this thesis work is the DLW-method and accelerometers.

2.3.4.1 Doubly labeled water (DLW)

To assess total energy expenditure, the DLW-method was used as the criterion measure.[16] The method utilizes the stable isotopes deuterium (^{2}H) and 18-Oxygen (^{18}O) and DLW is a mixture of the stable isotope labelled waters $^{2}H_2O$ and $H_2{}^{18}O$. The DLW equilibrates with the human body's water pool and uses the kinetics of the water turnover in the body to estimate the rate of carbon dioxide (CO_2) production, i.e. it does not measure respiratory gases directly. The isotope marked water molecules will distribute in the body water compartment and although water molecules are leaving our body as vapor or part of urinary, fecal or other fluids constantly, the body water pool is relatively stable in size as the input and output of water is generally the same.

To assess total energy expenditure, the elimination kinetics of the two stable isotopes are measured in urine using gas isotope ratio mass spectrometry.[16] The decline in ^{2}H is a function of the H_2O-turnover in the body while the decline in ^{18}O is a function of both the H_2O-turnover and CO_2-production. Since the oxygen in our body water and respiratory CO_2 are in equilibrium, the difference between ^{2}H and ^{18}O water turnover curves is ^{18}O lost from CO_2, **Figure 4**. The difference is integrated over a specified measurement period to determine total CO_2 production. Thereafter, the total energy expenditure can be calculated through standard equations[44] using an appropriate respiratory quotient (RQ) for the specific population. The RQ is the ratio between the CO_2 produced and the O_2 consumed and depends on our dietary composition as different macronutrients have different RQs.

Figure 4. Graph exemplifying the elimination of ^{2}H and ^{18}O through water turnover and the resulting difference representing the ^{18}O lost from CO_2.



Important to note is that in calculations of CO_2, corrections are made for isotopic exchange and fractioning. Further, the DLW technique relies heavily on four major assumptions; 1) that the body water pool is a steady state, single compartment pool with complete and rapid equilibration, 2) that the isotopes exit the body as only CO_2 or water, 3) that isotopes exit the body only while in isotopic equilibrium with body water, and 4) that the CO_2 and water lost from the body do not re-enter the body water pool.[16] The assumptions are generally robust.

2.3.4.2 Pedometers

Using pedometers to measure daily steps is an easy and inexpensive method to assess overall physical activity. While older pedometers were mechanical, newer versions are more often electronic. Pedometers are specifically designed to assess walking and will measure the number of steps taken during a defined time period. Reviews on pedometer methodology reach similar conclusions stating that it is a good overall method for total physical activity represented by step counts, but that it lacks the ability to assess intensity, frequency and duration of movement or energy expenditure.[45-48] While pedometer output has been strongly correlated with results from accelerometer measurements and direct observation, correlations with energy expenditure and self-reported physical activity have been moderate.[49] The highest accuracy in pedometer output has been found for step counts, less accurate results were seen for estimations of energy expenditure.[50] A wide variety in the precision of pedometer measurements has also been seen and while some pedometers measured steps within 3% of actual values, others had a larger variety of ±37%.[51] Due to variability in for example mechanisms and validity, the output of different pedometers is not comparable.

The number of days of pedometer wear required for a valid estimation of physical activity levels depends on a number of things. For example the specific research question, if the aim is to assess habitual physical activity or a snap-shot of the current activity level. Other factors include the characteristics of the study population and the available resources. However, the within-individual variability due to real life-

fluctuations decreases when the number of days measured increases.[52] Reactivity, i.e. changes in activity behavior caused by measurement of the behavior, among study participants wearing pedometers has been seen in several studies[53-55] but not all.[56] Under certain conditions there is reactivity to pedometer wear and participants who are able to view steps and instructed to log them may increase their daily steps by as much as 15 % during the time of monitoring .[47] Only viewing the steps causes less reactivity while use of sealed pedometers has little or no reactivity effect at all.[47]

2.3.4.3 Accelerometers (motion sensors)

Rapid development of accelerometer technology has led to many different monitors being available and has opened up for widespread use. Most accelerometers are small and easily wearable instruments that register acceleration on one or more planes. Information regarding the frequency, duration and intensity of an individual's physical activity can be indicated from accelerometer measurements[45], while qualitative and contextual information is not obtained. Many accelerometers today are tri-axial, i.e. they register acceleration in three planes, with sampling rates typically in the range of 40 to 100 Hertz (Hz). The large amount of information captured is usually comprised into epochs of lower resolution. Similar to data on pedometer wear, the number of measured days needed may differ. To assess habitual physical activity in adult populations, 3-5 days is likely to be sufficient.[57] Since habitual activity may differ between weekdays and weekend days, the wear period should include both. Few studies have assessed reactivity to accelerometer wear but their similarities to sealed pedometers indicate that the effects most likely are minor.

Results from accelerometer measurements are often referred to as counts due to the dimensionless nature of the data. Moderate-to-strong correlations have been seen between accelerometer counts and different physical activity measures such as oxygen consumption, physical activity energy expenditure and MET-hours.[57] A challenge for researchers is to define the counts and translate, or calibrate, the results into variables of for example energy expenditure or time spent at different intensity levels.[58] This is often done by performing a calibration study where accelerometer counts are compared to oxygen consumption during performance of pre-defined activities. Thereafter, cut-offs to classify the accelerometer output into categories of intensity or transform it into energy expenditure are developed based on the measured oxygen consumption. Pre-defined MET-values of performed activities may be used instead of measured oxygen consumption although they give less precise estimates. However, inconsistency between methods used in calibration studies has led to difficulties in comparing results from different studies and types of accelerometers.[59] While accelerometers capture both sedentary behaviors and higher intensities of physical activity, the sensitivity of measurements is poor in the lower range of activities and most non-ambulatory activities, e.g. bicycling and weight lifting, are not measured correctly.[45]

2.4 PROSTATE CANCER

2.4.1 The prostate

The prostate is a walnut sized gland, located just below the urinary bladder and in front of the rectum. It surrounds the upper part of the urethra and is surrounded by nerves controlling erection. The prostate is part of the male reproductive system and the main function is to produce fluid which protects and enriches sperm cells. The prostate starts to develop before birth, but typically grows during adolescence under regulation of the

male hormone testosterone and its byproduct dihydrotestosterone, and reaches full size around age 20. Among men older than 50 years, the prostate is commonly enlarged in a benign manner (benign prostatic hyperplasia). This usually harmless condition can in some cases cause problems with urination but is not related to prostate cancer.

2.4.2 Disease description

Prostate cancer is the most common cancer among Swedish men.[60] While it is very common in older ages it is very rare among men younger than 40 years. Almost all (90%) prostate cancers are adenocarcinomas and arise in the gland cells of the prostate. The remaining, rarer, types of prostate cancer arise from other types of cells. Early stage prostate cancer will most likely not cause any symptoms and can therefore be hard to detect. Early symptoms of prostate cancer may include frequent urination, difficulty maintaining a steady stream of urine, problems with erection and ejaculation, and blood in the urine. Late symptoms, often arising when the cancer has spread, include pain in the back or hips as a results of the cancer having metastasized. Weight loss and fatigue are also common symptoms for most cancers at a late stage.

Most prostate cancers are very slow growing and can remain asymptomatic for years from tumor initiation and some men will never experience any symptoms. In reality, many men, whether diagnosed or not, will live the rest of their lives without any symptoms of the prostate cancer and are likely to die from something unrelated to the cancer, such as cardiovascular disease. Nevertheless, there are more aggressive tumors that may metastasize to the bone or lymph nodes and cause premature death.

Although some prostate cancers are found after the patient has experienced symptoms, most cancer are asymptomatic and are detected as a result of a blood test showing elevated levels of prostate-specific antigen (PSA). A PSA-test indicating a possible tumor is followed-up by a physician examination and biopsies to confirm diagnosis. At the time of diagnosis it is important to determine if the tumor is likely to be aggressive or to grow more slowly having a better prognosis. Together with age, general health and other symptoms, the tumor grade and stage will guide treatment options. While more aggressive tumors of higher grade and stage may be treated using surgery, radiation therapy, hormone therapy, chemotherapy or other alternatives, patients with a slow growing early tumor can be followed-up with active surveillance where the tumor is monitored closely by a physician and regular checks of any potential tumor development are made.

2.4.3 Incidence and mortality

Prostate cancer is the second most common cancer in the world today and over 1 million men were diagnosed in 2012.[61] However, the incidence rates vary largely between different regions in the world with Australia, New Zealand, North America, and northern and western Europe having the highest rates, sometimes as high as 25 times the rate of some parts of Africa and Asia. Almost 70% of the total number of diagnosed men lives in the more developed regions of the world. From the mid 1980's to today, the incidence of prostate cancer has increased worldwide.[62] While there was a steep increase in the incidence of prostate cancer in Sweden during the late 1990's, rates have stabilized and even decreased slightly during recent years[62], see **Figure 5**. The introduction of the prostate-specific antigen (PSA) test during the late 1990's most likely explains the steep increase during this time period. The age-standardized

incidence rate in Sweden is approximately 100 per 100,000 men and around 9,600 men were diagnosed with the disease yearly between 2007 and 2011.[60]

The relative survival among men in Sweden with prostate cancer is good. The 5-year survival is over 90% and the 10-year survival just above 80%.[63] Nevertheless, around 2,400 Swedish men die as a result of their prostate cancer every year. The high incidence and relatively low mortality, see **Figure 5** for trends during the past decades, has resulted in a large number of living men having been diagnosed with prostate cancer. The prevalence of men that have ever been diagnosed (regardless of time since diagnosis or if the cancer is considered cured) in Sweden is almost 85,000.[60]

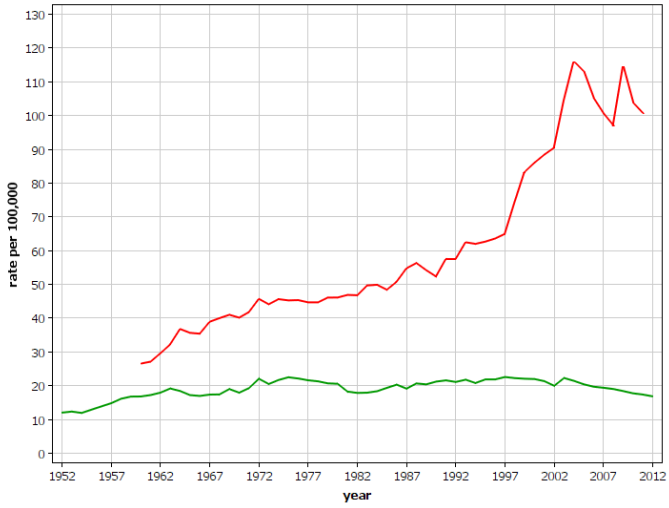


Figure 5. Prostate cancer incidence and mortality in Sweden between the years 1952 to 2012.

Source: NORDCAN © Association of the Nordic Cancer Registries (Generated and downloaded 29.8.2014)

2.4.4 Prostate Specific Antigen (PSA)

One possible explanation for the relatively steep increases in prostate cancer incidence in the late 1980's and 1990's is the introduction of the PSA-test.[62] PSA is an enzyme naturally present in low levels in the serum of healthy men. PSA-levels increase naturally with age but elevated levels may be a sign of disease such as prostate cancer, benign prostatic hyperplasia or inflammation. The intensity of testing varies around the world and may explain differences in incidence between countries. When the PSA-test was introduced, the rationale was to increase early detection of prostate cancers and reduce mortality from the disease. However, the test has led to increased numbers of men being diagnosed at lower PSA-levels and at younger ages.[64] Many men are therefore diagnosed even though the tumor might be slow growing and may never result in physical symptoms. The risk of over-diagnosis is another downside of the PSA-test. It has been estimated that 23-42% of cancers detected using the PSA-test are over-diagnosed and would never have caused any clinical problems.[65] The psychological burden of having been diagnosed with prostate cancer is sometimes greater than the physical burden of the disease itself. Adding to the controversy is that lack of evidence showing that PSA-testing reduces prostate cancer mortality.[64]

Sweden does not have a general screening program for prostate cancer. The National Board of Health and Welfare did an extensive review of the scientific literature and decided against it in 2013.[66] The decision was made based on the fact that the negative effects of a screening program, e.g. over-diagnosing and overtreatment, would exceed a potential increase in survival. Had a screening program for prostate

cancer been introduced, the mortality was estimated to decrease by 1 to 4 men per 1000 men after 10-15 years while 40-50 more men would be diagnosed with prostate cancer each year then if there were no screening program. An increased number of men with small, slowly growing tumors would be treated and thereby be at risk for potential side effects of treatment. Despite the lack of a national screening program, PSA-testing is common in Sweden and has increased during the past decade.[67] More than 65% of men without a previous prostate cancer diagnosis aged 60-69 years had a PSA-test in 2011.

2.5 PROSTATE CANCER EPIDEMIOLOGY

2.5.1 Body mass index and prostate cancer

Co-occurring with the increasing prostate cancer incidence today is the increasing prevalence of overweight and obesity. In Sweden, over 65% of men 45 years of age or older were overweight or obese in 2014.[15] Overweight, obesity, and prostate cancer affect substantial proportions of the male population but few specific risk determinants for prostate cancer have been identified to date. Body weight is of great interest to study as it is a modifiable lifestyle factor with the potential to influence the risk and development of prostate cancer.

Body weight is related to both metabolic and hormonal pathways, an example is fat mass which plays an important role in hormone metabolism.[68] Since prostate cancer is hormone related it is likely to be linked to anthropometric factors. Although previous studies suggest a possible association between BMI and the risk of prostate cancer, results are inconsistent and the relationship appears complex.[69] While previous studies have shown no association between BMI and the overall risk of prostate cancer or risk of low-grade cancer, a high BMI has been positively associated with aggressive or fatal prostate cancer.[70-73] More recently, a dual effect of obesity on prostate cancer risk has been suggested. A meta-analysis showed an increased risk of more advanced or aggressive disease and a decreased risk of early stage and less aggressive cancers with increasing BMI.[74]. A possible explanation for the association between BMI and risk of different prostate cancer subtypes is the fact that higher BMI has been associated with lower serum PSA concentrations[75], potentially leading to later detection of tumors. Indeed, plasma hemodilution yielding lower PSA values may be one explanation for delayed diagnosis and therefore poorer prognosis.[76]

The more consistent association between high BMI and increased risk of aggressive prostate cancer suggest that BMI might be of greater importance for the progression of prostate tumors rather than for tumor development.[77] A high BMI has been associated with an increased risk of both progression and prostate cancer specific mortality.[78] The association with prostate cancer specific mortality has recently been shown to be even more pronounced in men with more aggressive disease.[79]

2.5.2 Body mass index and PSA-levels

A possible explanation for the association between overweight and obesity and prostate cancer risk might be an effect of a high BMI on serum PSA-levels. Numerous studies have established an inverse association between BMI and PSA-levels.[75, 76, 80-86] An increased BMI may lead to decreased serum PSA-levels through mechanisms of; decreased testosterone levels[87], hemodilution[76] or a larger prostate size making it harder

to biopsy the prostate and verify diagnosis.[85, 88, 89] Factors that might influence PSA-levels are important to assess as most prostate cancer in developed countries today are detected by a biopsy directly following a PSA-test.

2.5.3 Weight change and prostate cancer

While most previous studies have investigated the effect of BMI or another measure of body composition, few studies have had the opportunity to study weight change, which is in fact what causes a specific BMI, in relation to prostate cancer. Two previous studies have shown an association between high weight gain during adulthood and an increased risk of aggressive or fatal prostate cancer.[90, 91] A large weight gain during adulthood has been associated with an increased risk of biochemical recurrence after a prostate cancer diagnosis and a weight gain around the time of a prostate cancer diagnosis has been associated with an almost doubled risk of cancer recurrence.[92, 93] Further, a weight gain of ≥2.5kg in the year before a radical prostatectomy increased the risk of biochemical recurrence by 65% compared to men who gained less weight.[94]

2.5.4 Physical activity and prostate cancer

Another modifiable life-style factor with the potential to influence prostate cancer risk and progression is physical activity. Physical activity has been linked to reduced overall mortality in the general population and there is consistent evidence linking increased levels to reductions in all-cause mortality among cancer survivors.[95, 96] Reductions in both breast cancer and colon cancer specific mortality has been shown whereas there is insufficient evidence for prostate cancer.[95] Physical activity has been systematically investigated in relation to prostate cancer risk and was in a review and meta-analysis on the topic shown to be inversely associated with prostate cancer risk with a 10% risk reduction when comparing men in the highest and lowest groups of physical activity.[97]

Few previous studies have been able to investigate the effects of post-diagnostic physical activity on prostate cancer progression and mortality. The first study, published by Kenfield et al.[98], investigated the association between physical activity and mortality among men with prostate cancer. Their results showed that men who walked ≥90 min/week at a normal to very brisk pace had a reduced risk of all-cause mortality by 46% compared with walking for shorter durations at an easier pace. For prostate cancer specific mortality, walking briskly for longer duration was suggestively, but not statistically significantly, associated with a lower mortality rate. Men engaging in vigorous activity ≥3 h/week had a 49% lower risk of all-cause mortality and a 61% lower risk of prostate cancer specific death compared to men engaging in <1 h/week of vigorous activity. In a second study, Richman et al.[99] investigated physical activity and prostate cancer progression and found that men walking briskly for ≥3 h/week had a 57% lower progression rate compared to men walking for shorter durations at an easier pace. They also showed that, independent of duration, brisk walking was associated with a 48% decrease in progression rate compared to walking at an easy pace. A suggestive, but non-significant, inverse association between vigorous activity and prostate cancer progression was also seen.

3 AIMS

The overall aims of this thesis were to study associations between body weight and physical activity and prostate cancer risk, progression and mortality as well as to evaluate the validity of the web-based physical activity questionnaire "Active-Q".

Specifically, we aimed to:

Study I
Study associations between Body Mass Index (BMI) at the time of diagnosis of localized prostate cancer and progression, overall- and prostate cancer specific mortality as well as weight change after diagnosis and overall- and prostate cancer specific mortality

Study II
Study associations between physical activity after diagnosis of localized prostate cancer and overall- and prostate cancer specific mortality

Study III
Assess the validity and reproducibility of Active-Q against the doubly labeled water method with regards to total energy expenditure and against pedometers with regards to total physical activity

Study IV
Assess the validity and reproducibility of Active-Q against accelerometers with regards to time spent at different intensity levels

Study V
Study associations between BMI and serum PSA-levels as well as prostate cancer risk

4 METHODS

4.1 VALIDATION STUDIES (STUDY III AND IV)

4.1.1 Background

In studies attempting to investigate an association between any exposure and an outcome, it is important to assess the validity of both the exposure assessment and the outcome to be able to take potential errors that may impact the results into consideration. Active-Q was originally developed for the LifeGene-study, a large prospective population based cohort.[20] In addition to clinical data collected at specific health centers, large amounts of information regarding lifestyle factors were to be collected entirely via the Web. When LifeGene was initiated, physical activity questionnaires were in general paper-based and not developed or validated for web-based use. Therefore, Active-Q was created and by efficient use web-based features, e.g. screening questions and follow-up patters, it was possible to create a questionnaire that only took a few minutes to respond to, yet assessed detailed information on physical activity. To validate Active-Q, the VALMA-study was performed during the spring of 2009 (**Study III**). The study population comprised adults, many young, and both men and women to reflect the future study participants in LifeGene. Thereafter, Active-Q was also included to measure physical activity in the large population-based STHLM-2 cohort which includes middle-aged and older men.[100] Since this study population is differed from that in LifeGene, we performed a second validation of Active-Q within the STHLM-2 study population (**Study IV**). During the spring of 2012 we began data collection for the VALTER-study. In **Study III** and **IV**, Active-Q is validated with regards to measuring total energy expenditure and time spent at different activity levels against the DLW method and accelerometers, respectively.

4.1.2 The Active-Q Physical Activity Questionnaire

Active-Q is a web-based, interactive physical activity questionnaire assessing habitual activity in adults >18 years of age. Physical activity during the past months is assessed within the four domains of; daily occupation, transportation, leisure time activities, and regular sporting activities. Additional sleeping hours are also assessed. A screening question assessing working status preceded the questions on daily occupation and subjects who respond that they are not working do not have to respond to questions related to occupation. Initial screening questions listing all the activities included in each domain are posed for transportation, leisure time activities and sporting activities. Only activities selected by the respondent in the screening are followed up regarding frequency and duration to reduce the total number of questions for each respondent. All questions have predefined answers of frequency and duration. Depending on the respondent's answers to screening questions and the resulting follow-up patterns, the total number of questions responded to range between 9 and 47 in the present version of the questionnaire. Active-Q was modified slightly after the first validation study and questions on sleeping hours and working status were added and alterations to the included sporting activities were made. All activities in Active-Q are linked to MET-values which enable classification into different levels of intensity and allows for calculations of energy expenditure.

