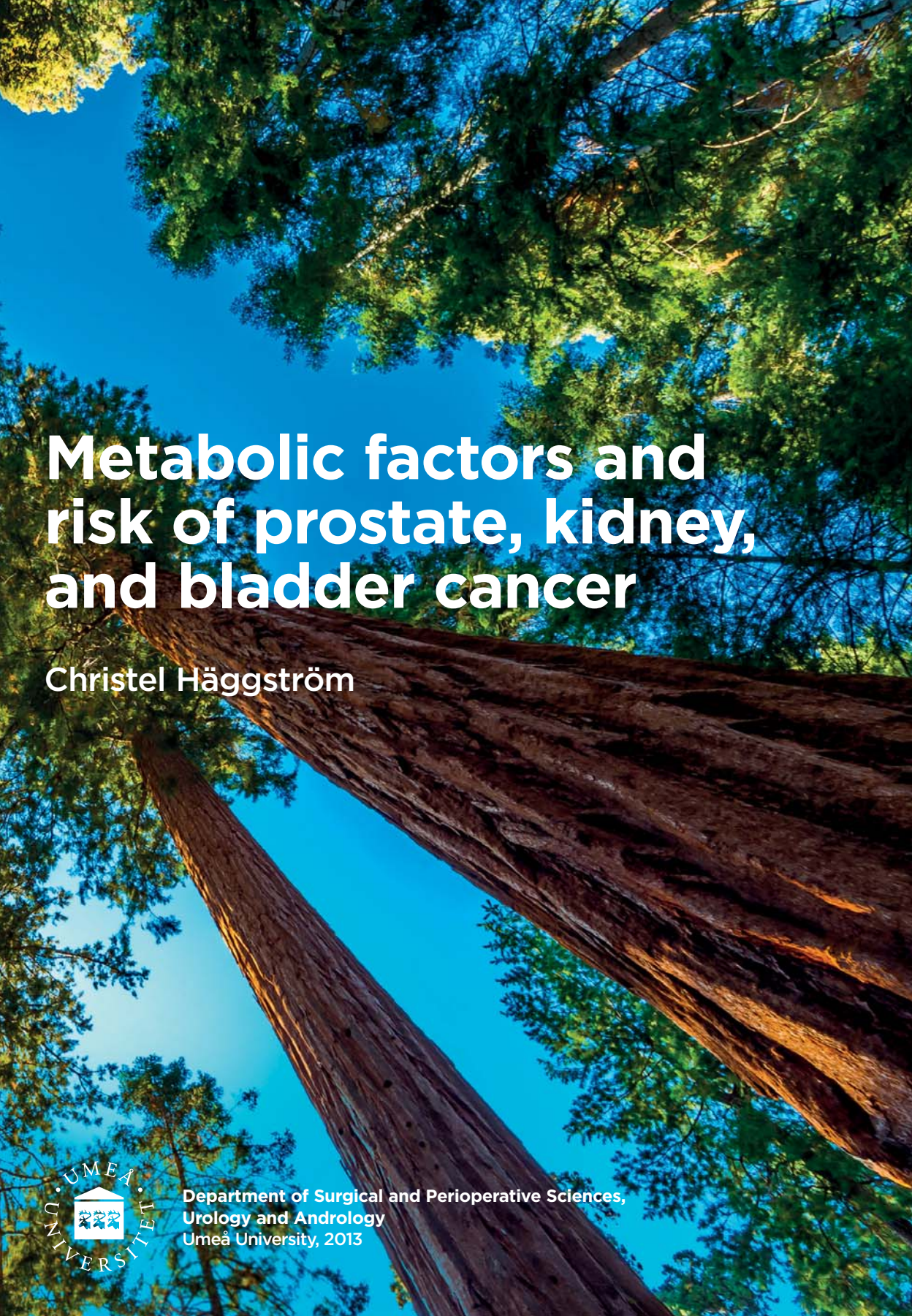

Metabolic factors and risk of prostate, kidney, and bladder cancer

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Umeå University, 2013

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Twenty years from now you will be more disappointed by the things you didn't do than by the ones you did do. So throw off the bowlines. Sail away from the safe harbour. Catch the trade winds in your sails. Explore. Dream. Discover.