4.1.3 Study design - VALMA

Data from the VALMA (VALidation of Methods Assessing diet and physical activity) study is analyzed in **Study III**. VALMA was originally designed and conducted to evaluate the validity and reproducibility of both a new web-based food frequency questionnaire, Meal-Q, and the physical activity questionnaire Active-Q.[101-103] The dietary part of the study design and the validity of Meal-Q, have been described previously and is beyond the scope of this thesis.[102, 103]

Study participants included men and women, aged 20 to 65 years, recruited during the spring of 2009 through public advertisements in Stockholm, Sweden. Requirements for participation included having an email address and access to the Internet. Participants were not allowed to be on any weight alteration diet, pregnant, or having given birth during the ten months prior to study start. In total, 180 healthy adults were recruited, there among a sub-group of 40 individuals included in DLW analyses. All participants were provided oral and written information before giving their written informed consent prior to study start. The study was approved by the Research Ethics Committee at the Karolinska Institutet, Stockholm, Sweden.

The design of the physical activity validation part of VALMA is shown if **Figure 6.** The total time of participation was 21 days. At an introductory meeting on day one, participants signed an informed consent, had their weight (kg) measured and received a pedometer for recording of steps. The first Active-Q questionnaire was emailed to participants on day seven and steps were self-recorded in a Web-based program during day 8 to 14. The second Active-Q questionnaire was emailed to participants on day 21, seven days after completing the registration. Individual usernames and passwords served as unique identifiers when responding to the questionnaires and recording steps. Directly following the first Active-Q responded to, participants were asked to respond to a short evaluation of the questionnaire and additional questions of current height, weight, level of education, and tobacco use. Study participants in the DLW sub-group were given the oral DLW dose on the first day of the study, collected their first urine sample on study site and thereafter collected one urine sample per day during the following ten days before returning the samples to study personnel.

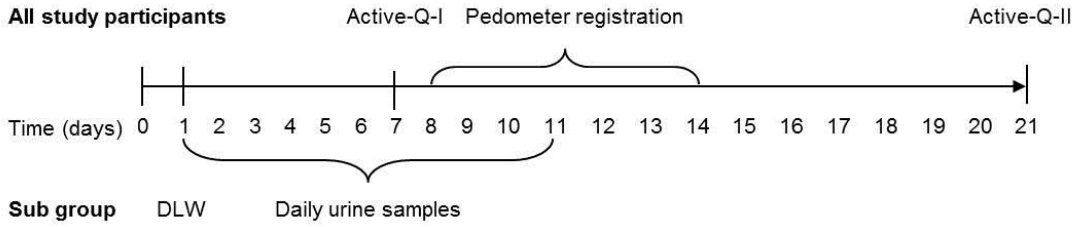


Figure 6. Study design of VALMA showing the timing of measurements using doubly labelled water (DLW) including collection of urine samples, pedometer registration, and response to the two Active-Q questionnaires (Active-Q-I and Active-Q-II) distributed.

4.1.3.1 Study participants

Out of the 180 initial participants in the VALMA-study, those not completing the study were excluded from analysis (n=3). Additionally, participants with incomplete data from the first Active-Q responded to, i.e. <1 hour of leisure time and sport activities together (n=6), who did not register their steps or who had registered <6 days of pedometer measurements (n=13) were excluded. In total, 158 participants were

included in validity analyses of Active-Q compared to pedometer data. The DLW sub-group originally comprised 40 participants of which 36 remained after the previous exclusions and the exclusion of one additional subject with implausible DLW data. For reproducibility analysis, participants with incomplete data from the second questionnaire were also excluded (n=8) leaving 150 participants in analysis.

4.1.3.2 Active-Q in the VALMA-study

Energy expenditure from Active-Q was calculated based on the assumption of 1 MET being equal to 1kcal · kg^{-1} · $hour^{-1}$.[19] To calculate the energy expenditure from activities in Active-Q, the activity's MET-value was multiplied by the respondents' weight, reported daily duration of the activity, and by a factor of 4.184 to convert values from kcal to kJ: $EE_{activity}(kJ/day) = MET_{activity} \cdot Weight(kg) \cdot Duration_{activity}(h/d) \cdot 4.184$. The crude total energy expenditure was estimated by summarizing the energy expenditure from all activities in Active-Q. Additional estimations of the total energy expenditure adjusted to 24-hours were calculated by adding eight hours of sleep to the crude estimate and compensating for all time diverging from 24-hours by adding or subtracting time using a MET-value of 2.0.[19, 104]

4.1.3.3 The Doubly labelled water method (DLW)

DLW was used to measure the average total daily energy expenditure during 11 consecutive days. In brief, standard DLW doses were prepared following a similar strategy to that of Trabulsi et al.[105] where a bulk dose of DLW was made by adding 44 g of $^{2}H_2O$ (99.98% sterility tested, CK Gas Products Ltd, Hampshire, UK) to 1 L 10% normalized $H_2{}^{18}O$ (SerCon Ltd, Cheshire, UK). Participants self-reported their body weight prior to study entry and those with a weight <75 kg or >75 kg were given 108 and 141 g of the bulk dose, respectively. A pre-dose urine sample was collected at study site before drinking the DLW and additional daily urine samples (5 ml, excluding the morning void) were collected during the following 10 days. Participants recorded the date and time of collection on each sample tube and kept the samples refrigerated before returning them to the study team. Samples were thereafter sent to the Medical Research Council, Human Nutrition Research, Cambridge, UK, for isotopic analysis,

Previous studies have described the principles of analyses of the isotopic enrichment in the samples[106, 107], and the slightly modified procedure used in the present study has also been described in more detail.[101] Isotope ratio mass spectrometry was used for analyses of the ratio between ^{2}H and ^{1}H. Assessment of the $^{18}O/^{16}O$ ratio was made using a continuous-flow isotope ratio mass spectrometer. Each batch of samples analyzed included analytical standards prepared in-house and traceable to the international standards, Vienna Standard Mean Ocean Water and Standard Light Arctic Precipitation. Using the equation by Schoeller et al.[108], total CO_2-production was estimated from the slopes and intercepts of isotope disappearance curves using data from urine samples collected on day 1-3 and 8-10. Total energy expenditure was calculated using the modified Weir equation[44] and a respiratory quotient (RQ) of 0.85.

4.1.3.4 Pedometers

An activity registration using pedometers was performed during seven consecutive days. Participants received a pedometer and were instructed to wear it at their waistline during time awake but to remove it when performing water activities. Total number of daily steps was self-recorded by participants in a web-based program. The average number of daily steps calculated for all participants who had registered at least six days.

4.1.4 Study design – VALTER

Data from the VALTER-study (VALidation against accelerometER) was analyzed in **Study IV**. VALTER was designed and conducted to evaluate and assess validity of Active-Q within a male population in which the questionnaire was already in use. All study participants responded to Active-Q on the Web twice and wore a GENEA-accelerometer[109] during seven consecutive days on two occasions. In addition, a calibration study of the accelerometers was also performed within a sub-group of participants to determine cut-points for classifying accelerometer data as sedentary/light, moderate or vigorous.

Study participants were recruited from the STHLM-2 cohort comprising men who during 2010 to 2012 underwent PSA-testing in Stockholm County, Sweden. Participants that enrolled in the cohort between March and May 2012 and who had agreed to be contacted for additional studies were invited to participate in VALTER. An invitation was emailed to 1,348 men in September 2012. Those who replied to the invitation were sent more detailed study information and were scheduled for an introductory meeting at Karolinska Institutet. All participants were given both written and oral information about the study and signed an informed consent prior to participation. In total, 167 men agreed to participate. The Research Ethics Committee at Karolinska Institutet, Stockholm, Sweden, approved the study.

Each participant was enrolled in VALTER during four weeks, the study design is shown in **Figure 7**. Participants attended an introductory meeting on day one of the study and received the first accelerometer to wear for seven days. Participants were instructed to wear the accelerometer continuously on their left wrist, irrespective of handedness, but to remove it during water-based activities. As a complement, they were also given a diary in which all occasions when the accelerometer was removed were to be noted. The first Active-Q questionnaire was administered via email later the same day and also included background questions on height, weight, year of birth, education level and handedness. After seven days, the accelerometer and the diary was returned to the research group via regular mail using a padded envelope with prepaid postage. Three weeks later, participants attended a second meeting and there received the second accelerometer to wear during seven days. The second Active-Q was administered via email later the same day and participants returned the accelerometer and the diary to the research group after seven days. Individual user-names and passwords served as identifiers for the questionnaires and the accelerometers had unique serial-numbers.

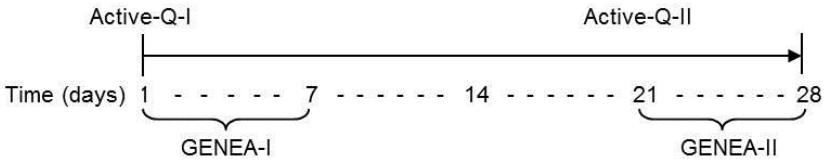


Figure 7. Study design of VALTER showing the timing of measurements using the GENEA accelerometer on two occasions and responding to the two Active-Q questionnaires (Active-Q-I and Active-Q-II) distributed.

A calibration of the accelerometers was performed in a sub-group of 22 participants who each wore two accelerometers on the same wrist while performing five predefined activities including: sitting, standing, walking at a pace of 3.2, 4.8 and 6.4 km/h (2, 3 and 4 mph). Each activity was performed for five minutes under supervision of study

personnel and counts from the middle three minutes of each activity performed were extracted for analysis.

4.1.4.1 Study participants

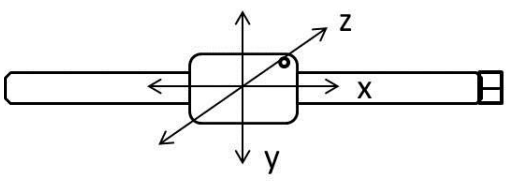
In total 167 men who agreed to participate in the VALTER-study. Out of them, men who did not complete the study (n=2) and men who had erroneous accelerometer data from the first (n=3) or second (n=4) week of accelerometer measurements were excluded. Additionally, as the accelerometer was worn on the left wrist, only men who reported being right-handed in the first questionnaire were included in analysis leaving 11 left handed-men for exclusion. In total, data from 148 men was analyzed.

4.1.4.2 Active-Q in the VALTER-study

Reported time spent at different activity levels was calculated by classifying activities in Active-Q into light-, moderate- or vigorous physical activities depending on the MET-value for each activity. Activities with a MET-value <3, 3-6 or >6 were classified as light, moderate or vigorous activity, respectively. An additional category of moderate-to-vigorous physical activity was also created and included all activities with a MET-value of 3 or above. Total time reported in each category was summarized.

4.1.4.3 The GENEA accelerometer

The GENEA (Gravity Estimator of Normal Everyday Activity) monitor (**Figure 8)** is a small and tri-axial accelerometer measuring vertical, anteroposterior and mediolateral movement at a rate up to 80 Hz with a dynamic range of ±6 g.[109] In the VALTER-study, acceleration was sampled at 40 Hz. The GENEA post-processing software (version 1.2.1) was used to summarize the raw 40 Hz tri-axial data into a signal vector magnitude (SVM) (gravity subtracted), by $SVMgs = \sum |\sqrt{x^2 + y^2 + z^2} - g|$. In the original GENEA software, g was assumed to be 1.00. The post-processing software output represents a mean r-g value per second during each specific minute. To obtain results as 1 minute epochs the output was multiplied by 60, resulting in the same effect as summarizing 60 1-s epochs. Since measures had been made at 40 Hz, the output was multiplied by 2 to make results comparable to a previous study using GENEA sampling at 80 Hz.[109] The SI unit of the outcome variable is g-seconds (g·s).



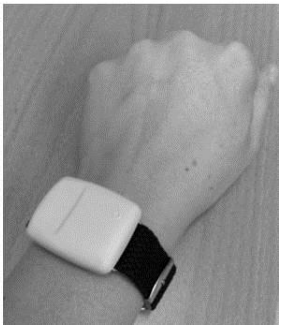


Figure 8. The GENEA-monitor is a small tri-axial accelerometer measuring vertical, anteroposterior and mediolateral movement.

In the additional calibration study, cut-points for classification of the GENEA output into different levels of intensity were developed for our specific study population. The SVM_{gs} for each measuring point of each activity performed during the calibration was calculated and plotted against the activities corresponding MET-value. The resulting straight line equation $y = 0.0019x + 1.3165$ was used to generate cut-points for accelerometer out-put corresponding to MET-values of 3.0 and 6.0, see **Figure 9**.

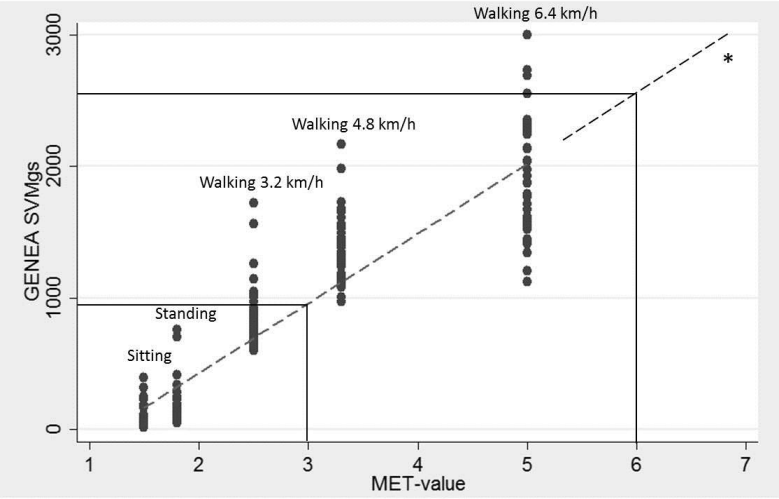


Figure 9. Displaying MET-values of the five activities performed during the calibration (x-axis) and average GENEA-output in SVMgs (y-axis) for each specific activity (n=22, 44 measuring points). Cut-offs for SVM_{gs} at MET-values 3 and 6 estimated using the resulting linear equation $y = 0.0019x + 1.3165$ are marked in the figure.

For analysis in the present study, data from six complete days was extracted from each week of accelerometer measurements starting at midnight on the first day the accelerometer was worn. Each minute output from the GENEA accelerometer with a SVM_{gs} of <961, 961≤2628 and >2628 were classified as light, moderate and vigorous activity, respectively. A combined category of moderate-to-vigorous activity was also created. Non-wear time recordings of activities with a MET-value >3 were corrected for by subtracting time from the light category and adding time to the moderate or vigorous categories depending on reported activity.

4.1.5 Statistical analysis

All analyses were performed using STATA version 13.0 (STATA Corporation, College Station, TX, USA). The significance level was set to $\alpha = 0.05$. The *significance level* is represented by *p*-values which tell us the strength of evidence against the null-hypothesis (i.e. that the true difference in the population is zero) given the data in our sample. The threshold of 0.05 is arbitrary but commonly used.

4.1.5.1 Descriptive analysis

Characteristics of participants in VALMA (**Study I**) and VALTER (**Study II**) are presented as absolute numbers and percentages and mean values and standard deviations (SD). In addition, the total range of quantitative variables and the interquartile range (IQR) are presented. Potential differences between groups were tested for using t-tests and chi-square tests for continuous and categorical variables respectively. A *t-test* compares the mean values of a variable between two groups while a *chi-square test* compares the distribution of a variable between the groups.

4.1.5.2 Validity analysis

The degree of association between the results from Active-Q and the reference method was assessed using Spearman rank correlation coefficients with confidence intervals

(CIs) obtained using the bootstrap method.[110] Total energy expenditure assessed with Active-Q and DLW was compared in the VALMA-study while the degree of association between times spent at light, moderate, vigorous or moderate-to-vigorous activity levels assessed between Active-Q and the GENEA accelerometer was assessed in the VALTER-study. A *correlation coefficient* (*r*), tells us the strength of a linear association between two variables. It ranges between -1 and 1 equals 0 if there is no correlation and -1 or 1 if there is a perfect straight negative or positive correlation. Spearman's rank correlation is non-parametric and based on ranks. The *bootstrap method* is a way of deriving confidence intervals (CIs) using resampling with replacement.

4.1.5.3 The Bland-Altman method

In addition to the Spearman correlation coefficients which do not detect systematic differences between methods, the *Bland-Altman technique*[111] was applied. The Bland-Altman plot provides a graphical evaluation of the association and is used to assess systematic differences and absolute agreement. It enables visual assessment and depicts the magnitude of measurement error and potential bias that might vary across the assessment range. The difference between the two methods is plotted on the y-axis and the mean value of the methods is plotted on the x-axis. The limits of agreement, ±2SD of the difference, are marked in the plot and provide a measure of variation.

4.1.5.4 Reproducibility analysis

The reproducibility (i.e. the amount of measurement error) of duplicated measurements between two admissions of Active-Q in **study I** and **II**, and the two weeks of wearing the GENEA accelerometer in **study II**, was assessed by computing *intraclass correlation coefficients* (ICCs)[112] using the ANOVA estimator. An ICC can range between 0 and 1 and represents the ratio of the between subject variance to the combination of the between and within subject (i.e. the measurement error) variance. The higher the ICC, the larger percentage of the total variability seen is due to between-subject variability and not measurement error, i.e. an ICC equal to 1 means complete reproducibility and no measurement error.

4.2 PROSTATE CANCER STUDIES (STUDY I, II AND V)

4.2.1 Background

Studies investigating potential associations between modifiable life-style factors, e.g. BMI and physical activity, and prostate cancer risk, progression and mortality are of great interest and public health concern. In **Study I** and **II** we investigate progression and mortality after a prostate cancer diagnosis and the impact of lifestyle. Modifiable lifestyle factors provide a unique opportunity for the individual himself to make choices, and potentially changes, to improve his own survival. In **Study V** we aim to assess the impact of BMI on the most common biological marker for prostate cancer diagnostics, PSA, as well as on prostate cancer risk. How important is it to consider a patient's BMI when interpreting results of serum PSA-level and can men by changing their lifestyle and BMI impact their own prostate cancer risk? Data used in Study V is obtained from the STHLM-2 cohort which was one of the first large studies to use the Active-Q physical activity questionnaire (validated in **Study III** and **IV**). Although not the main exposure in **Study V**, Active-Q was used to assess total physical activity which may be a confounder for the association between BMI and baseline PSA-levels and the risk of being diagnosed with prostate cancer during follow-up.

4.2.2 Study design - PROCAP

Data from the PROCAP (PROgression in CAncer of the Prostate)-study was analyzed in **Study I** and **II**. PROCAP is a population-based cohort and the study was initiated in 2007. Men diagnosed with localized prostate cancer between 1997 and 2002 were identified through the National Prostate Cancer Registry in Sweden[113] and invited to donate a blood sample and responded to a questionnaire. The aim of the study was to identify how lifestyle and genetic factors influence prognosis and survival among men diagnosed with localized prostate cancer.

PROCAP is an adjunct study to the National Prostate Cancer Registry (NPCR) of Sweden follow-up study, a retrospective, nationwide cohort study of patients with localized prostate cancer that has been described in more detail previously.[114] In Sweden, all incident cancers are reported to the National Cancer Registry (NCR)[115] while the National Prostate Cancer Registry (NPCR) includes more detailed information on all patients with a prostate cancer diagnosis including; serum PSA-levels, TNM-stage, tumor differentiation at time of diagnosis, and primary treatment within six months of diagnosis.[113, 116] In short, patients registered with a localized prostate cancer in the NPCR between January 1st 1997 (January 1st 1998 in one region) and December 31st 2002; <=70 years of age at diagnosis, a diagnostic serum PSA <20 ng/ml, local tumor stage T1-T2, no signs of lymph node or bone metastasis (NX or N0 and MX or M0, respectively) were eligible for inclusion in the NPCR of Sweden follow-up study. In total, 8,304 patients fulfilled the criteria and 7,960 (96%) accepted inclusion to the study. Information on date of last follow-up, reason for and date of termination of surveillance, subsequent PSA testing, signs of local progress, and distant metastasis was retrieved on one occasion (median time: four years after diagnosis) for each patient and was extracted from medical records by research nurses in each of six health care regions in Sweden.

All patients in the NPCR of Sweden follow-up study who were still alive in 2007 (n=7,074) were invited to PROCAP. In total 5,779 patients (82%) accepted inclusion and were asked to donate a blood sample and respond to a questionnaire. Half of the study participants chose to respond to a paper-questionnaire which was scanned into digital format and half chose to respond to a Web-questionnaire where results were directly saved in digital format. Results were checked for completeness by study personnel. All patients gave their written informed consent for participation. The PROCAP study has been approved by the research ethics committee at Karolinska Institutet, Stockholm, Sweden. The study design is shown in **Figure 10**.

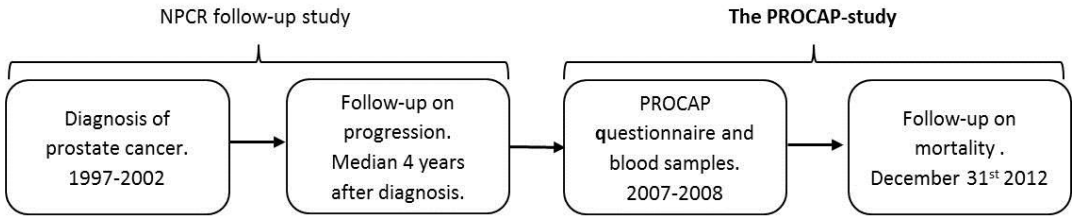


Figure 10. Study design for PROCAP and years of data collection and date of follow-up.

The present thesis includes two studies based on PROCAP data. In **Study I,** the association between body weight (BMI at time of diagnosis and weight change after diagnosis) and prostate cancer progression, prostate cancer specific and overall mortality was investigated. In **Study II**, physical activity after diagnosis and prostate cancer specific and overall mortality was studied.

4.2.2.1 Study participants

Among the 5,779 men who accepted inclusion to PROCAP, those with missing clinical (n=290) and questionnaire data (n=341) were excluded from all analysis. In mortality analysis with BMI or weight change as exposures, men with missing data on BMI (n=60) were excluded. Additional exclusions of men without data on progression (n=712) were made for analysis of progression. In analysis of physical activity as the exposure, men with incomplete physical activity data (n=525) were excluded. **Table 2** show the final numbers of men included in analysis presented in this thesis. Results using updated information did not differ substantially from the published results.

Table 2. Number of men included in analysis after study specific exclusions

Analysis	n	Comment
BMI and prostate cancer progression	4,376	Same as in publication
BMI and mortality	5,088	Updated information since publication
Weight change and mortality	5,088	Updated information since publication
Physical Activity and mortality	4,623	Same as in publication

4.2.3 Study design –STHLM-2

Data from the STHLM-2 cohort was analyzed in **Study V**. All men referred to a PSA-test in laboratories in Stockholm County between 2010 and 2012 were invited to participate in STHLM-2. Men who agreed to participate had their serum PSA-levels measured at the blood sampling visit for the PSA-test. Participants also donated additional blood and urine samples and were asked to respond to a questionnaire. A total of 24,966 men were included in the cohort that has been described previously.[100] Information on incident prostate cancers was obtained from the Swedish Cancer Registry (SCR)[115] and additional information on prostate cancer was obtained through the National Prostate Cancer Registry (NPCR)[113]. Participants were followed-up through registry linkage until the end of April 2014. The local ethics committee at Karolinska Institutet, Stockholm, Sweden, approved the study.

4.2.3.1 Study participants

In the present study, participants were excluded for analysis for several reasons and in consecutive order as follow: missing date of inclusion (n=34) or missing information on date of birth (n=101), missing questionnaire data (n=4,490), if having a prostate cancer diagnosis prior to inclusion (n=4,251), missing information on BMI (n=108) or PSA (n=52), and if reported BMI was <18.5 (n=61) or >50 kg/m^2 (n=42). In total, 15,829 men were included in the analysis of BMI and serum PSA-levels. A lag-time of six months was introduced for analysis of prostate cancer risk and men diagnosed with prostate cancer within 6 months of inclusion (n=500) were excluded to minimize reverse causation. The analysis of prostate cancer risk included a total of 15,329 men.

4.2.4 National Registers

4.2.4.1 The Swedish Cancer Register (SCR)

The SCR was founded in 1958 and covers the whole population in Sweden.[115] Data on prostate cancer diagnosis from the SCR was obtained for **Study V**. The registry holds three types of data including patient data (personal identification number, age, sex and

place of residence), medical data (for example tumor site, histological type and date of diagnosis), and follow-up data on date and cause of death and date of migration Health care providers are by law obligated to report newly detected cancers to the registry. Completeness of the SCR is high.[115]

4.2.4.2 The National Prostate Cancer Register (NPCR)

The NPCR of Sweden exists in part to improve and promote health among men in Sweden and to increase knowledge of prostate cancer by improving treatment and survival. **Study I** and **II** are based on data from the NPCR of Sweden follow-up study.[114] The NPCR includes detailed information on patients with a prostate cancer diagnosis and holds information on tumor stage, Gleason score, serum PSA-level and primary treatment.[113] The first regional prostate cancer register was started in 1987 in the south-east health care region in Sweden. Additional regions in the country followed the initiative during the 1990's. From January 1st 1998, the NPCR of Sweden includes all health care regions in the country. The registry has shown that information in the NPCR is of high quality and the registry captures >98% of all prostate cancer cases recorded in the Cancer Registry.[116]

4.2.4.3 The Cause of Death Register (CDR)

The CDR hold information on the deaths of all Swedish citizens, irrespective of the whether they died in Sweden or outside the country, and is complete from January 1st 1969.[117] Diagnoses are coded according to the international versions of ICD. Information on date and cause (prostate specific or other) of death was obtained from the CDR in **Study I** and **II**.

4.2.5 Assessment of exposures, outcomes and covariates

4.2.5.1 Exposure definitions

In **Study I** and **II**, current height, weight, and weight change since diagnosis was self-reported in the PROCAP questionnaire. Body mass index (BMI, kg/m^2) at diagnosis was estimated based on self-reported current height and weight, and weight change. In **Study V**, BMI at baseline was calculated based on self-reported current weight and height in the STHLM.2 questionnaire. Men were categorized by BMI as normal weight (<25 kg/m^2), overweight ($25<30$ kg/m^2) or obese (BMI ≥ 30 kg/m^2) in **Study I** and **II. In study V**, an additional category of BMI was included and men were categorized as normal weight (<25 kg/m^2), overweight ($25<30$ kg/m^2), obese level 1 (BMI $30<35$ kg/m^2) and obese level II (BMI ≥ 35 kg/m^2). BMI classifications were made as defined by the National Institute of Health.[10]

Study participants in PROCAP who reported a weight change were asked how many kilograms that was gained or lost. Based on the reported current weight and weight change, the percent weight change since diagnosis was calculated. Patients were thereafter categorized into three groups of: no change or a change <5 %, an increase in weight ≥5 % or a decrease in weight ≥5 %.

Physical activity in PROCAP was assessed using previously validated questions.[104] Participants were asked to report the daily time spent walking/bicycling and performing household work and the weekly time spent exercising "after diagnosis." Each activity category was assigned a MET-value using the Compendium of Physical Activity: walking/bicycling (MET=3.6), household work (MET=2.5) and exercise

(MET=5.5).[20] Daily time spent walking/bicycling had seven response intervals specified, household work six and exercise seven. In further analysis, the response intervals for each variable was combined and divided into two levels of exposure: walking/bicycling as <20 and ≥20 min/day, household work as <1 and ≥1 h/day, and exercising as <1 and ≥1 h/week. The reported time spent walking/bicycling, performing household work, and exercising was also multiplied by the activity specific MET-values and a categorical variable of recreational MET-hours per day with 2 levels (<5 and ≥5 MET-h/d) was created.

4.2.5.2 Outcome definitions

Disease progression is analyzed in relation to BMI in **Study I** and was defined according to primary treatment. Among those treated with curative intent (radiation therapy or radical prostatectomy), experiencing biochemical recurrence, local progress, or distant metastasis, was considered disease progress. Further, biochemical recurrence was defined differently depending on primary treatment.[118] For patients who underwent radiation therapy, biochemical recurrence was defined as a doubling in PSA above the post-treatment nadir value and exceeding at least 1 ng/ml. Among those treated with radical prostatectomy, two consecutive tests with PSA-levels >0.2 ng/ml defined biochemical recurrence (the date for this event was set to the first occasion). Among operated patients with only one registered PSA-test, a value>0.5 ng/ml was considered biochemical recurrence. Lastly, the event of termination of deferred treatment with biochemical progression as the reason for termination defined progress in patients on surveillance. Time to event in analysis was defined as the time from date of prostate cancer diagnosis to the date of the earliest observed progressive event for each treatment-specific definition. Patients on surveillance who ended their deferred treatment without any signs of disease progression were censored at the recorded date of termination and patients with no progressive event were censored at the last recorded date of follow-up.

Prostate cancer specific mortality and overall mortality are analyzed in relation to BMI and weight change in **Study I** and physical activity in **Study II**. Information on the he date of death and cause of death (prostate cancer specific or other) were obtained from the Swedish Cause of Death Registry using national identification numbers. Time to event in analysis was defined as time from date of prostate cancer diagnosis to the date of death reported in the registry or censoring at the end of follow-up on December 31st, 2012, whichever came first. Time since prostate cancer diagnosis was used as the underlying time scale in analysis and all patients were left truncated by study design at the date of inclusion to PROCAP.

In **Study V**, serum PSA was measured at baseline. Due to a skewed distribution, the variable was logarithmically transformed (log-PSA) before analysis to create a normal distribution. Further, information on incident prostate cancers was obtained from the NCR. Outcome end points were the first event of date of diagnosis, death or last registry linkage (April 22nd) 2014. To define prostate cancers according to severity, additional prostate cancer specific information was obtained through the NPCR and prostate cancers with a Gleason score <7 or ≥7 were defined as low- and high-grade.

4.2.5.3 Assessment of potential confounding factors

Additional lifestyle factors considered as potential confounders in **Study I** and **II** were: tobacco use, total energy intake, education level, overall stress during the last year, current occupation, and family history of prostate cancer were assessed.

Physical activity at age 50 was included as a potential confounder in analysis of BMI and weight change (**Study I**) and BMI and weight change were considered confounding factors in analysis of physical activity (**Study II**). Clinical variables including: PSA-level at diagnosis, TNM-stage, tumor grade and Gleason score at diagnosis, and primary treatment were also considered as potential confounders. Cut-points for categorical variables were based on established strata or arbitrarily defined prior to analysis. In **Study V**, factors considered as potential confounders were assessed at baseline and included: age at inclusion, education level, smoking status, level of stress, family history of prostate cancer and physical activity derived from Active-Q.

4.2.6 Sensitivity analysis

In analysis of mortality (**Study I and II**) sensitivity analysis where men who died within 18 months of responding to the questionnaire were carried out. In **Study V**, sensitivity analysis with a lag-time of 6 months was carried out. The lag-time was introduced to examine if the exposures potentially had been affected by illness which may also be associated with death (**Study I** and **II**) or prostate cancer (**Study V**), i.e. reversed causality.

4.2.7 Statistical analysis

All analyses were performed using STATA version 13.0 (STATA Corporation, College Station, TX, USA). The significance level was set to $\alpha = 0.05$.

4.2.7.1 Characteristics

Distributions and means of demographic and clinical variables were studied across BMI categories (**Study I** and **V**) and groups of total recreational MET-h after diagnosis (**Study II**). Statistically significant associations were tested for using chi-square test for categorical variables and one-way ANOVA for continuous variables. Differences in HRs for men in the different exposure categories were compared using the *log-rank test*. Progression free (**Study I**), overall and prostate cancer specific survival (**Study I and II**) were analyzed using the *Kaplan-Meier method* to estimate survival curves graphically displaying the cumulative survival probability on the y-axis against follow-up time on the x-axis. For results from log-rank tests and Kaplan-Meier curves we refer to **paper I** and **II**.

4.2.7.2 Multivariable linear regression

In **Study V**, the association between BMI and serum PSA-levels at baseline was assessed using multivariable *linear regression* models. A regression analysis gives an estimation of the relationship between a continuous numerical dependent outcome variable and one or more independent exposure variables, which may or may not be continuous. A *linear regression* model estimates the best fitting linear function, i.e. the best fitting straight line between outcome and exposure variables, to describe an association. Because of the logarithmic transformation of the outcome variable, results are interpreted as percent change in serum PSA-levels with increasing BMI. BMI was included in models both as a continuous and categorical exposure. The association between BMI and serum PSA was studied separately for all men, men diagnosed with prostate cancer during the follow-up, and men without a diagnosis during follow-up. Unadjusted, age-adjusted and multivariable-adjusted regression models were fitted.

4.2.7.3 Cox proportional hazards regression

To study the effect of an exposure on the time-to-event (progression or death), survival analysis assessing the exposures effect on the outcome per time-unit, creating event rates, were used. The *Cox proportional hazards regression* compares the hazards among exposed and unexposed. It relies on the assumptions that the ratio of the hazards between the two groups is constant over the time scale and that it is based on considering risk sets of the individuals who are still at risk each time an event occurs. The proportional hazards assumption was tested using Schoenfelds residuals. No statistically significant deviations from the assumption were seen in **Study I, II** or **V**. The reliability of the point estimate (i.e. the HR) is given by the *95% confidence interval* which provides a range of values which we are fairly confident to include the "true" population estimate. If we were to repeat the same study many times, assuming that all variation is random, we would find the "true" estimate in 95% of the samples.

Cox proportional hazards regression models were fitted to estimate unadjusted, age-adjusted and multivariable-adjusted hazard rate ratios (HRs) with 95% confidence intervals (95% CIs) in the analysis of risk, progression and mortality. In **Study I** and **II**, the underlying time scale was time since prostate cancer diagnosis and patients were left truncated by study design at the date of inclusion to PROCAP. All exposure variables were included as categorical exposures in the models. End points in analysis of progression were the earliest observed progressive event as defined in paragraph 4.2.5.2 or last date of follow-up. In mortality analysis, end points were date of death or last date of follow-up (Dec 31st 2012), whichever came first. In **Study V**, BMI was analyzed both as continuous and categorical. Time from inclusion to STHLM-2 was used as the underlying time-scale. End points were date of diagnosis, death or last registry linkage (April 22nd) 2014, whichever came first.

4.2.7.4 Selection of confounding factors

To assess potential confounding by measured covariates, we tested if the covariates were statistically associated with both the exposures and the outcomes. The association between covariates and exposure was assessed using linear regression models and the association between covariates and outcome was assessed using Cox proportional hazards models. Covariates were considered confounders and included in multivariable adjusted models if statistically significantly associated with both the exposures and the outcomes or if prior subject matter knowledge indicated an association.

4.2.7.5 Survival splines

Survival splines were used in **Study V**. To illustrate the dose-response relationship between serum PSA-levels and BMI, natural (cubic) linear regression splines were fitted with knots at BMI=25 and 30 kg/m^2 .[119] To summarize the fitted spline models, regression standardization was used, in which the predicted means obtained from the multivariable adjusted spline function are standardized to the confounder distribution in the sample.[5] Separate analyses were made for all men, men diagnosed with prostate cancer during the follow-up, and men not diagnosed during follow-up. To illustrate the association between BMI and prostate cancer risk, natural (cubic) Cox regression splines were fitted with knots at BMI=25 and 30 kg/m^2, and summarized through regression standardization. This analysis produces standardized "survival" (i.e. cancer-free) probabilities, as a function of time since inclusion into the study. The association between BMI and prostate cancer risk was studied separately for all cancer types, low-grade, and high-grade cancer, respectively.

5 RESULTS

5.1 VALIDATION STUDIES

5.1.1 Characteristics - VALMA

Characteristics of study participants are displayed in **Table 3**. A majority of the study participants were women (n=124, 78%), had >12 years of education (n=129, 82%), and were mostly never smokers (n=107, 69%). No differences were seen between men and women with regards to education or smoking status but more women than men had a BMI <20 kg/m^2 while current snuff use was more common among men. There were no differences between the sexes with regards to crude energy expenditure (not adjusted) assessed with Active-Q, total MET-hours/day or average number of daily steps. However, men had a higher total energy expenditure (adjusted to 24-hours) assessed with Active-Q and DLW compared to women. No differences of characteristics were seen between participants in the DLW sub-group and the other participants.

Table 3. Characteristics and results from measurements in the VALMA study (n=158)

	Mean	(SD)	Median	Min-Max	IQR
Age, years	32.6	(11.6)	28	21-63	24-38
BMI, kg/m^2	23.1	(3.8)	22.7	16.3-44.7	20.7-24.1
Active-Q-I					
Energy expenditure[1], kj/day	6,599	(3,278)	5,959	1,618-22,872	4447-7738
Total energy expenditure[2], kj/day	11,630	(2,867)	11,264	5,507-22,644	9,579-12,963
Total MET-hours/day	22.4	(10.2)	20.9	4.3-88.2	16.0-26.1
Active-Q-II[3]					
Energy expenditure[1], kj/day	6,270	(2,747)	5,602	1,576-15,798	4,423-7,209
Total energy expenditure[2], kj/day	11,718	(2,772)	11,380	5,983-20,853	9,917-12,750
Total MET-hours/day	21.3	(7.9)	20.1	3.7-52.3	16.0-24.9
Reference measures					
Total energy expenditure DLW[4], kj/day	11,207	(2,284)	10,924	7,375-17,310	9,858-12,057
No. daily steps	8,533	(3,042)	8,194	2,513-18,410	6,579-10,047

[1]Crude, [2]Adjusted to 24-hours, [3]n=150, [4]DLW sub-group, n=36. BMI, Body Mass Index; DLW, Doubly Labelled Water; kJ, kilo-joule; IQR, Interquartile range

5.1.2 Characteristics - VALTER

Characteristics of participants in the VALTER-study are shown in **Table 4**. Half of the participants had an education >12 years (n=74, 50%), 57% reported to be working full- or part-time (n=85) and a slightly more than half were ≥65 years of age (n=81, 55%). Men <65 years of age reported working to a higher degree than men >65 years. In accelerometer measurements, men <65 years of age had fewer minutes spent in light physical activity and more minutes spent in moderate and moderate-to-vigorous physical activity. There was a borderline statistically significant difference in time measured spent in vigorous physical activity. There were no differences between the age groups with regards to reported time on any activity level in Active-Q.

Table 4. Characteristics and results of time spent in light, moderate, vigorous and moderate-to-vigorous (LPA, MPA, VPA and MVPA, respectively) physical activity levels in the VALTER study (n=148)

	Mean	(SD)	Median	Min-Max	IQR
Age, years	65.4	(8.7)	66	33 – 86	61 – 71
BMI, kg/m^2	25.7	(2.9)	25.4	19.6 – 35.6	23.5 – 27.5
Active-Q-I					
LPA min/day	1,301	(123)	1,339	849 – 1,440	1,281 – 1,382
MPA min/day	121	(120)	84	0 – 555	51 – 135
VPA min/day	18	(26)	6	0 – 130	0 – 29
MVPA min/day	139	(123)	101	0 – 591	58 – 159
Active-Q-II					
LPA min/day	1,301	(139)	1,355	680 – 1,428	1,275 – 1,390
MPA min/day	116	(123)	69	0 – 557	41 – 148
VPA min/day	22	(42)	9	0 – 289	0 – 29
MVPA min/day	139	(139)	85	12 – 760	50 – 165
GENEA reference measures					
LPA min/day	1,392	(28)	1,393	1,255 – 1,437	1,380 – 1,409
MPA min/day	46	(27)	44	3 – 182	31 – 56
VPA min/day	3	(6)	1	0 – 43	0 – 3
MVPA min/day	48	(28)	47	3 – 186	32 – 60

IQR, Interquartile range

5.1.3 Validity

5.1.3.1 Compared to doubly labelled water (DLW)

Spearman correlation coefficients between energy expenditure without and with adjustments to 24-hours and total MET-hours assessed with Active-Q and total energy expenditure measured with DLW were r=0.43 (95% CI: 0.19-0.67), r=0.52 (95% CI: 0.32-0.71) and r=0.28 (95% CI: -0.05-0.60), respectively. Bland-Altman plots showing the absolute agreement between the two methods are shown in **Figure 11**. Without adjustments to the energy expenditure from Active-Q, the mean difference between the methods was -4147kJ. When results were adjusted to total energy expenditure during 24-hours, the mean difference between the methods was 447 kJ. The plots showed no clear trends of proportional error or differences between men and women.