Mark Twain

Abstract

Background: Prostate cancer is the most common cancer in Sweden with around 10,000 new cases every year. Kidney and bladder cancer are less common with 1,000 and 2,000 new cases annually, respectively. The incidence of these cancer sites is higher in developed, than in developing countries, suggesting an association between lifestyle and cancer risk. The aims of this thesis were to investigate body mass index (BMI), blood pressure, and blood levels of glucose, total cholesterol, and triglycerides as risk factors for prostate, kidney, and bladder cancer. Furthermore, we aimed at assess probabilities of prostate cancer and competing events, all-cause death, for men with normal and high levels of metabolic factors.

Material and methods: This thesis was conducted within the Metabolic Syndrome and Cancer project (Me-Can), a pooled cohort study with data from 578,700 participants from Norway, Sweden, and Austria. Data from metabolic factors were prospectively collected at health examinations and linked to the Cancer and Cause of Death registers in each country.

Results: High levels of metabolic factors were not associated with increased risk of prostate cancer, but high levels of BMI and blood pressure were associated with risk of prostate cancer death. The probability of prostate cancer was higher for men with normal levels of metabolic factors compared to men with high levels, but the probability of all-cause death, was higher for men with high levels than for those with normal levels. For both men and women, high levels of metabolic factors were associated with increased risk of kidney cancer (renal cell carcinoma). Furthermore, blood pressure for men and BMI for women were found as independent risk factors of kidney cancer. High blood pressure was associated with an increased risk of bladder cancer for men.

Conclusions: High levels of metabolic factors were associated to risk of kidney and bladder cancer and to death from kidney, bladder, and prostate cancer. Compared to men with normal levels, men with high levels of metabolic factors had a decreased probability of prostate cancer but an increased probability of all-cause death.

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II C. Häggström, T. Stocks, G. Nagel, J. Manjer, T. Bjørge, B. Lindkvist, H. Concin, A. Engeland, H. Ulmer, R. Selmer, S. Tretli, G. Hallmans, H. Jonsson, P. Stattin. Competing risk analysis of metabolic factors and prostate cancer. Submitted.

III C. Häggström, K. Rapp, T. Stocks, J. Manjer, T. Bjørge, H. Ulmer, A. Engeland, M. Almqvist, H. Concin, R. Selmer, B. Ljungberg, S. Tretli, G. Nagel, G. Hallmans, H. Jonsson, P. Stattin. Metabolic factors associated with risk of renal cell carcinoma. PLoS One. 2013;8(2):e57475

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Abbreviations

40-y	Age 40-programme
5ARI	5-alpha reductase inhibitors
AP	Attributable proportion due to interaction
BMI	Body Mass Index
CI	Confidence interval
CONOR	Cohort of Norway
DAG	Directed acyclic graph
HR	Hazard ratio
ICD	International Statistical Classification of Diseases
IGF-1	Insulin-like growth factor 1
Me-Can	Metabolic syndrome and Cancer project
mmHg	millimetre mercury
mmol	millimol
MPP	Malmö Preventive Project
NCS	Norwegian Counties Study
Oslo	Oslo study I cohort
PSA	Prostate specific antigen
RCC	Renal cell carcinoma
RDR	Regression dilution ratio
RERI	Relative excess risk due to interaction
RR	Relative risk
S	Synergy index
SD	Standard deviation
VIP	Västerbotten Intervention Project
VHM&PP	Vorarlberg Health Monitoring and Prevention Programme
WHO	World Health Organization

Background

Cancer epidemiology

Epidemiology investigates patterns, causes, and effects of health and disease conditions in populations. Epidemiological cancer research has uncovered significant associations such as the role of smoking in developing lung cancer and the role of human papilloma virus infection in developing cervical cancer. As the third largest cause of death worldwide (after cardiovascular and infectious diseases), cancer is a major health problem [1]. In Sweden, cancer is the second largest cause of death [2]. Worldwide, the most common cancer for women is breast cancer and for men, lung cancer. Other common cancer sites are the colon, rectum, prostate, liver, stomach, and cervix uteri [3].

As a complex system of trillions of cells, the human body continuously produces new cells as old cells die. However, at times, cells start to behave unexpectedly, sometimes giving rise to cancer tumours. The probability of developing cancer tumours depend both on inherited individual risk factors given at birth, and modifiable risk factors that an individual is exposed to during life. Family history of cancer contributes to 5-10% of total cancer diagnoses [4, 5], whereas five modifiable risk factors – tobacco, alcohol, high BMI, low fruit and vegetable intake, and physical inactivity – contributes to 24% of new cancer diagnoses and 30% of cancer deaths worldwide [6]. Among those, smoking is the most important risk factor, contributing to one-fourth of the cancers in developed countries among men [7].

Prostate cancer

Prostate cancer is the most common cancer among men in developed countries, with incidences up to 20 times higher compared to developing countries [8] (**Figure 1**).

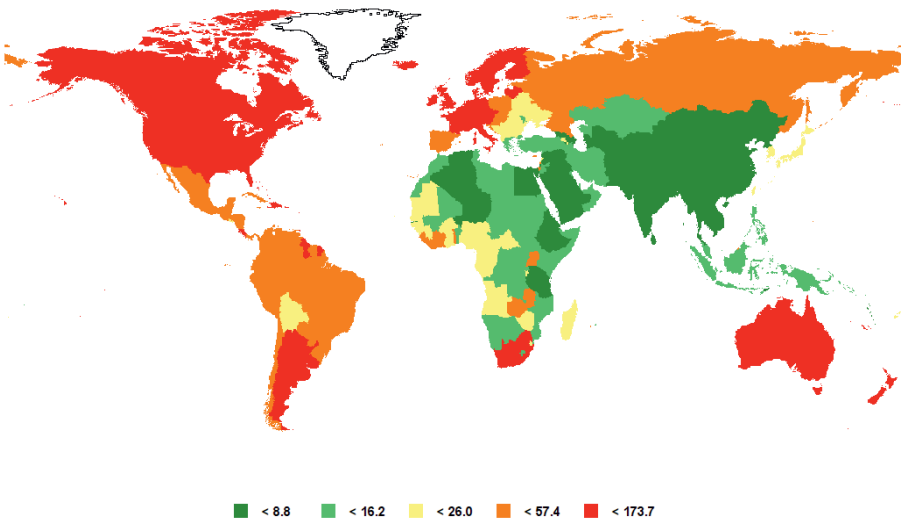

Figure 1. Prostate cancer incidence, as a proportion per 100,000 persons per year. Figure from GLOBOCAN 2008 v2.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [9].

The probability of prostate cancer among men below 75 years old is 12% in the Nordic countries, and in Sweden, there are almost 10,000 new cases every year [10]. Risk factors of prostate cancer are high age, heredity, and ethnicity [11]. Family history, when a first or second degree relative has prostate cancer contributes to 14% of the cases [4]. There are no established preventable risk factors of prostate cancer [3].

Prostate cancer is a very heterogeneous disease. At detection, the aggressiveness, size and spread of the cancer are investigated. Depending on these factors, prostate cancers are divided into risk categories, ranging from low-risk groups (when a small tumour slowly grows inside the prostate) to high-risk groups (when the tumour grows outside the prostate and with metastases in other parts of the body).

During the last decades there has been an increase in incidence of prostate cancer, mainly due to improved detection methods using serum levels of prostate specific antigen (PSA) as a marker for risk of prostate cancer. PSA is a protein that is produced in the prostate, and a fraction of PSA is leaked through the membranes of the prostate into the blood and into the circulation. PSA can be measured in serum or plasma from blood and an elevated level of PSA could indicate cancer in the prostate. It could also be signs of benign enlargement of the prostate or inflammation in the prostate gland (prostatitis). Men diagnosed with prostate cancer detected by a PSA test without any clinical symptoms are generally at lower risk.