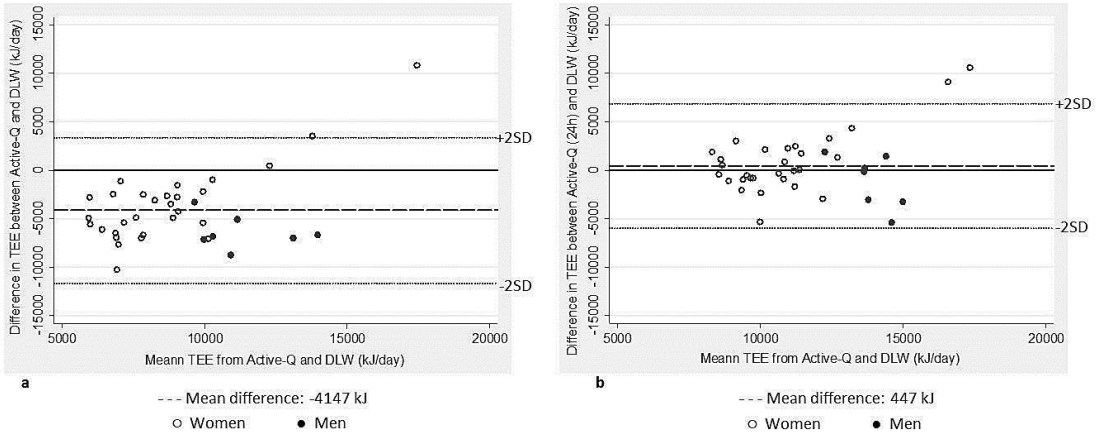


Figure 11. Bland-Altman plots of the absolute agreement between energy expenditure assessed with Active-Q and doubly labelled water (DLW). Each point represents one participant (n=36). The mean of the two methods is displayed on the x-axis while the absolute difference is displayed on the y-axis. **a**. Energy expenditure assessed with Active-Q (without adjustments) , **b**. Total energy expenditure assessed with Active-Q (adjusted to 24-hours) and DLW

5.1.3.2 Compared to pedometers

Spearman correlation coefficients between energy expenditure with and without adjustments to 24-hours and total MET-hours assessed with Active-Q and the average number of daily steps measured were r = 0.07 (95%CI: -0.11-0.25), r = -0.12 (95%CI: -0.23-0.02) and r = 0.20 (95%CI: 0.08-0.33), respectively. Similar results were obtained in analysis of men and women separately (data not shown).

5.1.3.3 Compared to the GENEA accelerometer

Spearman correlation coefficients between time spent in light, moderate, vigorous and moderate-to-vigorous physical activity assessed with Active-Q (adjusted to 24-hours) and average time per day from GENEA measurements were r = 0.35 (95%CI: 0.19-0.51), r = 0.27 (95%CI: 0.11-0.43), r = 0.54 (95%CI: 0.41-0.67) and r =0.35 (95%CI: 0.20-0.50), respectively. Correlation coefficients among men <65 years were slightly lower for all categories except vigorous activity (data not shown). For men ≥65 years, correlation coefficients were higher for all categories except vigorous activity (data not shown). Bland-Altman plots showing the absolute agreement between times at different intensity levels assessed with Active-Q and accelerometers are shown in **Figure 12**. The mean difference between the methods (Active-Q minus GENEA) was -91, 76, 15 and 91 min/day for light, moderate, vigorous and moderate-to-vigorous physical activity, respectively. Clear trends of decreased accuracy with increasing time spent in moderate and vigorous activities was seen while a decreased accuracy at less time spent in light physical activity was seen. Men <65 years appear to over-report vigorous activities to a greater extent than older men.

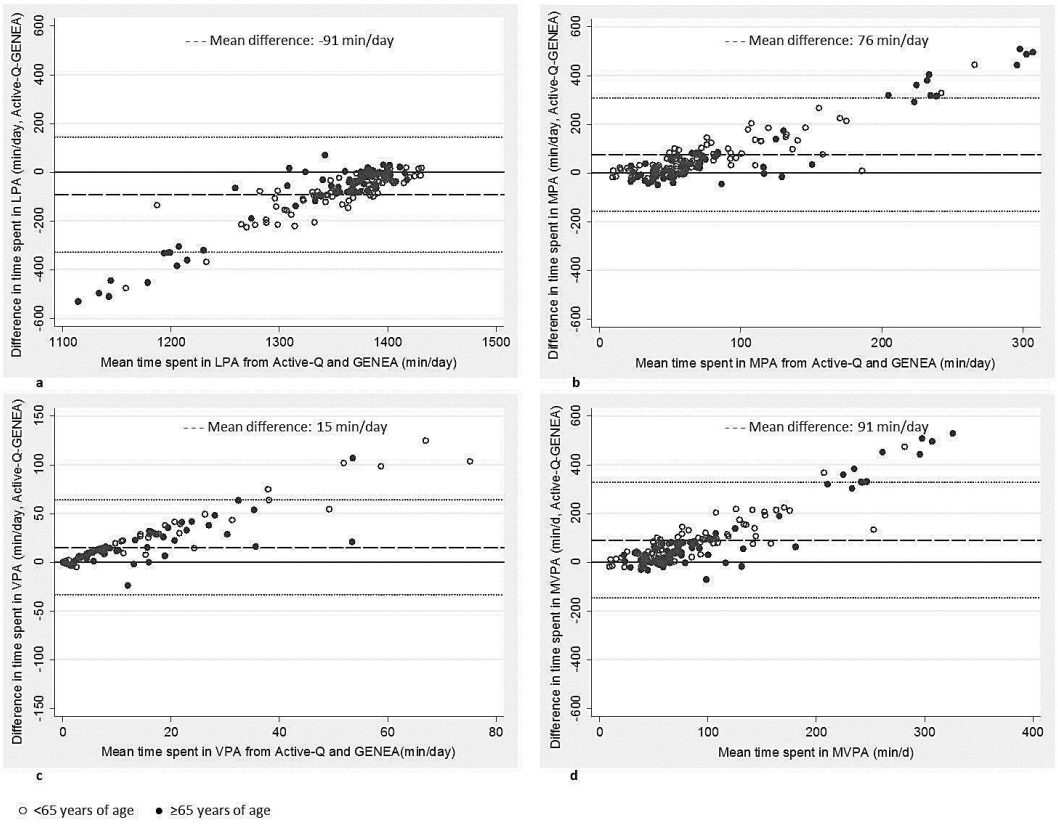


Figure 12. Bland-Altman plots of the absolute agreement between times spent at different activity levels assessed with Active-Q and GENEA accelerometers. Each point represents one participant (n=148). The mean of the two methods is displayed on the x-axis while the difference is displayed on the y-axis. **a**) Light Physical Activity (LPA) **b)** Moderate Physical Activity (MPA) **c)** Vigorous Physical Activity (VPA) **d)** Moderate-to-Vigorous Physical Activity (MVPA)

5.1.4 Reproducibility

Intraclass correlation coefficients (ICCs) for variables of energy expenditure with and without adjustments to 24-hours and total MET-hours assessed in the first and second Active-Q were r = 0.74 (95%CI: 0.67-0.81), r = 0.87 (95%CI: 0.83-0.91) and r = 0.66 (95%CI: 0.56-0.75), respectively. Results were similar for men and women separately although ICCs for women were slightly higher than those for men (data not shown)

ICCs for variables of time spent in light, moderate, vigorous and moderate-to-vigorous physical activity assessed in the first and second Active-Q responded to were r = 0.67 (95%CI: 0.58-0.76), r = 0.69 (95%CI: 0.60-0.77) , r = 0.51 (95%CI: 0.39-0.63) and r = 0.67 (95%CI: 0.58-0.76), respectively. While results were similar for men <65 and ≥65 years of age for time spent in vigorous activities, ICCs were slightly higher among the older men compared to the younger for the other three categories (data not shown).

5.1.5 Active-Q in VALMA and VALTER

Results from Active-Q were similar on a group level when comparing variables of energy expenditure, total MET-hours and time spent at different intensity levels between men in VALMA and VALTER, the latter divided into age categories <65 years and ≥65 years, **Figure 13**. Men ≥65 years in VALTER reported lower un-adjusted energy expenditure, less daily MET-hours, and less time spent at in vigorous physical activity compared to men in VALMA. Men in VALTER reported less time in vigorous physical activity then men in VALMA.

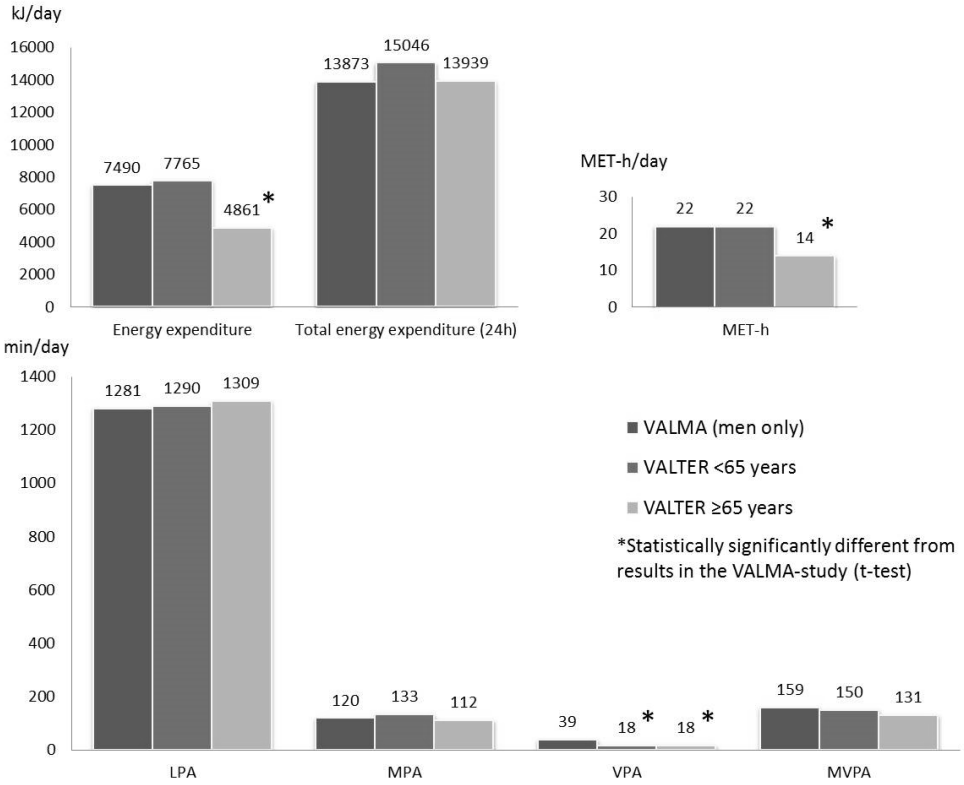


Figure 13. Results from the Active-Q used in VALMA (men only, n=34) and VALTER studies (<65 years of age, n=64, and ≥65 years of age, n=79). Comparisons are made for variables of energy expenditure (not adjusted), total energy expenditure (adjusted to 24-hours), total daily MET-hours, daily time spent in light, moderate, vigorous and moderate-to-vigorous physical activity levels (LPA, MPA, VPA and MVPA)

5.2 PROSTATE CANCER PROGRESSION AND MORTALITY

5.2.1 Characteristics

Among study participants included in analysis of BMI and weight change, progression was experienced among 639 (14.6%) men. During the follow-up, 211 (4.1%) prostate cancer specific deaths and 628 (12.3%) deaths of any cause were recorded. The mean age of participants at time of diagnosis was 63.0 years and the mean BMI was 26.2 kg/m^2. Men with a high BMI were younger than men with a lower BMI. Distributions of exposure variables in **Study I** and **II** are shown in **Table 5**. Additional characteristics, including clinical data, are published in **Paper I** and **II**.

Table 5. Exposure characteristics of study participants included in additional analysis by BMI at diagnosis

	All		**BMI <25**		**BMI 25<30**		**BMI ≥30**		***P*[4]**
	(n=5,088)		(n=1,881)		(n=2,640)		(n=567)		
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	
Weight change since diagnosis									.000
No change	3,871	(76.1)	1,545	(82.1)	1,981	(75.0)	345	(60.9)	
>5% Increase	771	(15.2)	239	(12.7)	437	(16.6)	95	(16.8)	
>5% Decrease	446	(8.8)	97	(5.2)	222	(8.4)	127	(22.4)	
Total recreational MET-h									.000
<5 MET-h/day	1,190	(23.4)	400	(21.3)	604	(22.9)	186	(32.8)	
≥5 MET-h/day	3,898	(76.6)	1481	(78.7)	2,036	(77.1)	381	(67.2)	
Walking/biking after diagnosis									.000
<20 minutes per day	1,103	(23.7)	355	(20.6)	573	(23.8)	175	(33.9)	
≥20 minutes per day	3,548	(76.3)	1,370	(79.4)	1,836	(76.2)	342	(66.2)	
Household work after diagnosis									<.01
<1 hour per day	1,617	(34.9)	568	(33.0)	834	(34.7)	215	(41.7)	
≥1 hours per day	3,023	(65.2)	1,152	(67.0)	1,570	(65.3)	301	(58.3)	
Exercising after diagnosis									.000
<1 hour per week	1,914	(41.2)	686	(40.0)	960	(39.8)	268	(51.9)	
≥1 hours per week	2,729	(58.8)	1,031	(60.1)	1,450	(60.2)	248	(48.1)	

5.2.2 Body Mass Index and progression

No statistically significant associations were seen between BMI and prostate cancer progression in multivariable-adjusted analysis, **Figure 14**. For additional results, see the published **Paper I**.

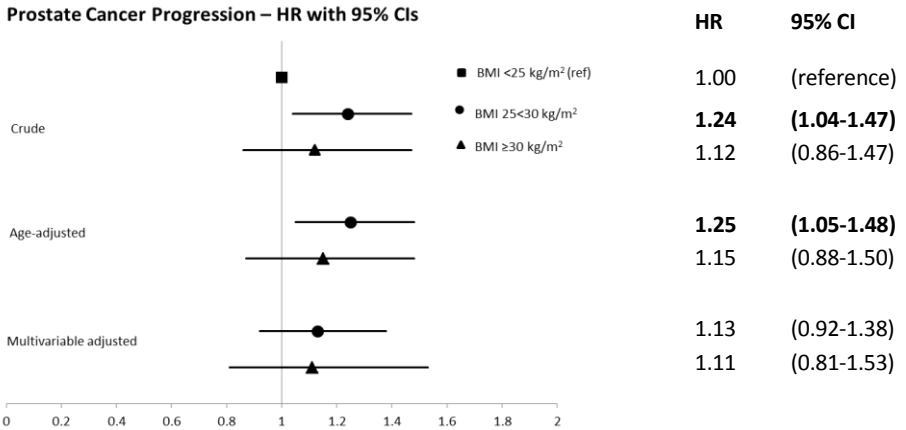


Figure 14. Crude, age-adjusted and multivariable adjusted Hazard Ratios (HR) with 95% Confidence Intervals (CI) are presented for prostate cancer progression by BMI-categories: <25 (ref), 25<30 and ≥30 kg/m^2. The multivariate model is adjusted for age at diagnosis, primary treatment, Gleason score, PSA, TNM-stage, smoking, and physical activity at age 50.

5.2.3 Body Mass Index and mortality

Increased rates of prostate cancer specific mortality were seen among men with a BMI ≥30 kg/m^2 compared to men with a BMI <25 kg/m^2 in crude and age-adjusted analysis but not in multivariable adjusted models with and without lag-time. Men with a BMI >30 kg/m^2 had statistically significantly higher overall mortality rates compared to men with a BMI <25 kg/m^2 in both crude and adjusted models with and without lag-time. Results from Cox proportional hazard regression models are shown in **Figure 15.** Detailed information and additional results are published in **Paper I**.

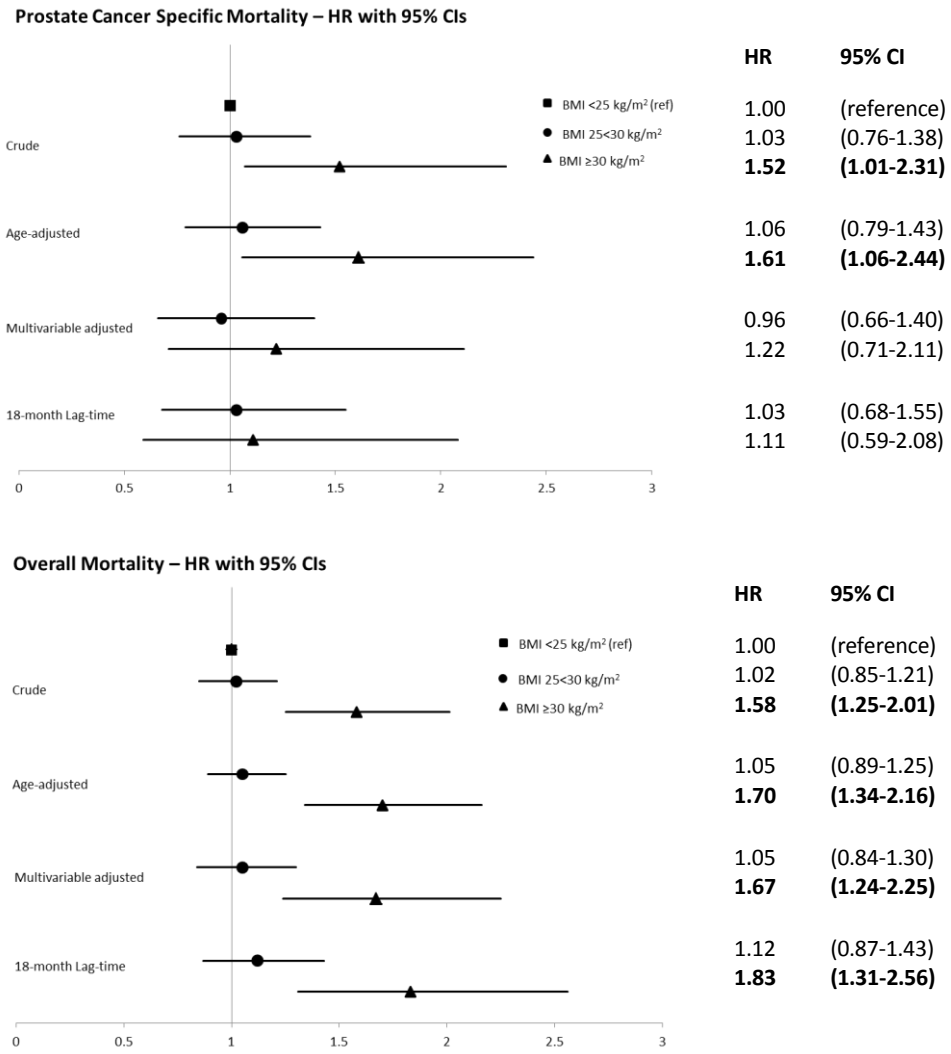


Figure 15. Crude, age-adjusted and multivariable adjusted with and without lag-time. Hazard Ratios (HR) with 95% Confidence Intervals (CI) are presented for prostate cancer specific and overall mortality according to BMI-categories: <25 kg/m^2 (reference), 25<30 kg/m^2 and ≥30 kg/m^2. Multivariable models are adjusted for age at diagnosis, primary treatment, Gleason score, PSA, TNM-stage, smoking, and physical activity at age 50.

5.2.4 Weigh change and mortality

Prostate cancer specific mortality rates were higher among men who had reported a weight increase >5% since diagnosis compared to men who reported a stable weight. Men who reported a weight decrease >5% had higher prostate cancer specific mortality rates in crude, age-adjusted and multivariable adjusted models without lag-time but the association was not statistically significant after the introduction of 18-months lag-time. Overall mortality rates did not differ between men who reported a weight increase >5% from diagnosis and men with a stable weight. Men who reported a weight decrease >5% had higher overall mortality rates compared to men with a stable weight. Results from Cox proportional hazard regression models are shown in **Figure 16**. Additional results are published in **Paper I**.