In 1997, an increase in incidence of prostate cancer was noted in Sweden [12, 13] (**Figure 2**), an increase that coincided with the time PSA began to be used to test for prostate cancer. This thesis defines the period in time from 1997 as the PSA era. Since 1997, mean age of diagnosis has been around 70 years and more than 90% of these men survived more than five years [10].

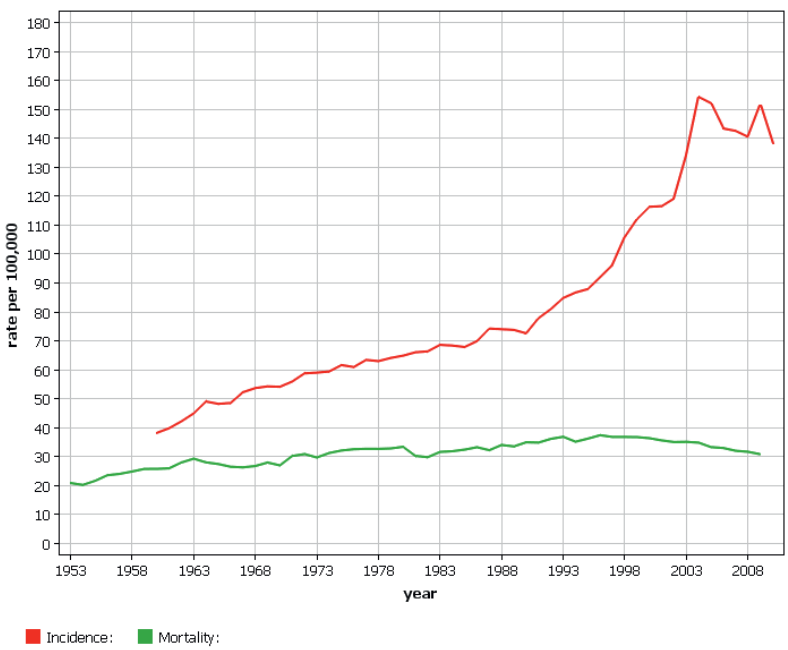

Figure 2. Trends in incidence and mortality of prostate cancer in the Nordic countries. Figure from NORDCAN:Cancer Incidence, Mortality, Prevalence and Survival in the Nordic Countries, Version 5.3 [10].

Many of the geographical areas with high incidence of prostate cancer also have high incidence of the metabolic syndrome, a state of metabolic aberrations originating from high intake of an energy-dense diet in combination with a sedentary lifestyle. However, studies investigating the associations between the metabolic syndrome and prostate cancer have been inconsistent [14, 15]. In addition, studies investigating associations between metabolic aberrations and prostate cancer have been inconclusive; most large studies on obesity have found a modest increase in risk of prostate cancer [16, 17]. Diabetes mellitus type 2, on the other hand, has consistently been associated with a decreased risk of prostate cancer [18, 19]. It is not been confirmed whether these associations have changed due to uptake of PSA for detection of prostate cancer. In the PSA era, recent studies have reported an increased risk of prostate cancer among men with high socioeconomic status [20, 21].

From an individual's perspective, it is important to consider other events that influence the probability of diagnosis and death from prostate cancer. Many men at risk of prostate cancer are also at increased risk for death due to high age, and men with metabolic aberrations are at increased risk for death, mainly due to cardiovascular diseases [22]. To the best of our knowledge, the probabilities of prostate cancer and competing events have never been investigated for men with metabolic aberrations. However, a few studies use various methods to account for competing risks with inconsistent results [23-25].

Kidney cancer

Each year in Sweden, there are around 1,000 new cases of kidney cancer, twice as many among men than among women. The mean age of diagnosis is around 70 years, 70% survive more than five years, and more than half of the men and women diagnosed with kidney cancer die from their cancer [10].

Approximately 80% of all kidney cancers are renal cell carcinomas (RCC); when the tumour originates from the renal medulla where the blood is filtered to produce urine. The most common symptom of RCC is blood in the urine and some people experience pain in the lower back on the same side as the affected kidney.