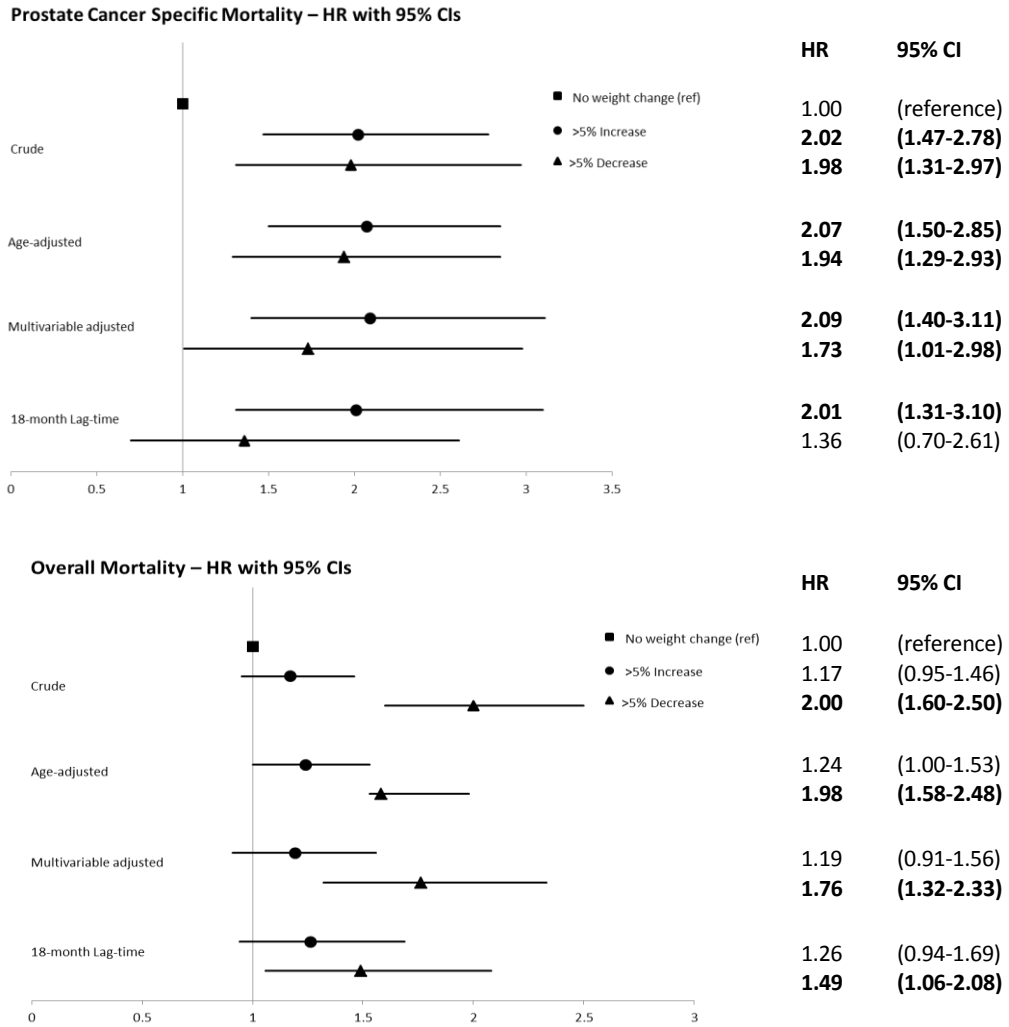


Figure 16. Crude, age-adjusted and multivariable adjusted with and without lag-time. Hazard Ratios (HR) with 95% Confidence Intervals (CI) are presented for prostate cancer specific and overall mortality according to categories of weight change since diagnosis: No change (reference), >5% increase, >5% decrease. Multivariable models are adjusted for age at diagnosis, primary treatment, Gleason score, BMI at diagnosis, PSA, TNM-stage, smoking, and physical activity at age 50.

5.2.5 Physical activity and mortality

A clear indication of lower prostate cancer specific mortality can be seen for men with higher levels of all activities assessed: total recreational activity, walking or bicycling, household work and exercise. However, statistically significantly lower prostate cancer specific mortality rates were only seen in multivariable adjusted analysis for men who walked or bicycled ≥20 min/day compared to men who walked or bicycled less and for men who exercised ≥1 h/week compared to men who exercised less. Higher levels of all physical activity categories assessed were associated with lower overall mortality rates. Results from Cox proportional hazard regression models are shown in **Figure 17.** Additional results are published in **Paper II**.

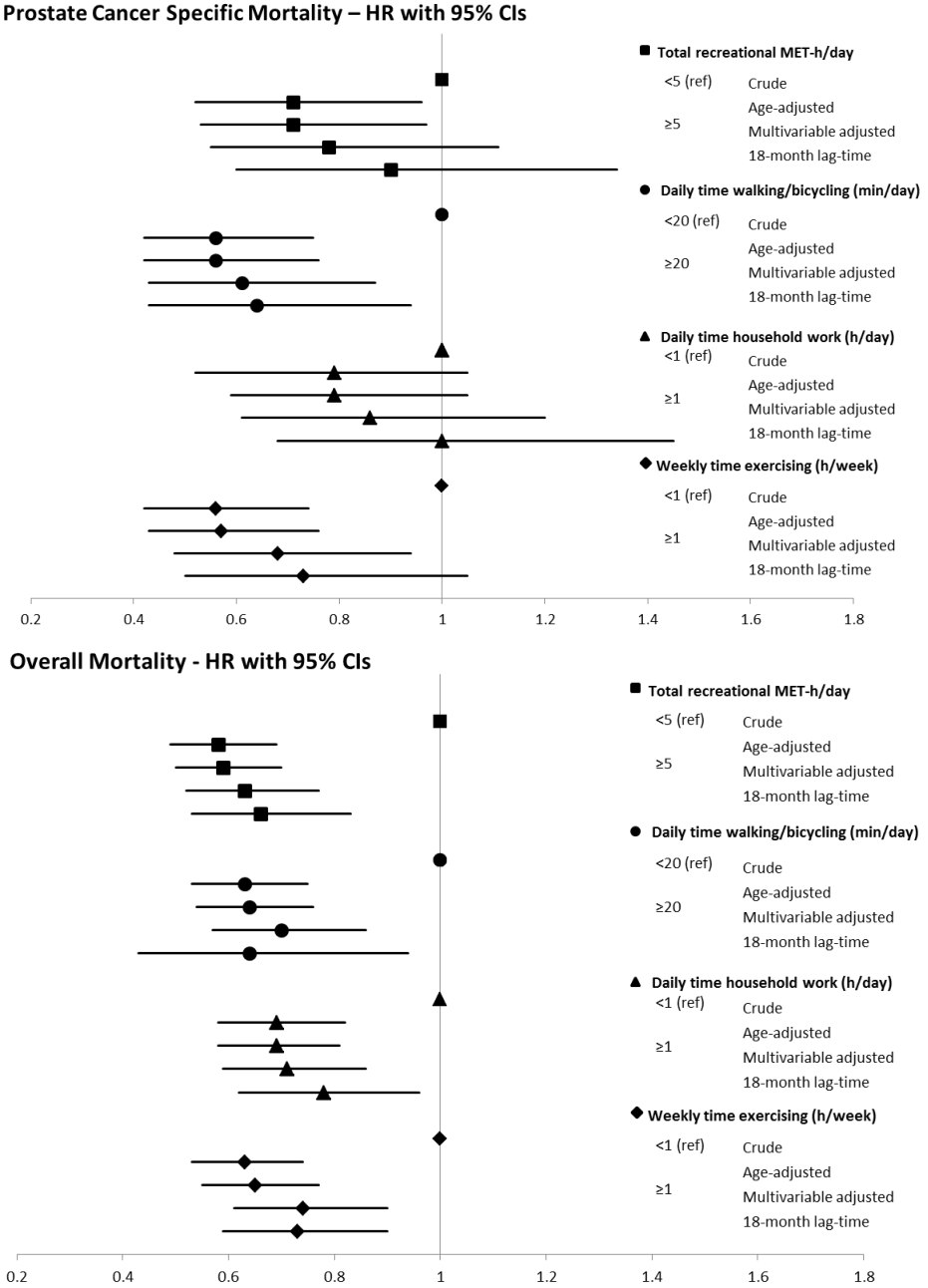


Figure 17. Crude, age-adjusted and multivariable adjusted with and without lag-time. Hazard Ratios (HR) with 95% Confidence Intervals (CI) are presented for prostate cancer specific and overall mortality by physical activity categories. Total recreational physical activity: <5 MET-h/day vs. ≥5 MET-h/day; daily walking/bicycling: <20 min/day vs. ≥20 min/day; daily household work: <1 h/day vs. ≥1 h/day; weekly exercise: <1 h/week vs. ≥1 h/week. Multivariable models are adjusted for age at diagnosis, primary treatment, Gleason score, PSA, BMI at diagnosis and weight change.

5.3 PROSTATE CANCER RISK AND PSA-LEVELS

5.3.1 Characteristics

For detailed characteristics of all study participants divided by BMI-categories we refer to **Table 1** in **Study V**. In brief, the mean age, BMI and PSA-level of study participants at baseline were 65.2 years, 26.4 kg/m^2 and 4.3 ng/ml, respectively. A higher BMI was associated with younger age, less physical activity, lower level of education and increased stress levels. In total 452 men were diagnosed with prostate cancer during the follow-up. Of the diagnosed cancers, 158 (35%) were classified as low-grade and 294 (65%) were classified as high-grade by Gleason score <7 or ≥7.

5.3.2 Body Mass Index and serum PSA-levels

Serum PSA-levels decreased with increasing BMI and among all men in the study, PSA decreased by 1.6% (95%CI: -2.1 to -1.1) for every one unit increase in BMI (kg/m^2) in multivariable adjusted models. Larger decreases in PSA-levels were seen with increasing BMI-category, results from crude, age- and multivariable adjusted models from comparisons of BMI-categories are shown in **Figure 18**. In sub-group analysis of men who were diagnosed with prostate cancer during the follow-up and men who were not, no statistically significant decreases in serum PSA-levels were seen among men that were diagnosed while results for those not diagnosed were similar to the whole group. Linear regression splines of the association between BMI and serum log-PSA-levels confirm results from regression models. Figures and further details can be found in the manuscript for **Study V**.

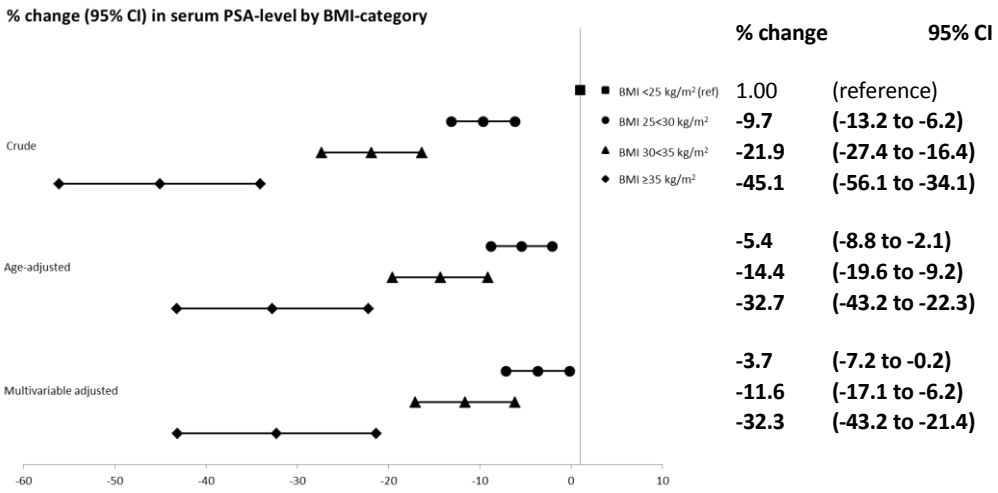


Figure 18. Results from crude, age-adjusted and multivariable adjusted multiple linear regression models of percent change in baseline PSA-levels with 95% confidence intervals by BMI-category. Multivariable models are adjusted for age at baseline, time spent on a moderate-to-vigorous physical activity level (h/day), education, smoking status, stress and family history of prostate

5.3.3 Body Mass Index and prostate cancer risk

A higher rate of high-grade prostate cancer was seen among men with a BMI >35 kg/m^2 compared to men with a BMI <25 kg/m^2 in the age-adjusted model. No other associations were seen for all, low-grade or high-grade prostate cancer. However, point estimates for high-grade cancer indicate increased rates with higher BMI. Detailed results and figures showing the standardized "survival" (i.e. cancer-free) probabilities obtained from Cox regression splines can be found in the manuscript for **Study V**.

6 DISCUSSION

6.1 VALIDATION STUDIES

Making inferences about an association between an exposure and an outcome is directly dependent of the validity of the exposure and outcome assessments. The *validity* tells us how well a method is able to measure what is supposed to be measured implies *reliability*, or *reproducibility*, which ensures us that we will get the same results with repeated measurements. The importance of a well-designed validation study should not be underestimated.

6.1.1 Methodological considerations

6.1.1.1 Study design

The study design of **Study III** and **IV** are similar. Sample sizes are in the same range as previous studies using pedometers, accelerometers or doubly labeled water.[36, 120] While pedometers and accelerometers are feasible to use in larger samples, DLW is expensive and requires more work which limits large scale use. Both studies include relative short periods of data collection although ideally, the time-frame of measurements by the reference method used should mirror the time-frame assessed by the method being validated. Active-Q assessed habitual physical activity during the past year (**Study III**) and the past months (**Study IV**) while the reference methods assessed the average daily total energy expenditure during 11 days (DLW) and the average physical activity during 12 days (GENEA) at approximately the time of responding to the questionnaire. To better mirror a similar time-frame, repeated measures with the reference method over a longer period of time, before responding to the questionnaire, would have been desirable. This was, however, not possible due to practical reasons. The timing of repeated assessments for determining reproducibility is also important to consider. The time period between assessments must be long enough so that the participants do not remember their previous answers, which potentially can inflate the reproducibility due to correlated errors, but needs to be short enough so that the true physical activity behavior has not changed due to, for example, seasonal variation.

Within the VALTER-study, a calibration of the GENEA accelerometer to classify output into different intensity levels was performed. Monitor output was compared to direct observation of specific activities with defined MET-levels. The range of MET-values of included activities was quite narrow, ranging from 1.5 to 5, and included mainly activities of locomotor movement (e.g. walking, running). Ideally, a broader range of different activities, also including higher MET-values, should have been used.[121] Equation patterns based on locomotor movement tend to lead to underestimations of physical activity when compared to lifestyle activities.[58] Although we created cut-offs and defined the measured activity by intensity to enable comparisons to Active-Q, it has been suggested that researchers should focus more on raw data output and discontinue the development and use of cut-points to define intensity categories .[121] The use of raw acceleration information that has not been transformed according to monitor specific equations, allows for direct comparison between different monitors.

6.1.1.2 The use of MET-values

A major limitation when using MET-values (paragraph 2.3.1.1) to represent the energy cost of specific activities is that the defined value of 1 MET as 1 kcal·kg^{-1} body weight·h^{-1} or conversely an oxygen consumption of 3.5 ml O_2·kg^{-1} body weight·minute^{-1}, is derived from a sample of adult and normal weight men.[122] This may not be suitable for other individuals or populations. Assuming the same MET-value for a specific activity for all individuals neglects variations in both mechanical and metabolic efficiency and may potentially lead to misclassification of energy expenditure and time spent at different intensity levels.[19]

6.1.1.3 Choice of reference method

The choice of reference methods is critical and depends on what construct of physical activity you intend to validate, for example if you aim to validate constructs of total physical activity, time spent at a certain intensity level or energy expenditure. No matter what construct you aim to validate, it is important to choose a reference method with uncorrelated errors to the method you are validating. If the two methods have correlated errors, validity may be overestimated. In this thesis work, self-reported physical activity has been compared to three different objective physical activity methods including DLW, pedometers and accelerometers, covering a broad range of activity constructs.

6.1.1.4 Validity

Within a validation study, there are many different concepts of validity. The type of validity assessed depends both on the type of method being validated and the choice of reference method. *Construct validity* refers to the association between physical activity measured with any type of method and a physiological variable related to physical activity, e.g. aerobic capacity. *Relative validity* is assessed when a method is validated against a similar instrument, for example comparing a questionnaire to another self-reported instrument such as a diary. Since two self-reported methods are subject to correlated errors, a high correlation does not necessarily mean that the methods are valid. *Criterion validity* is determined when validating a self-reported method against an objective instrument, for example comparing total physical activity levels from a questionnaire to results from accelerometers. Lastly, *absolute validity* is assessed when comparing results of the same absolute outcome assessed with the method under validation and measured using an objective instrument, for example total energy expenditure assessed by a questionnaire and measured by DLW. Self-reported instruments, e.g. physical activity questionnaires, usually show poor to moderate criterion validity and lower absolute validity.[48]

High accuracy implies absence of both random errors that affect precision, and absence of systematic errors that affect validity. While the magnitude of random error is inversely proportional to sample size, systematic errors may affect validity negatively even in very large samples. If a systematic error affects all individuals in a study population, it can for example affect the individuals' absolute results of energy expenditure, it may still allow for correct ranking of the individuals according to their energy expenditure. Such non-differential systematic error is less critical than a systematic error that differs between groups in a study population.

6.1.1.5 External validity

The external validity describes how generalizable our results are to other populations. Study participants in **Study III** were young and mainly females while participants in **study IV** were older men recruited within a specific cohort. The two studies represents very different groups but are both self-selected and participants may be more interested and motivated than the general population. Our results of validity and reproducibility may therefore be somewhat overestimated compared to if we used a random sample from the general population.

6.1.2 Main findings and interpretation

6.1.2.1 Validity

The Active-Q questionnaire showed moderate correlations to the gold standard DLW for assessment of total energy expenditure adjusted to 24-hours (r=0.52). The correlation when comparing crude energy expenditure assessed by Active-Q was not surprisingly lower (r=0.42). This variable does not represent total energy expenditure during 24-hours which the DLW measure does. Our results are line with the majority of validation studies comparing total energy expenditure from a physical activity questionnaire and DLW with correlation coefficients ranging between r=0.14-0.64.[36, 38, 123] However, all physical activity questionnaires previously validated against DLW have, to the best of our knowledge, been paper-based making direct comparison to the web-based Active-Q difficult.

The validity of self-reported total energy expenditure is generally high when compared to a gold standard method but should be interpreted with caution. The total energy expenditure depends to a large degree on the individual's body weight and therefore incorporates an element of BMR, which explains a lot of the variation in energy expenditure and is likely to yield high correlations by definition. Physical activity only explains a small part of the variation in our total energy expenditure. It is therefore not surprising that when comparing total MET-h from Active-Q, which does not include BMR, and total energy expenditure from DLW, the resulting correlation is lower (r=0.28) than those for variables of energy expenditure. Similarly, correlation coefficients comparing energy expenditure assessed with Active-Q to total daily steps, representing physical activity behavior, are also low (r = 0.07 and r = -0.12) and not statistically significant. A comparison of total MET-h from Active-Q and daily steps yielded a higher correlation coefficient (r = 0.20) as the latter compares similar constructs of activity.

The Bland-Altman plots did not show clear trends of bias across the range of total energy expenditure or any substantial differences between men and women. No systematic over-reporting of energy expenditure was seen and the mean difference between total energy expenditure adjusted to 24-hours from Active-Q and DLW was small (447kJ). However, the Bland-Altman plots show that the total energy expenditure of two individuals (above +2SD of the mean difference) was clearly overestimated in Active-Q. One individual was obese (BMI = 44.7kg/m^2) and an example of the limitations with using standardized MET-values when calculating energy expenditure. The other individual was a professional athlete who reported more than 10 hours of weight training, jogging and athletics per day. This exemplifies another limitation of MET-values and pre-defined response alternatives as the intensity level of any activity reported is assumed to be constant during the whole reported time interval. This is,

however, most likely not the case for long athletic sessions where the more intense activity is probably broken up by less intense periods.

For calculations of total energy expenditure from DLW, a standard respiratory quotient (RQ) of 0.85, suitable in a population with a western diet where 30-35% of the energy intake comes from fat, was used. This corresponds to the intake among study participants in VALMA.[103] Using an RQ that is not suitable for the macronutrient intake in a population will have negative effects on the accuracy of measurements.

For time spent at a vigorous activity level, a moderate correlation coefficient was seen between Active-Q and accelerometer measurements (r=0.54). Lower correlations were seen for time spent at light, moderate and moderate-to-vigorous activity levels (r=0.27-0.35). The correlations were somewhat lower among men <65 years of age and somewhat higher among older men. Our results are in line with the validity seen for different constructs of activity in other questionnaires compared to accelerometer data.[36, 124, 125] However, most previous validation studies have been performed in younger populations. One systematic review focusing on physical activity questionnaires for elderly (>55 years) showed varying results of validity and none of the studies included validated time spent at different intensity levels making comparisons to our results difficult.[126] Among adults >65 years of age, Siebling et al.[127] showed poor correlations (r=0.01-0.27) between time spent at MET-levels corresponding to the definition of light, moderate and vigorous activity in our study.