Until recently, incidence of RCC has increased [26, 27], a trend that can be partly explained by improved detection methods [28]. However, this increase may also have been due to an increasing prevalence of risk factors [26]. Smoking is an established risk factor for RCC, and compared to non-smokers, male smokers have approximately 50% and female smokers have approximately 20% increased risk [27]. Most studies have also found excessive body weight to be a risk factor, with a stronger association among women [27]. Furthermore, diabetes type 2 among women [29] and high BMI and blood pressure among men [30] have been suggested as independent risk factors for RCC. However, these studies had no data for blood lipids, which may be a mediator of these associations. Another study reported that high levels of triglycerides were associated with risk of RCC [31] and found that the association was stronger among obese participants, but no data for smoking or hypertension were included in the analyses.

Thus, less is known about lipids [31, 32] and glucose [31, 33] and it is also unclear if any of the metabolic factors independently increase risk, or if they are part of the same pathway, or interact with risk for RCC. Most studies on metabolic factors and risk for RCC have used dichotomized levels of exposure; however, it remains to be shown if there is a threshold level with a distinct risk increase or if the association between increasing levels of metabolic factors and risk is linear.

Bladder cancer

Bladder cancer is the fourth most common cancer among men in developed countries and the seventh in developing countries [3]. Every year in Sweden, around 2,000 new cases, around three times as many in men as in women, are found. The mean age is around 75 years and nearly 80% survive more than five years [10].

The strongest risk factor for bladder cancer is smoking, which contributes to 50% of the cases among men and 30% among women [34]. The second largest risk factor is occupational exposure to chemicals in a variety of industries, a risk factor that may contribute to 5-25% of cases [35]. In Africa, schistosomiasis infections (from the *Schistosoma haematobium* virus) have been associated with bladder cancer and contribute to 3% of all bladder cancer cases worldwide [36]. There are no established preventive factors, but some studies suggest that high intake of fluids may decrease the risk of bladder cancer [35]. The main symptom is, similar to kidney cancer, dark urine due to blood. Other symptoms of bladder cancer are pain during urination and recurrent urinary tract infections.

Two large studies have investigated glucose levels in relation to risk of bladder cancer: one study reported an association with bladder cancer death among men (no data reported for women) [33] and one more recent study from the Me-Can project reported an association between high glucose and risk of bladder cancer among women [37]. Studies investigating other metabolic factors have been small and the results are inconsistent [38-41].

Aims

The overall aim of this thesis was to study the association between metabolic factors, in single and combination, and risk of prostate, kidney and bladder cancer.

Specific aims for prostate cancer (paper I, and II) were to investigate:

- If there were any changes in association between metabolic factors and risk of prostate cancer due to introduction of PSA testing.

- Probabilities of prostate cancer, prostate cancer death, and competing events using competing risk analysis.

Specific aims for kidney cancer (renal cell carcinoma, RCC, paper III) and bladder cancer (paper IV) were to investigate:

- If any of the metabolic factors independently increased risk of RCC, or whether they are part of the same pathway, or biological interact on risk of RCC.

- If the associations between increasing levels of metabolic factors and risk of RCC were linear.

- If smoking modified the associations between metabolic factors and risk of RCC and bladder cancer.

Material and methods

The Me-Can project

In 2006, the Metabolic Syndrome and Cancer Project (Me-Can) was initiated to study the associations between metabolic factors and cancer risk in a large data set. Me-Can is a pooled cohort study consisting of cohorts from Norway, Sweden, and Austria (**Figure 3**).