A clear trend of increased over-reporting of time spent performing moderate and vigorous activities was seen with increasing levels of moderate and vigorous activity in the Bland-Altman plots. A corresponding under-reporting of light activities was seen among men reporting lower levels of light activity. The mean difference between the methods was fairly large in relation to the total time spent in moderate, vigorous and moderate-to-vigorous activity, but smaller for light activity. Over-reporting of time spent moderate-to-vigorously active and under-reporting of sedentary time have been seen previously in comparisons of questionnaire and accelerometer data, although the mean differences between methods were smaller than in the present study.[128] One explanation for the low agreement between Active-Q and accelerometer data may be the inability of accelerometers to capture all activities. Movements from activities such as bicycling or swimming are not measured by the accelerometer and could contribute to the discrepancy between the methods. Accelerometers also fail to capture static and non-ambulatory activities, for example carrying a heavy load or walking uphill.[45] This would, however, not have been captured in Active-Q either and should not have a major impact on our results. The discrepancy between the time-period reflected in Active-Q and the two weeks of accelerometer measurements may also have contributed to the differences.

Comparisons of results from Active-Q measurements in both **Study III** (men only) and **IV** (men divided into sub-categories of <65 and ≥65 years of age), showed similar levels of energy expenditure and physical activity. However, men ≥65 years of age reported lower levels or total MET-h and crude energy expenditure compared to men <65 years in the same study and men in the other study. This difference may partly be explained by the assessment of occupational activity. More men <65 years of age are likely working compared to older men and will report the duration, frequency and intensity of working time. While the lack of occupation is thought to lead to reporting of more leisure time activities, this replacement may not be equal to time reported for work. The lower level of crude energy expenditure may also partly be explained by

older men having a lower BMI, i.e. a lower weight, than younger men leading to lower estimations of energy expenditure in this group.

6.1.2.2 Reproducibility

The ICCs for energy expenditure with and without adjustments to 24-hours from Active-Q were 0.74 and 0.87, respectively. For total MET-h and time spent at different activity levels, ICCs ranged between 0.51 and 0.66. The higher agreement for variables of energy expenditure is most likely due to the fact that variability in energy expenditure is largely explained by the individual's BMR. Nevertheless, our results are similar to those of other physical activity questionnaires, the median ICC in a recent review was 0.68.[36] The same review also showed that shorter time periods between assessments were associated with higher ICCs.

6.2 PROSTATE CANCER RISK, PROGRESSION AND MORTALITY

6.2.1 Methodological considerations

6.2.1.1 Study design

A major limitation to the PROCAP-study (**Study I** and **II**) is the *left-truncation* of study participants, i.e. the conditioning on being alive 5 to 10 years after prostate cancer diagnosis for inclusion in the study. The left-truncation time (i.e. the time from diagnosis to inclusion) only depends on time from diagnosis and is most likely random and independent of the survival time. The problem of left truncation is illustrated from a causal inference point of view in the **Figure 19**. In this DAG, X is the exposure (BMI, weight change, or physical activity), D_1 is an indicator of whether the patient died before the truncation point (i.e. inclusion), and D_2 is an indicator of whether the patient died at a specific later point in time (i.e. during the follow-up). All potential measured and unmeasured confounders are denoted by U. To simplify the argument we assume that all variables are binary (0/1) with 1=exposed/dead. In the situation of left truncation we cannot study the association between X and D_1, but are forced to study the association between X and D_2, conditional on D_1 being equal to 0 (i.e. alive). Using standard arguments from the causal inference literature[129] we induce a non-causal association component between X and D_2 through D_1. However, it can be argued that this association is likely to have the opposite sign as the true causal effect, thereby forcing the association towards a null effect. Suppose that we observe, for a given patient with D_1=0, that X=1 (exposed). Generally, X=1 increases the probability of D_1=1, so to "explain" why D_1=0 for this given patient, the probability of U=0 must increase. This, in turn, increases the probability of D_2=0. Hence, by conditioning on D_1=0 we are likely to induce an inverse association between X=1 and D_2=0.

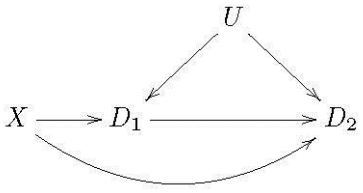


Figure 19. DAG illustrating bias due to left truncation.

While exposure assessment in **Study V** was done prospectively at baseline, a limitation to **Study I** and **II** is that the assessment of exposures in PROCAP was made in retrospect several years after the prostate cancer diagnosis. Erroneous recall of information may lead to misclassification of the true exposures which in turn may lead to an invalid estimate of the associations between exposures and outcomes. However, we believe that neither progression nor mortality is likely to have had a major impact on the reporting of exposure variables. Potential misclassification is therefore likely to be non-differential, biasing the estimates towards a null effect.

Random error does inherently occur in a sample randomly selected from the whole population, i.e. random variation may occur due to chance at selection also in population based studies such as PROCAP and STHLM-2. Random error leads to a lack of precision in estimates and uncertainty of measurements. The magnitude of random error is inversely proportional to sample size.

6.2.1.2 Reversed causality

Reversed causality is usually defined as the situation occurring when an outcome precedes and causes an exposure instead of the exposure causing the outcome.[5] However, in studies of body weight and mortality, the term reversed causation has been used to describe the situation when both the exposure and outcome are affected by a third factor, e.g. weight loss, caused by an underlying illness.[130] Even though this is rather a case of confounding (paragraph 2.1.1.2), the concept of reversed confounding has become commonly used to describe when an association between body weight and mortality is biased by weight-loss caused by pre-existing illness.[131] We performed sensitivity analysis using a 18-month long lag-time and men who experienced the outcome (death in **Study I** and **II**, and prostate cancer incidence in **Study V**) within 18-months of exposure assessment were excluded from analysis to avoid bias from reversed causation.

6.2.1.3 Internal and external validity

Internal validity refers to the validity of results within the study population and is a prerequisite for *external validity* which refers to how generalizable the results are to other populations. The internal validity is threatened by *confounding*, *selection bias* and *information bias*.[5]

6.2.1.4 Confounding

Confounding (paragraph 2.1.1.2) is the effect of a third factor on an exposure-outcome association and not controlling for confounding may bias the observed association. While confounding can be addressed directly in the study design (e.g. by randomization or matching), it can also be addressed at the analysis stage by controlling for known and measured confounders in statistical models. Adjustment of multiple confounders can be done simultaneously in regression models. To assess potential confounding by covariates in **Study I**, **II** and **V**, we tested if the covariates were statistically associated with both the exposures and the outcomes using linear regression and Cox proportional hazards models. In the end, the final inclusion of covariates in statistical models was based both on results of associations and subject matter knowledge. Even if we try to control for confounding, there may always be unknown, unmeasured or residual confounding affecting the results. *Residual confounding* due to measurement errors within measured confounder variables may remain even after adjustments.

6.2.1.5 Selection bias

Selection bias occurs when the association between an exposure and an outcome is different among study participants compared to the whole population which also include those who did not participate in the study. Selection bias is a threat to the internal validity as well as the external validity as it limits generalizability of the results to the other populations. Results in **Study I**, **II** or **V** are unlikely affected by selection bias to any large extent as both studies are population based with high participation rates and complete follow-up.

6.2.1.6 Information bias

The most common type of information bias is misclassification bias. *Differential misclassification* is information bias within the exposure variable that is influenced by disease status, i.e. it may occur if the exposure is assessed after the outcome and the outcome affects recall of the exposure, or the other way around. Differential misclassification of the exposure should not be of major concern in **Study I**, **II** or **V** where the exposure has been assessed before the outcomes with one exception. In analysis of prostate cancer progression (**Study I**), the exposure status was assessed after the progression event. However, we do not believe recall bias is an issue here since any event of progression is unlikely to have influenced reporting or neither body weight nor physical activity.

Even in studies where the exposure is measured before the outcome, *non-differential misclassification* may occur. If the exposure variable is dichotomous, non-differential misclassification may attenuate the results but when the exposure variables have three or more levels we cannot be sure of the direction of the potential bias. Measurement errors may also occur when continuous exposure variables are analyzed as categorical using arbitrary cut-offs. Categorization is a balance between creating relevant cut-offs and groups that have different enough exposure levels, at the same time as statistical power is ensured by a sufficient number of subjects in each category.

Exposures in **Study I** and **II** are self-reported retrospectively while BMI in **Study V** is based on self-reported current weight and height. Although correlations between self-reported and measured weight and height are strong, the long-term recall is influenced by current weight.[132, 133] Over-reporting of height, under-reporting of weight and consecutive under-estimations of BMI, is generally seen.[134] Increased under-estimations of weight are seen with increasing BMI.[135, 136]. Individuals who have experienced a large reduction in weight tend to over-estimate their previous weight in long-term recalls.[137] The validity of self-reported changes in weight is not well studied but errors in self-reports of weight change appear to be random.[138] The use of BMI as a proxy for body fat is also a limitation and has been discussed in paragraph 2.2.

Self-reported physical activity is commonly over-estimated.[39] This may be due to social desirability and memory bias, the latter more common among older individuals who may have cognitive difficulties in recalling activities.[40] Although the physical activity questionnaire used in **Study II** has been previously validated, difficulties of having to recall information from several years ago may have increased misclassification. Self-reported questionnaires to assess physical activity are discussed in paragraph 2.3.3.1.

6.2.2 Main findings and interpretations

6.2.2.1 Body Mass Index and prostate cancer progression and mortality (Study I)

BMI was not associated to progression or prostate cancer specific mortality. However, point estimates indicate increased rates of progression and cancer specific mortality among men in the higher categories of BMI compared to men in the reference group (<25kg/m^2). Higher overall mortality rates were seen among men with a BMI ≥30 kg/m^2 compared to the reference.

The consistent association between a high BMI and an increased risk of aggressive prostate cancer suggest that BMI may have an impact on progression rather than tumor development.[77] Most previous studies, but not all[139], have found associations between a high BMI and an increased risk of biochemical recurrence.[78, 92, 140-144] In contrast to the previous findings, we did not find any association between BMI and progression. Higher rates of prostate cancer specific mortality with increasing BMI have also been reported repeatedly.[78, 145-148] The association has been suggested to be more pronounced in men with aggressive disease.[79] Since our study only included men diagnosed with localized prostate cancer, the latter may explain why we, in contrast to other studies, did not find an association between BMI and prostate cancer specific mortality. The increased rates of overall mortality we saw among men with a high BMI, could be a result of an increased risk of for example cardiovascular disease which is strongly associated with high BMI.

Several possible mechanisms linking adiposity and prostate cancer have been proposed with the main hypothesis being that increased adiposity causes hormonal and metabolic changes. These changes include alterations of pathways for insulin and insulin-like growth factors (IGFs), sex hormone levels, and altered adipokine signaling.[149] High BMI is associated with hyperinsulinemia that through the reduction of IGF-binding proteins generates increased serum levels of IGF-I, which promote tumor development.[150] Additionally, high adiposity leads to lowered androgen levels and decreased serum testosterone, the latter associated with an increased risk of aggressive prostate tumors.[151] Altered levels of adipokines as a result of obesity will affect levels of leptin and adiponectin that may promote tumor development.[149] Similar mechanisms are most likely involved in the associations between weight change and physical activity, and prostate cancer.

6.2.2.2 Weight change and mortality (Study I)

A weight increase of >5% since diagnosis was associated with increased prostate cancer specific mortality rates compared to the reference group of men having reported a stable weight. A weight reduction >5% was associated with higher prostate cancer specific mortality in multivariable adjusted models without lag-time but the association did not remain in sensitivity analysis. The opposite was seen for overall mortality rates that were not statistically significantly different for men who increased in weight but higher among men who decreased in weight compared the men who kept a stable weight.

Large weight gain during adulthood has been associated with an increased risk of biochemical recurrence and aggressive or fatal prostate cancer.[90-92] Few studies looking at the effects of weight change in close approximation to or after the cancer diagnosis have been published. One study has shown an association between weight gain 5 years before and 1 year after a prostate cancer diagnosis and an increased risk

of cancer recurrence.[93] Another study showed that a large weight gain in the year before a radical prostatectomy increased the risk of biochemical recurrence compared to maintaining a stable weight.[94] In line with previous findings, we showed increased rates of prostate cancer specific mortality among men who experienced a larger weight gain compared to men who kept a stable weight. The results were statistically significant also in sensitivity analysis which strengthens our finding and indicates that the weight gain was unlikely to have been caused by the disease itself or other illness. An increased rate of prostate cancer specific mortality was also seen among men who decreased in weight but the attenuation of this association in sensitivity analysis indicate the weight loss may have been due to illness, i.e. reversed causality (paragraph 6.2.1.2). Hormonal and metabolic pathways are altered by the level of adiposity and therefore also likely to be affected by a weight change once a tumor has developed. Suggested mechanisms for the association between adiposity and prostate cancer are described in paragraph 6.2.2.1.

Our results are based on self-reported weight change and we do not know whether this was intentional or not. It is possible that an intentional weight change has different effects than an unintentional which may be caused by other factors such as disease, health issues, or malnutrition. While intentional weight loss among individuals with a high BMI may have positive effects on health and survival, an unintentional weight loss may be the result of poor health and thereby be associated with higher mortality. Weight maintenance or intentional weight change to improve health after diagnosis may be used as complements to treatment to improve survival.

6.2.2.3 Physical activity and mortality (Study II)

Lower prostate cancer specific mortality rates were seen for men who walked or bicycled ≥20 min/day and for men who exercised ≥1 h/week compared to men who walked, bicycled or exercised less. Higher levels of total recreational activity (≥5 MET-h/day), walking or bicycling (≥20 min/day), household work (≥1 h/day) and exercise (≥1 h/week) were associated with lower overall mortality rates compared to lower levels of activity in all categories.

Consistent evidence has linked increased physical activity to reductions in all-cause mortality among cancer survivors but evidence for prostate cancer specific mortality is still inadequate.[95] While physical activity has been inversely associated with prostate cancer risk[97], the effects of post-diagnostic physical activity on progression and mortality have only been investigated in two previous studies to the best of our knowledge. Kenfield et al.[98] showed reductions in both all-cause and prostate cancer specific mortality among men who engaged in vigorous physical activity ≥3 h/week compared to men who performed the activity <1 h/week. Higher levels of walking were associated with decreased all-cause mortality and indicated a decrease of prostate cancer specific mortality. Richman et al.[99] showed lower rates of progression among men who walked briskly for ≥3 h/week compared to men walking less and at an easier pace. Independent of walking duration, the authors also showed that walking at brisk pace was associated with a decreased progression rate compared to walking at an easier pace. Our results are in line with the previous studies, although we see positive effects at lower levels of physical activity, and show lower overall and prostate cancer specific mortality rates among physically active men.

The effects of physical activity on prostate cancer progression seem to partly work through similar, but opposite, mechanisms as BMI. Suggested mechanisms include

effects of physical activity on pathways of adipokine signaling, insulin and insulin-like growth factors (IGFs), and inflammation.[152] Alterations in adipokine levels as a result of obesity have been associated to tumor development.[149] Physical activity may counteract this effect. Increased aerobic fitness, i.e. a favorable change in body composition, following physical activity has been correlated to beneficial effects on adipokine levels in men with prostate cancer.[153] Regular exercise may also affect the serum IGF-axis resulting in lower levels of serum insulin and IGF-1. Increased levels of IGF binding protein-1 in vivo has been associated with reduced proliferation and increased apoptosis of prostate tumor cells in vitro.[154, 155] Serum extracted directly after strenuous exercise has also been shown to reduce proliferation of prostate tumor cells in vitro.[156] This indicates that physical activity may have acute effects on tumor growth. Lastly, inflammation has been suggested to play a role in prostate cancer development and progression.[157] Physical activity may have beneficial effects on inflammation by reducing levels of pro-inflammatory C-reactive protein.[158]

6.2.2.4 Body Mass Index and serum PSA-levels (Study V)

Higher BMI was associated with decreased serum PSA-levels among all men in the study. While an association was seen for men who were not diagnosed with prostate cancer during the follow-up, no association between BMI and PSA-levels was seen among men who were diagnosed during the follow-up.

Our results are in line with most previous studies that have found and established an inverse association between BMI and PSA-levels among men without prostate cancer.[75, 76, 80-86] An increasing BMI has also been associated to less rapid increases in PSA-levels as compared to PSA-changes in men with lower BMI.[159] Some studies have, however, found no association between BMI and PSA-levels.[89, 160, 161] Studies of the association among men with prostate cancer are fewer and the association less clear. Three cohort studies showed associations between higher BMI and lower levels of pre-operative serum PSA among men who underwent radical prostatectomy.[76] Another study found no association.[87] In line with the latter study, we could not see an association between BMI and serum PSA among men who were diagnosed with prostate cancer during the follow-up. However, baseline PSA-levels were higher among men who were diagnosed during the follow-up compared to men who were not.

A suggested explanation for the association between BMI and PSA-levels is hemodilution, i.e. a dilution of the total PSA amount due to larger plasma volume. This explanation is strengthened by several studies showing associations between BMI and plasma volumes as well as BMI and serum PSA concentrations concomitant to not seeing any differences in PSA-mass by BMI.[76, 82] Another explanation is decreased levels of circulating androgens, which are important for normal growth and differentiation of the prostate, seen with increasing BMI.[162]

Factors that may influence PSA-levels are important to assess as most prostate cancers today are detected through a biopsy following the results of a PSA-test. If hemodilution due to a high BMI masks an increased PSA-mass caused by a growing tumor, detection of the cancer may be delayed. Delayed cancer detection in men with a high BMI might also be a result of difficulties to biopsy since a high BMI has been associated to increased prostate weight and volume.[85, 88, 89]

6.2.2.5 Body Mass Index and prostate cancer risk (Study V)

We saw no association between the risk of prostate cancer and BMI. However, point estimates for high grade prostate cancer indicate increased rates among men in the higher BMI-categories compared to men with a BMI <25 kg/m^2.

Prostate cancer is hormone related and likely to be linked to anthropometric factors. The association between BMI and prostate cancer risk is therefore well studied but results are, however, inconsistent.[69] While BMI has been positively associated with the risk of advanced or fatal prostate cancer, inverse associations with overall risk and the risk of localized disease have been shown.[70-74, 163] The association between BMI and risk of high-grade prostate cancer may be explained by a poorer prognosis following delayed detection and diagnosis.[76] In line with previous findings, we found no association between BMI and the risk of overall or low grade prostate cancer. Our results indicate an increased rate of high-grade prostate cancer among men with a BMI ≥35kg/m^2 compared to men with a BMI <25kg/m^2. The wide confidence intervals around point estimates in sub-category analysis of low- and high-grade prostate cancer indicate uncertainty within our measurement. This is most likely due to the short follow-up time which limits the power in statistical analysis. Longer follow-up time would increase the number of incident prostate cancers and the power of statistical analysis.

7 CONCLUSIONS

Study I and II

In a large prospective cohort study of more than 5,000 men diagnosed with localized prostate cancer we found:

- No association between BMI and prostate cancer progression
- That men with a BMI ≥30 kg/m^2 had an 83% increased overall mortality rate compared to men with a BMI <25 kg/m^2
- No association between BMI and prostate cancer specific mortality
- That men who experienced a reduction in body weight by >5% after diagnosis had an almost 50% higher overall mortality rate compared to men who kept a stable weight
- That men who experienced an increase in body weight by >5% after diagnosis had a doubled prostate cancer specific mortality rate compared to men who kept a stable weight
- That men who reported higher levels of total recreational activity, walking or bicycling, household work and exercise had approximately 20-35% lower overall mortality rates compared to less active men
- That men who reported higher levels of walking or bicycling and exercise had 30% lower prostate cancer specific mortality rates compared to less active men

Study III and IV

The validity of the web-based physical activity questionnaire Active-Q was assessed in two validation studies by comparing results from the questionnaire to the three different reference methods: doubly labeled water, pedometers and accelerometers. Our results showed:

- Moderate validity for assessment of total energy expenditure compared to the doubly labeled method
- Poor validity for assessment of total MET-h compared to daily steps from pedometers
- Moderate validity for assessment of time spent at light, moderate, vigorous and moderate-to-vigorous physical activity levels compared to accelerometers
- Good reproducibility with regards to total energy expenditure, total MET-h and time spent at different activity levels

Study V

In a population based prospective cohort study of approximately 15,000 men we found:

- That men with a higher BMI had reduced levels of serum PSA
- No association between BMI and prostate cancer risk
- A suggestive association between high BMI and high-grade prostate cancer

8 FUTURE PERSPECTIVES

Results from this thesis have added small pieces to the large and complex puzzle that is prostate cancer etiology and survival after a prostate cancer diagnosis. The association between lifestyle factors and prostate cancer remains complex but it is clear that lifestyle matters. Maintenance of a healthy weight and being physically active provide strategies for men to improve their own health and survival.

The high incidence of prostate cancer is a major public health concern. To date, few studies have been able to study the impact of lifestyle after diagnosis due to a lack of data. The PROCAP-study offered a unique opportunity to assess the impact of lifestyle on prostate cancer progression and mortality in a large group of men diagnosed with localized prostate cancer. While this thesis work has focused on the impact of BMI, weight change and physical activity, there may be other lifestyle factors, such as diet or stress for example, that are equally important to study in the future.

In addition to previous studies, we were able to study the effects of weight change after prostate cancer diagnosis on mortality. However, we were not able to separate unintentional from intentional weight loss. Intentional weight loss to reach a body weight within the normal range have positive effects on cardiovascular mortality and could potentially have beneficial effects also on prostate cancer specific mortality as it counteracts the effects of high BMI. Future intervention studies looking at the effects of intentional weight change would therefore be an interesting next step.

Co-occurring with the high incidence of prostate cancer is the high prevalence of overweight and obesity. Since high BMI has an effect on PSA-levels, there is a need for studies aiming to improve guidelines on how to integrate information on BMI in the interpretation of PSA-values. If early detection of prostate cancer among overweight and obese men is hindered by the association between BMI on PSA, it is of great public health concern and needs to be addressed.

We also showed that physical activity reduced both overall- and prostate cancer specific mortality rates. Very reasonable levels of activity, 20 minutes of walking or bicycling per day or more and one hour of exercise per week, was enough. However, engaging in more physical activity than that may lead to even stronger effects. It is also possible that aerobic activities may have different effects than muscle strengthening activities. Future intervention studies randomizing men diagnosed with prostate cancer into different types of activity at different durations would be the next step to clarify what impact different types and durations of physical activity have on tumor progression and survival as well as quality of life for this group of patients.

We all know that physical activity is good for our health and yet it is so hard to get off the couch and into our running shoes. When faced with a cancer diagnosis, we may however reevaluate our lives and decide that it is time for a change and actually implement that change! Many ask themselves the question “What can I do to survive my cancer?” Now, the health care system has an important role in informing men about potential lifestyle changes that may help improve survival and quality of life. This is a golden opportunity to help the individual patient but also to improve public health in general.

Inconsistent associations between results from different studies can sometimes be attributed to methodological flaws and difficulties in assessing exposures. Physical activity is most often measured through self-reported questionnaires in large studies and it is important to use a validated method. The web-based physical activity questionnaire Active-Q that has been described in this thesis work provides a valid assessment method and is included in several large scale epidemiological studies, including the LifeGene, Karma, STHLM-2 and STHLM-3studies. To date, more than 100,000 study participants have responded to the questionnaire.

During the past years, using the Web to perform large data collections has become increasingly common. The days of using paper-based questionnaires that had to be printed, mailed to study participants at a high cost, filled-out very meticulously, mailed back to the researchers, checked for completeness and scanned into digital format are soon history. Instead, here are the days of efficient questionnaire design in web-based programs where automatic checks for completeness can be implemented, there are no costs for printing, distribution or scanning of the questionnaire and results are automatically stored in digital format. The rapid technology development has also enabled data collections through the use of smartphones and applications ("apps"). Technology will continue to improve and change the way we collect data and also the type of information we collect. We have a potential gold mine of information regarding lifestyle already in our smartphones; did you know most smartphones have a built in accelerometer? Now we just have to find a way to implement this in research. Imagine what we could do!

My hope is that this thesis will contribute to the field of cancer research as well as encourage the use of validated questionnaires to assess physical activity in future studies. I also hope that our findings will contribute to the lives of the many men with prostate cancer, giving them means to influence their own survival and encourage them to have a healthy and physically active lifestyle.

Drawing by Nils Bonn

9 ACKNOWLEDGEMENTS

When writing these acknowledgements I am overwhelmed by the number of people to thank for making this thesis become reality and for cheering me on during the years. You have all played an important role. Thank You!

The many financers who made this thesis work possible: **Cancerfonden, Fernströms stiftelse, FORTE, Gålö-stiftelsen, KI-fonder och stiftelser, Radiumhemmet,** and **Robert Lundbergs stiftelse** that funded projects and travel grants that enabled me to participate in scientific conferences and international collaborations around the world.

My main supervisor **Katarina Bälter** who believed in me and made these four years reality. Thank you for teaching me about the world of research, epidemiology, the value of travelling and collaborating, how to keep a balance between work and life and for encouraging me to do things I would have never imagined myself capable of doing a few years ago. Thank you for sharing your family and friends during travels when I was far away from my own and thank you **Olle Bälter** who welcomed me as well.

My co-supervisor **Ylva Trolle Lagerros** for being a source of inspiration and for always making time for me in your busy schedule. Thank you for sharing your research group at KEP and for cheering me on at every step of the way to this thesis.

My co-supervisors **Fredrik Wiklund** and **Henrik Grönberg** for being an extra support at MEB and for sharing your knowledge within the field of prostate cancer research.

Arvid Sjölander, the ever present statistical support. Thank you for taking the time to explain and repeat the statistics I needed in a very pedagogical way.

All fantastic **study participants** in the VALMA, VALTER, PROCAP and STHLM-2 studies. Without you, this research would have never happened.

All current and former co-workers, PhD-students and friends at MEB who have made going to work a pleasure during these years. Especially: **Anna Kähler, Anne Örtqvist, Camilla Ahlqvist, Carolyn Cesta, Denny Rönngren, Gunilla Sonnebring, Jiaqi Huang, Ralf Kuja-Halkola, Robert Karlsson, Robert Szulkin, Roohi Rustum**, **Tong Gong** and **Vilhelmina Ullemar.**

Anna Cantarutti, Camilla Sjörs, Erika Björnström, Michael Jan, Patrick Bergman, Sandra Ekström, and **Yanina Taynard**, whom I have worked particularly close to in different projects. If I hadn't had the opportunity to work with such talented people, I would have known a lot less today. **Thang Trinh**, my current office mate, for being a friend and for all the wonderful baked goods you've brought to work.

Fellow nutritionists **Anna Westerlund**, **Erika Ax** and **Madeleine Svensson** for conversations about nutrition, health and life in general.

To all the wonderful people I met during my travels to the US. **Eric Rimm**, **Marian Neuhouser** and **Pamela Surkan** for sharing their knowledge and letting me visit and work with them. **Elinor Fondell** for sharing your expertise during my visit to HSPH and your family in Boston. **Doris Boutain**, for unexpected friendship across the US.

Irene Shui for being a friend when I was far away from my own. **Harold** and **Ann Pebbles** for so kindly welcoming me to the family in Seattle.

To my friends on the inside ;) and, nowadays, outside of MEB. I can't imagine the past years without you and hope for many more to come. **Maria Sandberg** for always being there with an honest opinion during our many long talks over too long breakfasts, coffees, lunches and dinners. **Adina Feldman** for understanding my passion for Veronica and Logan and for always being there through some kind of social media making Cambridge feel close to Stockholm. **Martin Fransson** for having the kindest heart of all and for listening and offering thoughtful advice at all times. **Lisa Möller** for always having a word of encouragement close and for sharing your friends in both Stockholm and Boston. **Therese Ljung** for always having a smile to spare making my day happier and for talks about food, recipes and new restaurants. **Sara Christensen** my former office mate with whom I shared many efficient and some not so efficient days in the office, for our many talks and laughs and the occasional singing. **Iffat Rahman** for our many lunch talks about life inside and outside of academia. **Alexander Granqvist** for being an inspiration and showing us that you can do whatever you want. **Thomas Frisell** for the many interesting and funny discussions. **Karin Sundström, Lovisa Högberg** and **Miriam Elfström** for being sources of inspiration. **Björn Schelin, Mats Ljung**, **Bruno Raposo, Fredrik Havasi** and **Anders Carlson** for making such great additions to the gang. **Christina Persson** and **Sven Wennerström** for staying close even when far away.

To everyone in **Stockholm Starlight**, my fantastic choir that has brought so much positive energy and happiness into my life.

Jessica Magnusson, who I met at the nutrition program. I'm greateful for having been friends ever since that first week. Thank you for being here and sharing your family including **Jesper, Laura** and **Ellinor**. **Fredrik Rosqvist**, my other friend from the nutrition program. Thank you for inspiring me to want to know more (your enthusiasm when it comes to nutrition is catching) and for introducing **Marion**.

Sandra Backlund, thank you for listening to endless rants about life and everything else during long telephone calls and offered your honest opinion. **Jonas Hällgren**, for making me smile. **Fredrik von Wiesz**, for discussions big and small. **Sofia Anderberg**, for well needed long-lunches. **Malin Carlsson**, my fellow Starlightare and sewing enthusiast for sharing your positive outlook on life.

Till **Mormor**, **Farmor** och **Farfar**. Även om ni är långt borta så finns ni alltid nära.
Tack farfar för bilden.

Philip för pepp och ärliga åsikter när vi väl lyckas ses ☺

Mamma och **Georg** för att ni finns där när det behövs och alla andra gånger också.

Pappa för att du tror på mig och låter mig veta hur stolt du är.

10 REFERENCES

1. Caspersen CJ, Powell KE, and Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. *Public Health Rep*, 1985. 100(2):126-31.
2. World Health Organization. Global recommendations on physical activity for health. 2010: Geneva. ISBN 978-92-4-159-997-9
3. Finucane MM, Stevens GA, Cowan MJ, et al. National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. *Lancet*, 2011. 377(9765):557-67.
4. Jemal A, Bray F, Center MM, et al. Global cancer statistics. *CA Cancer J Clin*, 2011. 61(2):69-90.
5. Rothman KJ, Greenland S, Lash TL. Modern Epidemiology, Third Edition. Lippincott, Williams & Wilkins 2008.
6. Ekman A and Litton JE. New times, new needs; e-epidemiology. *Eur J Epidemiol*, 2007. 22(5):285-92.
7. van Gelder MM and Pijpe A. E-epidemiology: a comprehensive update. *OA Epidemiology*, 2013. 1(1):5.
8. Statistics Sweden. Use of computers and the Internet by private persons in 2010. Statistics Sweden, R&D and IT unit. 2014: Stockholm. [Swedish]
9. Lee SY and Gallagher D. Assessment methods in human body composition. *Curr Opin Clin Nutr Metab Care*, 2008. 11(5):566-72.
10. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: executive summary. Expert Panel on the Identification, Evaluation, and Treatment of Overweight in Adults. *Am J Clin Nutr*, 1998. 68(4):899-917.
11. Okorodudu DO, Jumean MF, Montori VM, et al. Diagnostic performance of body mass index to identify obesity as defined by body adiposity: a systematic review and meta-analysis. *Int J Obes (Lond)*, 2010. 34(5):791-9.
12. Prentice AM , Jebb SA. Beyond body mass index. *Obes Rev*, 2001. 2(3):141-7.
13. Flegal KM, Shepherd JA, Looker AC, et al. Comparisons of percentage body fat, body mass index, waist circumference, and waist-stature ratio in adults. *Am J Clin Nutr*, 2009. 89(2):500-8.
14. World Health Organization. Global Status Report on nuncommunicable diseases. 2014: Geneva. ISBN 978-92-4-156485-4
15. Public Health Agency of Sweden. Nationella Folkhälsoenkäten, nationella och regionala resultat, Levnadsvanor. [Database in Swedish] Accesed 2015/02/16 Avaliable at: www.folkhalsomyndigheten.se
16. Davidsson L (Editor). International Atomic Energy Agency: Assessment of body composition and total energy expenditure in humans using stable isotope techniques. *IAEA human health series No. 3.* 2009: Vienna.
17. Schofield WN. Predicting basal metabolic rate, new standards and review of previous work. *Hum Nutr Clin Nutr*, 1985. 39(1):5-41.
18. Caspersen CJ. Physical activity epidemiology: concepts, methods, and applications to exercise science. *Exerc Sport Sci Rev*, 1989. 17: 423-73.
19. Ainsworth BE, Haskell WL, Leon AS, et al. Compendium of physical activities: classification of energy costs of human physical activities. *Med Sci Sports Exerc*, 1993. 25(1):71-80.

20. Ainsworth BE, Haskell WL, Herrmann SD, et al. 2011 Compendium of Physical Activities: A Second Update of Codes and MET Values. *Medicine and science in sports and exercise*, 2011. 43(8):1575-1581.
21. Ainsworth BE, Haskell WL, Whitt MC, et al. Compendium of physical activities: an update of activity codes and MET intensities. *Med Sci Sports Exerc*, 2000. 32(9):498-504.
22. Browning RC, Baker EA, Herron JA, and Kram R. Effects of obesity and sex on the energetic cost and preferred speed of walking. *J Appl Physiol*, 2006. 100(2):390-8.
23. Ravussin E, Bogardus C. Relationship of genetics, age, and physical fitness to daily energy expenditure and fuel utilization. *Am J Clin Nutr*, 1989. 49(5):968-75.
24. Brownson RC, Boehmer TK, and Luke DA. Declining rates of physical activity in the United States: what are the contributors? *Annu Rev Public Health*, 2005. 26:421-43.
25. Hagstromer M, Kwak L, Oja P, and Sjostrom M. A 6 year longitudinal study of accelerometer-measured physical activity and sedentary time in Swedish adults. *J Sci Med Sport*, 2014. [Epub ahead of print]
26. Matthews CE, George SM, Moore SC, et al. Amount of time spent in sedentary behaviors and cause-specific mortality in US adults. *Am J Clin Nutr*, 2012. 95(2):437-45.
27. Wilmot EG, Edwardson CL, Achana FA, et al. Sedentary time in adults and the association with diabetes, cardiovascular disease and death: systematic review and meta-analysis. *Diabetologia*, 2012. 55(11):2895-905.
28. World Health Organisation. Global health risks: mortality and burden of disease attributable to selected major risks. 2009: Geneva.
29. Nordic Counsil of Ministers. Nordic Nutrition Recommendations 2012 - Integrating nutrition and physical activity. 2014. Avaliable at: http://dx.doi.org/10.6027/Nord2014-002 Accessed: 2015/02/17
30. Haskell WL, Lee IM, Pate RR, et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Med Sci Sports Exerc*, 2007. 39(8):1423-34.
31. Haskell WL. Physical activity by self-report: a brief history and future issues. *J Phys Act Health*, 2012. 9(1):5-10.
32. Sallis JF and Saelens BE. Assessment of Physical Activity by Self-Report: Status, Limitations, and Future Directions. *Res Q Exerc Sport*,2000. 71(2):1-14.
33. Shephard RJ. Limits to the measurement of habitual physical activity by questionnaires. *Br J Sports Med*, 2003. 37(3):197-206.
34. Prince SA, Adamo KB, Hamel ME, et al. A comparison of direct versus self-report measures for assessing physical activity in adults: a systematic review. *Int J Behav Nutr Phys Act*, 2008. 5:56.
35. Ferrari P, Friedenreich C, and Matthews CE. The role of measurement error in estimating levels of physical activity. *Am J Epidemiol*, 2007. 166(7):832-40.
36. Helmerhorst HJ, Brage S, Warren J, et al. A systematic review of reliability and objective criterion-related validity of physical activity questionnaires. *Int J Behav Nutr Phys Act*, 2012. 9:103.
37. Pereira MA, FitzerGerald SJ, Gregg EW, et al. A collection of Physical Activity Questionnaires for health-related research. *Med Sci Sports Exerc*, 1997. 29(6):1-205.

38. van Poppel MN, Chinapaw MJ, Mokkink LB, et al. Physical activity questionnaires for adults: a systematic review of measurement properties. *Sports medicine*, 2010. 40(7):565-600.
39. Rasmussen LB, Matthiessen J, Biltoft-Jensen A, and Tetens I. Characteristics of misreporters of dietary intake and physical activity. *Public Health Nutr*, 2007. 10(3):230-7.
40. Stewart AL, Mills KM, King AC, et al. CHAMPS physical activity questionnaire for older adults: outcomes for interventions. *Med Sci Sports Exerc*, 2001. 33(7):1126-41.
41. Craig CL, Marshall AL, Sjostrom M, et al. International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc*, 2003. 35(8):1381-95.
42. Bull FC, Maslin TS, and Armstrong T. Global physical activity questionnaire (GPAQ): nine country reliability and validity study. *J Phys Act Health*, 2009. 6(6):790-804.
43. Ainsworth B, Cahalin L, Buman M, and Ross R. The current state of physical activity assessment tools. *Prog Cardiovasc Dis*, 2015. 57(4):387-95.
44. Weir JB. New methods for calculating metabolic rate with special reference to protein metabolism. *J Physiol*, 1949. 109(1-2):1-9.
45. Butte NF, Ekelund U, and Westerterp KR. Assessing physical activity using wearable monitors: measures of physical activity. *Med Sci Sports Exerc*, 2012. 44(1):5-12.
46. Corder K, Brage S, and Ekelund U. Accelerometers and pedometers: methodology and clinical application. *Curr Opin Clin Nutr Metab Care*, 2007. 10(5):597-603.
47. Tudor-Locke C, Bassett DR, Shipe MF, and McClain JJ. Pedometry methods for assessing free-living adults. *J Phys Act Health*, 2011. 8(3):445-53.
48. Warren JM, Ekelund U, Besson H, et al. Assessment of physical activity - a review of methodologies with reference to epidemiological research: a report of the exercise physiology section of the European Association of Cardiovascular Prevention and Rehabilitation. *Eur J Cardiovasc Prev Rehabil*, 2010. 17(2):127-39.
49. Tudor-Locke C, Williams JE, Reis JP, and Pluto D. Utility of pedometers for assessing physical activity: convergent validity. *Sports Med*, 2002. 32(12):795-808.
50. Crouter SE, Schneider PL, Karabulut M, and Bassett DR, Jr. Validity of 10 electronic pedometers for measuring steps, distance, and energy cost. *Med Sci Sports Exerc*, 2003. 35(8):1455-60.
51. Schneider PL, Crouter SE, Lukajic O, and Bassett DR, Jr. Accuracy and reliability of 10 pedometers for measuring steps over a 400-m walk. *Med Sci Sports Exerc*, 2003. 35(10):1779-84.
52. Baranowski T, Masse LC, Ragan B, and Welk G. How many days was that? We're still not sure, but we're asking the question better! *Med Sci Sports Exerc*, 2008. 40(7):544-9.
53. Clemes SA and Deans NK. Presence and duration of reactivity to pedometers in adults. *Med Sci Sports Exerc*, 2012. 44(6):1097-101.
54. Clemes SA, Matchett N, and Wane SL. Reactivity: an issue for short-term pedometer studies? *Br J Sports Med*, 2008. 42(1):68-70.
55. Clemes SA and Parker RA. Increasing our understanding of reactivity to pedometers in adults. *Med Sci Sports Exerc*, 2009. 41(3):674-80.