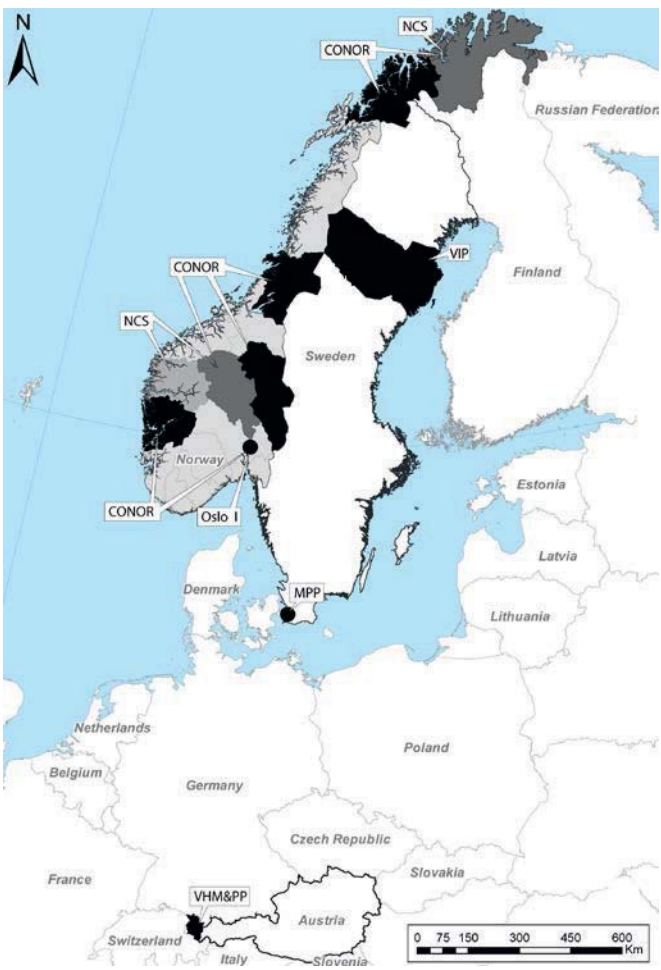

Figure 3. Map with location of cohorts included in Me-Can. The 40-y cohort includes all counties in Norway (all grey- and black-marked areas in Norway), NCS includes areas ▫ and ▪, the CONOR includes areas ▪ and ■, and further cohorts (marked in black) are Oslo I, VHM&PP, VIP, and the MPP. Figure reproduced from Stocks et al. [42].

The purpose of the Me-Can project, pooling and cleaning of data has previously been described in detail [42]. In short, the cohorts included in the project were: from Norway – the Oslo study I (Oslo), Norwegian Counties Study (NCS), the Cohort of Norway (CONOR) and the Age 40 programme (40-y); from Sweden – the Västerbotten Intervention Project (VIP), and Malmö Preventive Programme (MPP); and from Austria – the Vorarlberg Health Monitoring and Prevention Programme (VHM&PP). All participants in Me-Can had undertaken one or several health examinations where height and weight were measured and a sample of plasma, serum, or blood was taken. After cleaning the data and randomly excluding some of the Norwegian data to not exceed 50%, the Me-Can project consisted of 578,700 participants [42].

In paper IV, all 578,700 participants were included in the study. In paper III, only participants with complete data on all metabolic factors were included, resulting in slightly lower number of participants. In paper I and II, only men were included, and in paper II, different follow-up times were used than in paper I.

Endpoints

Participants were linked to the National Cancer Registry in Norway and Sweden and to the Vorarlberg State Cancer Registry in Austria to identify cancer diagnoses. Cancer diagnoses were classified according to The International Classification of Diseases, seventh revision (ICD-7): for paper I and paper II, code 177 was selected; for paper III, codes 180.0 and 180.9 were selected; and for paper IV, code 181 was selected. In paper III, we selected cases of RCC (not all cases of kidney cancer) due to their different characteristics. Data from the cancer registries were available until December 31, 2003 in Austria, 2005 in Norway, and 2006 in Sweden. In paper I, paper III, and paper IV, only participants with a selected cancer diagnosis as primary cancer diagnosis were selected; in paper II, all men diagnosed with prostate cancer were selected, and around 5% of these cases were secondary or later cancer diagnoses among men already diagnosed with cancer at another site.

The data were linked to the National Cause of Death Registry in each country to identify causes of death, which were coded according to Eurostat European shortlist for causes of death [43]. In Norway and Sweden, data were also linked to the Registry of Total Population and Population Changes for assessment of migration (data not available in Austria). Data from the cause of death registers were available up to December 31, 2003 in Austria, and 2004 in Norway and Sweden.