56. Matevey C RL, Dawson E, Tudor-Locke C. Lack of Reactivity During Pedometer Self-Monitoring in Adults. *Measurement in Physical Education and Exercise Science*, 2006. 10(1):1-11.
57. Trost SG, McIver KL, and Pate RR. Conducting accelerometer-based activity assessments in field-based research. *Med Sci Sports Exerc*, 2005. 37(11): 531-43.
58. Welk GJ. Principles of design and analyses for the calibration of accelerometry-based activity monitors. *Med Sci Sports Exerc*, 2005. 37(11 Suppl): p. S501-11.
59. Matthews CE. Calibration of accelerometer output for adults. *Med Sci Sports Exerc*, 2005. 37(11):512-522.
60. Engholm G FJ, Christensen N, Kejs AMT, Johannesen TB, Khan S, Milter MC, Ólafsdóttir E, Petersen T, Pukkala E, Stenz F, Storm HH. . NORDCAN: Cancer Incidence, Mortality, Prevalence and Survival in the Nordic Countries. Version 7.0 (17.12.2014). Association of the Nordic Cancer Registries. Danish Cancer Society. Avaliable at: http://www.ancr.nu
61. Ferlay J SI, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray, F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. 2013, International Agency for Research on Cancer. Avaliable at: http://globocan.iarc.fr
62. Center MM, Jemal A, Lortet-Tieulent J, et al. International variation in prostate cancer incidence and mortality rates. *Eur Urol*, 2012. 61(6):1079-92.
63. Bergman O, Hont G, Johansson E. Cancer i siffror 2013. The National Board of Health and Welfare. 2013:Stockholm. [Swedish]
64. Saman DM, Lemieux AM, Nawal Lutfiyya M, and Lipsky MS. A review of the current epidemiology and treatment options for prostate cancer. *Dis Mon*, 2014. 60(4):150-4.
65. Draisma G, Etzioni R, Tsodikov A, et al. Lead time and overdiagnosis in prostate-specific antigen screening: importance of methods and context. *J Natl Cancer Inst*, 2009. 101(6):374-83.
66. The National Board of Health Welfare. *Screening för prostatacancer - Rekommendation och bedömningsunderlag*. 2013. [Swedish]
67. Nordstrom T, Aly M, Clements MS, et al. Prostate-specific antigen (PSA) testing is prevalent and increasing in Stockholm County, Sweden, Despite no recommendations for PSA screening: results from a population-based study, 2003-2011. *Eur Urol*, 2013. 63(3):419-25.
68. Hsing AW, Sakoda LC, and Chua S, Jr. Obesity, metabolic syndrome, and prostate cancer. *Am J Clin Nutr*, 2007. 86(3):843-57.
69. Allott EH, Masko EM, and Freedland SJ. Obesity and Prostate Cancer: Weighing the Evidence. *European Urology*, 2013. 63(5):800-809.
70. Giovannucci E, Liu Y, Platz EA, et al. Risk factors for prostate cancer incidence and progression in the health professionals follow-up study. *Int J Cancer*, 2007. 121(7):1571-8.
71. MacInnis RJ and English DR. Body size and composition and prostate cancer risk: systematic review and meta-regression analysis. *Cancer Causes Control*, 2006. 17(8):989-1003.
72. Rodriguez C, Freedland SJ, Deka A, et al. Body mass index, weight change, and risk of prostate cancer in the Cancer Prevention Study II Nutrition Cohort. *Cancer Epidemiol Biomarkers Prev*, 2007. 16(1):63-9.
73. Stocks T, Hergens MP, Englund A, et al. Blood pressure, body size and prostate cancer risk in the Swedish Construction Workers cohort. *Int J Cancer*, 2010. 127(7):1660-8.

74. Discacciati A, Orsini N, and Wolk A. Body mass index and incidence of localized and advanced prostate cancer-a dose-response meta-analysis of prospective studies. *Annals of Oncology*, 2012. 23(7):1665-1671.
75. Baillargeon J, Pollock BH, Kristal AR, et al. The association of body mass index and prostate-specific antigen in a population-based study. *Cancer*, 2005. 103(5):1092-5.
76. Banez LL, Hamilton RJ, Partin AW, et al. Obesity-related plasma hemodilution and PSA concentration among men with prostate cancer. *JAMA*, 2007. 298(19):2275-80.
77. Mistry T, Digby JE, Desai KM, and Randeva HS. Obesity and prostate cancer: a role for adipokines. *Eur Urol*, 2007. 52(1):46-53.
78. Cao Y and Ma J. Body-mass index, prostate cancer-specific mortality and biochemical recurrence:a systematic review and meta-analysis. *Cancer Prev Res (Phila)*, 2011. 4(4):486-501.
79. Haque R, Van Den Eeden SK, Wallner LP, et al. Association of body mass index and prostate cancer mortality. *Obes Res Clin Pract*, 2014. 8(4):374-81.
80. Barqawi AB, Golden BK, O'Donnell C, et al. Observed effect of age and body mass index on total and complexed PSA: analysis from a national screening program. *Urology*, 2005. 65(4):708-12.
81. Beebe-Dimmer JL, Faerber GJ, Morgenstern H, et al. Body composition and serum prostate-specific antigen: review and findings from Flint Men's Health Study. *Urology*, 2008. 71(4):554-60.
82. Grubb RL, 3rd, Black A, Izmirlian G, et al. Serum prostate-specific antigen hemodilution among obese men undergoing screening in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. *Cancer Epidemiol Biomarkers Prev*, 2009. 18(3):748-51.
83. Han JH, Choi NY, Bang SH, et al. Relationship between serum prostate-specific antigen levels and components of metabolic syndrome in healthy men. *Urology*, 2008. 72(4):749-55.
84. Kristal AR, Chi C, Tangen CM, et al. Associations of demographic and lifestyle characteristics with prostate-specific antigen (PSA) concentration and rate of PSA increase. *Cancer*, 2006. 106(2):320-8.
85. Oh JJ, Jeong SJ, Lee BK, et al. Does obesity affect the accuracy of prostate-specific antigen (PSA) for predicting prostate cancer among men undergoing prostate biopsy. *BJU Int*, 2013. 112(4):E265-71.
86. Rundle A and Neugut AI. Obesity and screening PSA levels among men undergoing an annual physical exam. *Prostate*, 2008. 68(4):373-80.
87. Freedland SJ, Platz EA, Presti JC, Jr., et al. Obesity, serum prostate specific antigen and prostate size: implications for prostate cancer detection. *J Urol*, 2006. 175(2):500-4.
88. Kopp RP, Han M, Partin AW, et al. Obesity and prostate enlargement in men with localized prostate cancer. *BJU Int*, 2011. 108(11):1750-5.
89. Ochiai A, Fritsche HA, and Babaian RJ. Influence of anthropometric measurements, age, and prostate volume on prostate-specific antigen levels in men with a low risk of prostate cancer. *Urology*, 2005. 66(4):819-23.
90. Bassett JK, Severi G, Baglietto L, et al. Weight change and prostate cancer incidence and mortality. *International Journal of Cancer*, 2012. 131(7):1711-1719.
91. Wright ME, Chang SC, Schatzkin A, et al. Prospective study of adiposity and weight change in relation to prostate cancer incidence and mortality. *Cancer*, 2007. 109(4):675-84.

92. Strom SS, Wang XM, Pettaway CA, et al. Obesity, weight gain, and risk of biochemical failure among prostate cancer patients following prostatectomy. *Clinical Cancer Research*, 2005. 11(19):6889-6894.
93. Joshu CE, Mondul AM, Menke A, et al. Weight gain is associated with an increased risk of prostate cancer recurrence after prostatectomy in the PSA era. *Cancer Prev Res (Phila)*, 2011. 4(4):544-51.
94. Whitley BM, Moreira DM, Thomas JA, et al. Preoperative weight change and risk of adverse outcome following radical prostatectomy: results from the Shared Equal Access Regional Cancer Hospital database. *Prostate Cancer Prostatic Dis*, 2011. 14(4):361-6.
95. Ballard-Barbash R, Friedenreich CM, Courneya KS, et al. Physical activity, biomarkers, and disease outcomes in cancer survivors: a systematic review. *J Natl Cancer Inst*, 2012. 104(11):815-40.
96. Lollgen H, Bockenhoff A, and Knapp G. Physical activity and all-cause mortality: an updated meta-analysis with different intensity categories. *Int J Sports Med*, 2009. 30(3):213-24.
97. Liu Y, Hu F, Li D, et al. Does physical activity reduce the risk of prostate cancer? A systematic review and meta-analysis. *Eur Urol*, 2011. 60(5):1029-44.
98. Kenfield SA, Stampfer MJ, Giovannucci E, and Chan JM. Physical activity and survival after prostate cancer diagnosis in the health professionals follow-up study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*, 2011. 29(6):726-32.
99. Richman EL, Kenfield SA, Stampfer MJ, et al. Physical activity after diagnosis and risk of prostate cancer progression: data from the cancer of the prostate strategic urologic research endeavor. *Cancer research*, 2011. 71(11):3889-95.
100. Nordstrom T, Aly M, Eklund M, et al. A genetic score can identify men at high risk for prostate cancer among men with prostate-specific antigen of 1-3 ng/ml. *Eur Urol*, 2014. 65(6): p. 1184-90.
101. Bonn SE, Trolle Lagerros Y, Christensen SE, et al. Active-q: validation of the web-based physical activity questionnaire using doubly labeled water. *Journal of medical Internet research*, 2012. 14(1):e29.
102. Christensen SE, Moller E, Bonn SE, et al. Relative validity of micronutrient and fiber intake assessed with two new interactive meal- and Web-based food frequency questionnaires. *J Med Internet Res*, 2014. 16(2):e59.
103. Christensen SE, Moller E, Bonn SE, et al. Two new meal- and web-based interactive food frequency questionnaires: validation of energy and macronutrient intake. *J Med Internet Res*, 2013. 15(6):e109.
104. Norman A, Bellocco R, Bergstrom A, and Wolk A. Validity and reproducibility of self-reported total physical activity--differences by relative weight. *Int J Obes Relat Metab Disord*, 2001. 25(5):682-8.
105. Trabulsi J, Troiano RP, Subar AF, et al. Precision of the doubly labeled water method in a large-scale application: evaluation of a streamlined-dosing protocol in the Observing Protein and Energy Nutrition (OPEN) study. *Eur J Clin Nutr*, 2003. 57(11):1370-7.
106. Assah FK, Ekelund U, Brage S, et al. Accuracy and validity of a combined heart rate and motion sensor for the measurement of free-living physical activity energy expenditure in adults in Cameroon. *International journal of epidemiology*, 2011. 40(1):112-20.
107. Bluck LJC. Doubly labelled water for the measurement of total energy expenditure in man – progress and applications in the last decade. *Nutrition Bulletin*, 2008. 33:80-90.

108. Schoeller DA, Ravussin E, Schutz Y, et al. Energy expenditure by doubly labeled water: validation in humans and proposed calculation. *Am J Physiol*, 1986. 250(5 Pt 2):823-30.
109. Esliger DW, Rowlands AV, Hurst TL, et al. Validation of the GENEA Accelerometer. *Medicine and science in sports and exercise*, 2011. 43(6):1085-93.
110. Haukoos JS and Lewis RJ. Advanced Statistics: Bootstrapping confidence intervals for statistics with "difficult" distributions. *Academic Emergency Medicine*, 2005. 12(4):360-365.
111. Bland JM and Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet*, 1986. 1(8476): p. 307-10.
112. Lee J, Koh D, and Ong CN. Statistical evaluation of agreement between two methods for measuring a quantitative variable. *Comput Biol Med*, 1989. 19(1):61-70.
113. Van Hemelrijck M, Wigertz A, Sandin F, et al. Cohort Profile: The National Prostate Cancer Register of Sweden and Prostate Cancer data Base Sweden 2.0. *Int J Epidemiol*, 2012. 42(4):956-67.
114. Stattin P, Holmberg E, Bratt O, et al. Surveillance and deferred treatment for localized prostate cancer. Population based study in the National Prostate Cancer Register of Sweden. *J Urol*, 2008. 180(6):2423-30.
115. Barlow L, Westergren K, Holmberg L, and Talback M. The completeness of the Swedish Cancer Register: a sample survey for year 1998. *Acta Oncol*, 2009. 48(1):27-33.
116. Tomic K, Sandin F, Wigertz A, et al. Evaluation of data quality in the National Prostate Cancer Register of Sweden. *Eur J Cancer*, 2015. 51(1):101-11.
117. National Board of Health and Welfare. *Cause of Death Regsiter*. 2014. Avaliable at: http://www.socialstyrelsen.se/register/dodsorsaksregistret Accessed: 2015/02/17
118. Szulkin R, Holmberg E, Stattin P, et al. Prostate cancer risk variants are not associated with disease progression. *The Prostate*, 2012. 72(1):30-9.
119. De Boor C. A Practical Guide to Splines (Revised Edition). 2001.
120. Plasqui G, Bonomi AG, and Westerterp KR. Daily physical activity assessment with accelerometers: new insights and validation studies. *Obes Rev*, 2013. 14(6):451-62.
121. Freedson P, Bowles HR, Troiano R, and Haskell W. Assessment of physical activity using wearable monitors: recommendations for monitor calibration and use in the field. *Med Sci Sports Exerc*, 2012. 44(1):1-4.
122. Byrne NM, Hills AP, Hunter GR, et al. Metabolic equivalent: one size does not fit all. *J Appl Physiol (1985)*, 2005. 99(3):1112-9.
123. Neilson HK, Robson PJ, Friedenreich CM, and Csizmadi I. Estimating activity energy expenditure: how valid are physical activity questionnaires? *Am J Clin Nutr*, 2008. 87(2):279-91.
124. Dyrstad SM, Hansen BH, Holme IM, and Anderssen SA. Comparison of self-reported versus accelerometer-measured physical activity. *Med Sci Sports Exerc*, 2014. 46(1):99-106.
125. Lee PH, Macfarlane DJ, Lam TH, and Stewart SM. Validity of the International Physical Activity Questionnaire Short Form (IPAQ-SF): a systematic review. *Int J Behav Nutr Phys Act*, 2011. 8:115.
126. Forsen L, Loland NW, Vuillemin A, et al. Self-administered physical activity questionnaires for the elderly: a systematic review of measurement properties. *Sports Med*, 2010. 40(7):601-23.
127. Siebeling L, Wiebers S, Beem L, et al. Validity and reproducibility of a physical activity questionnaire for older adults: questionnaire versus

accelerometer for assessing physical activity in older adults. *Clin Epidemiol*, 2012. 4:171-80.
128. Golubic R, May AM, Benjaminsen Borch K, et al. Validity of Electronically Administered Recent Physical Activity Questionnaire (RPAQ) in Ten European Countries. *PLoS One*, 2014. 9(3):e92829.
129. Greenland S. Quantifying biases in causal models: classical confounding vs collider-stratification bias. *Epidemiology*, 2003. 14(3): p. 300-6.
130. Willett WC, Dietz WH, and Colditz GA. Guidelines for healthy weight. *N Engl J Med*, 1999. 341(6):427-34.
131. Flegal KM, Graubard BI, Williamson DF, and Cooper RS. Reverse causation and illness-related weight loss in observational studies of body weight and mortality. *Am J Epidemiol*, 2011. 173(1):1-9.
132. Bulik CM, Wade TD, Heath AC, et al. Relating body mass index to figural stimuli: population-based normative data for Caucasians. *Int J Obes Relat Metab Disord*, 2001. 25(10):1517-24.
133. Kovalchik S. Validity of adult lifetime self-reported body weight. *Public Health Nutr*, 2009. 12(8):1072-7.
134. Gorber SC, Tremblay M, Moher D, and Gorber B. A comparison of direct vs. self-report measures for assessing height, weight and body mass index: a systematic review. *Obesity reviews : an official journal of the International Association for the Study of Obesity*, 2007. 8(4):307-26.
135. Bostrom G and Diderichsen F. Socioeconomic differentials in misclassification of height, weight and body mass index based on questionnaire data. *Int J Epidemiol*, 1997. 26(4):860-6.
136. Nyholm M, Gullberg B, Merlo J, et al. The validity of obesity based on self-reported weight and height: Implications for population studies. *Obesity*, 2007. 15(1):197-208.
137. Dahl AK and Reynolds CA. Accuracy of recalled body weight--a study with 20-years of follow-up. *Obesity*, 2013. 21(6):1293-8.
138. Field AE, Aneja P, and Rosner B. The validity of self-reported weight change among adolescents and young adults. *Obesity*, 2007. 15(9):2357-64.
139. Tomaszewski JJ, Chen YF, Bertolet M, et al. Obesity is not associated with aggressive pathologic features or biochemical recurrence after radical prostatectomy. *Urology*, 2013. 81(5):992-6.
140. Bassett WW, Cooperberg MR, Sadetsky N, et al. Impact of obesity on prostate cancer recurrence after radical prostatectomy: data from CaPSURE. *Urology*, 2005. 66(5):1060-5.
141. Efstathiou JA, Chen MH, Renshaw AA, et al. Influence of body mass index on prostate-specific antigen failure after androgen suppression and radiation therapy for localized prostate cancer. *Cancer*, 2007. 109(8):1493-8.
142. Ly D, Reddy CA, Klein EA, and Ciezki JP. Association of body mass index with prostate cancer biochemical failure. *J Urol*, 2010. 183(6):2193-9.
143. Palma D, Pickles T, Tyldesley S, and Prostate Cohort Outcomes I. Obesity as a predictor of biochemical recurrence and survival after radiation therapy for prostate cancer. *BJU Int*, 2007. 100(2):315-9.
144. Strom SS, Kamat AM, Gruschkus SK, et al. Influence of obesity on biochemical and clinical failure after external-beam radiotherapy for localized prostate cancer. *Cancer*, 2006. 107(3):631-639.
145. Efstathiou JA, Bae K, Shipley WU, et al. Obesity and mortality in men with locally advanced prostate cancer: analysis of RTOG 85-31. *Cancer*, 2007. 110(12):2691-9.

146. Gong Z, Agalliu I, Lin DW, et al. Obesity is associated with increased risks of prostate cancer metastasis and death after initial cancer diagnosis in middle-aged men. *Cancer*, 2007. 109(6):1192-202.
147. Haggstrom C, Stocks T, Ulmert D, et al. Prospective Study on Metabolic Factors and Risk of Prostate Cancer. *Cancer*, 2012. 118(24):6199-6206.
148. Ma J, Li H, Giovannucci E, et al. Prediagnostic body-mass index, plasma C-peptide concentration, and prostate cancer-specific mortality in men with prostate cancer: a long-term survival analysis. *Lancet Oncol*, 2008. 9(11):1039-47.
149. Roberts DL, Dive C, and Renehan AG. Biological mechanisms linking obesity and cancer risk: new perspectives. *Annu Rev Med*, 2010. 61:301-16.
150. Renehan AG, Frystyk J, and Flyvbjerg A. Obesity and cancer risk: the role of the insulin-IGF axis. *Trends Endocrinol Metab*, 2006. 17(8):328-36.
151. Schnoeller T, Jentzmik F, Rinnab L, et al. Circulating free testosterone is an independent predictor of advanced disease in patients with clinically localized prostate cancer. *World J Urol*, 2013. 31(2):253-9.
152. McTiernan A. Mechanisms linking physical activity with cancer. *Nat Rev Cancer*, 2008. 8(3):205-11.
153. Mina DS, Connor MK, Alibhai SM, et al. Exercise effects on adipokines and the IGF axis in men with prostate cancer treated with androgen deprivation: A randomized study. *Can Urol Assoc J*, 2013. 7(11-12):692-8.
154. Barnard RJ, Leung PS, Aronson WJ, et al. A mechanism to explain how regular exercise might reduce the risk for clinical prostate cancer. *Eur J Cancer Prev*, 2007. 16(5):415-21.
155. Barnard RJ, Ngo TH, Leung PS, et al. A low-fat diet and/or strenuous exercise alters the IGF axis in vivo and reduces prostate tumor cell growth in vitro. *Prostate*, 2003. 56(3):201-6.
156. Rundqvist H, Augsten M, Stromberg A, et al. Effect of acute exercise on prostate cancer cell growth. *PLoS One*, 2013. 8(7): e67579.
157. Sutcliffe S and Platz EA. Inflammation in the etiology of prostate cancer: an epidemiologic perspective. *Urol Oncol*, 2007. 25(3):242-9.
158. Galvao DA, Taaffe DR, Spry N, et al. Combined resistance and aerobic exercise program reverses muscle loss in men undergoing androgen suppression therapy for prostate cancer without bone metastases: a randomized controlled trial. *J Clin Oncol*, 2010. 28(2):340-7.
159. Wallner LP, Morgenstern H, McGree ME, et al. The effects of body mass index on changes in prostate-specific antigen levels and prostate volume over 15 years of follow-up: implications for prostate cancer detection. *Cancer Epidemiol Biomarkers Prev*, 2011. 20(3):501-8.
160. Thompson IM, Leach R, Troyer D, et al. Relationship of body mass index and prostate specific antigen in a population-based study. *Urol Oncol*, 2004. 22(2):127-31.
161. Wright JL, Lin DW, and Stanford JL. The effect of demographic and clinical factors on the relationship between BMI and PSA levels. *Prostate*, 2011. 71(15):1631-7.
162. Platz EA and Giovannucci E. The epidemiology of sex steroid hormones and their signaling and metabolic pathways in the etiology of prostate cancer. *J Steroid Biochem Mol Biol*, 2004. 92(4):237-53.
163. Vidal AC, Howard LE, Moreira DM, et al. Obesity increases the risk for high-grade prostate cancer: results from the REDUCE study. *Cancer Epidemiol Biomarkers Prev*, 2014. 23(12):2936-42.