Risk factors

The single metabolic factors studied were body mass index (BMI), blood pressure and glucose, triglycerides and total cholesterol. BMI was calculated as weight divided by height squared. Blood pressure was the actual pressure from the blood on the walls of the vessels and was measured in two parts, the systolic and the diastolic blood pressures. Levels of glucose, triglycerides and total cholesterol were measured in plasma, serum or blood. Because these levels are influenced by the time since last meal, fasting time before health examination was registered. Other covariates included in the statistical analyses were smoking, age at health examination, birth cohort, and cohort.

Ethical considerations

Participants at health examinations in Sweden and Austria provided written informed consent to participate. In Norway, participants were invited to come to health examinations; questionnaires were included with these invitations. During the health examination, participants provided their completed questionnaire and this was accepted by the Data Inspectorate as informed consent, but not written consent. Written consent was obtained from 1994 in Norway. The Me-Can project was approved by The Research Review Board of Umeå, Sweden, the Regional Committee for Medical and Health Research Ethics, Southeast Norway, and the Ethikommission of the Land Vorarlberg, Austria.

Statistical methods

General methods

Because the risk of prostate, kidney, and bladder cancer increases with higher age, attained age was used as timescale in all analyses, counted from the date of birth until date of event or censoring. To minimize the probability of reverse causation, follow-up time started one year after the date of baseline health examination. We considered smoking, age at health examination, cohort, and birth cohort as confounders in the association between metabolic factors and risk, and those factors were included in all analyses.

We analysed metabolic factors divided into quintiles, in categories defined by the World Health Organisation (WHO) [44, 45] and transformed to standardized variables, z-scores. The general assumption within these analyses was that the association between increasing metabolic factors and risk was linear. To compare the metabolic factors with each other, single metabolic factors were transformed to the same scale with zero as mean and one as standard deviation, calculated as: $z = (x - \mu)/\sigma$, where μ is the mean, σ is the standard deviation, and x is the actual level of the exposure. Mid blood pressure was defined as (systolic+diastolic blood pressure)/2. In addition, all transformed exposures were summarized and transformed into a composite score to assess combined effect of all these metabolic factors. In paper IV, this variable was called the metabolic syndrome (MetS) score. BMI and blood pressure was divided into quintiles and transformed to z-scores separately for cohort and sex, while glucose, triglycerides, and cholesterol were divided into quintiles and transformed to z-scores separately for cohort, sex, and fasting time.

In paper II and for some analyses in paper III, we could not analyse metabolic factors as continuous variables. To compare results between metabolic factors, we used z-scores dichotomized at z=1, which means that the exposed group consisted of the participants with the highest 16% of each metabolic factor or the composite score and the non-exposed group consisted of men in the bottom 84%. In paper II, the non-exposed group were denoted men with normal levels of metabolic factors and the exposed group, men with high levels.

Risk assessment using hazard ratios (paper I, III, and IV)

Cox proportional hazards regression model was used to investigate associations between metabolic factors and risk of prostate, kidney, and bladder cancer. In analyses of risk of cancer diagnosis, participants were followed to date of prostate, kidney (RCC), or bladder cancer diagnosis, or until censoring due to other cancer diagnosis, death, emigration, or end of follow-up (last date of available data from each Cancer Registry), whichever occurred first. To analyse risk of cancer death, participants were followed to date of prostate, kidney (RCC), or bladder cancer death, or until censoring due to other causes of death, emigration, or end of follow-up (last date of available data from each Cause of Death Registry), whichever occurred first.

In these models, the hazard functions were assumed to be proportional over timescale; these assumptions were checked graphically and tested with Schoenfeld residuals for metabolic factors, smoking (never, current, or former smoker), age at health examination (in categories in paper I, continuous in paper III and IV), and birth cohort (in categories). In paper I, we found violations for birth cohort and age at health examination and chose to stratify for these covariates within the Cox models. In addition, all Cox models were stratified for cohort.

Hazard ratios (HRs) using Cox models were calculated in three ways:

1. Using exposures divided into quintiles, with the lowest quintile as reference. The mean (in paper I and IV) and the median value (in paper III) of each quintile were used to test for linear trend across quintiles. All these analyses were adjusted for BMI (except for the analysis of BMI).

2. Using exposures transformed to z-scores, as described previously, in two different approaches. Firstly, to analyse a separate Cox model for each single exposure and secondly, to analyse only one Cox model containing all exposures (mutually adjusted model), in order to investigate in exposures differed depending on if other metabolic factors were included in the models. In paper II the results differed between those two models and we decided to add one exposure at the time to the model in order to find out which ones of the exposures that attenuated each other.

3. Using categories defined by WHO (only in paper IV).

Competing risk analysis (paper II)

Competing risk analysis was used to investigate probability of prostate cancer, prostate cancer death, and competing events. In these analyses, participants were followed until the first date of either the main event or the competing event or until date of censoring due to emigration or end of follow-up (last date of available data from Cause of Death registers) in two different analyses. Prostate cancer and prostate cancer death were the main events in the two analyses. All-cause death and death from causes other than prostate cancer were the competing events.

For main and competing events in each analysis, we calculated cumulative incidence functions [46] and sub distribution hazard ratios based on Fine and Gray regression [47] for men with normal and high levels of metabolic factors as previously described. The cumulative incidence functions were interpreted as probabilities and the p-values from Fine and Gray regression were interpreted as a test for difference in probability between high and normal levels of metabolic factors. Attained age was used as time scale, and smoking status, birth cohort, age at health examination, and cohort were included in the models in all analyses. The cumulative incidence functions were calculated based on Cox regression models where smoking and age at heath examination were allowed to have different effects on main and competing event, in addition to each metabolic factor. The assumption of proportional hazards in the Cox regression model was tested with Schoenfeld residuals and was found to be valid.

Subgroup analysis according to PSA introduction (paper I, and II)

To investigate changes in associations between metabolic factors and risk of prostate cancer due to the introduction of PSA for prostate cancer detection, we performed subgroup analyses for follow-up ending in December 31, 1996, and starting in January 1, 1997, respectively. This cut-point was chosen because at that date an increase in the incidence of prostate cancer was noted in Sweden [12, 13] and before that date the increase had been noted in Norway [48] and Austria [49]. These two periods have been denoted pre-PSA and PSA era. In paper II, no subgroup analysis was done for prostate cancer death.

Biological interaction, splines and absolute risks (paper III)

To further investigate interplay between metabolic factors on risk of RCC, we calculated the biological interaction between metabolic factors using relative excess risk due to interaction (RERI), attributable proportion due to interaction (AP), synergy index (S), and their 95% confidence intervals [50]. In these calculations, the z-scores were dichotoimized at z=1, as previously described.

To test whether the associations between metabolic factor and risk were linear, restricted cubic polynomial splines were plotted using exposures in z-scores and the mutually adjusted model. We used knots at the 5^{th}, 35^{th}, 65^{th}, and 95^{th} percentiles in these models. The fit of the spline model was tested versus a fit using a linear model with likelihood-ratio test.

Absolute risks, the probability of developing RCC for quintiles of the composite score, were calculated as described by Gail et al. [51], taking into account survival from competing risks.

Multiplicative interaction (paper I, III, and IV)

We used the Wald test (paper III and IV) and the likelihood ratio test (paper I) to test for interaction between pair wise exposures and between exposures and smoking. In papers I and IV, we used both diagnosis and death of prostate and bladder cancer as endpoints. In paper III, diagnosis of RCC was endpoint in these analyses. In paper III and IV, these analyses were performed separately for men and women. We adjusted the significance level for multiple testing with the Bonferroni correction [52]. To further investigate smoking as an effect modifier in paper III and IV, we calculated HRs in strata of smoking status.

Correction for random errors (paper I, III, and IV)

If one or more of the covariates included in a Cox model are estimated with error, HR will be biased, so-called regression dilution bias. The errors can originate from random error at measurement as well as from short or long time variation around the “true” individual level.

We corrected HRs for random errors using methods based on regression dilution ratio described by Wood et al. [53]. In these calculations, data from

participants who had undergone repeated health examinations in Me-Can were used, in total 133,820 participants with 406,364 health examinations. One of two methods for correction was used; direct adjustment of the HR using the estimated regression dilution ratio (RDR) or replacing the actual covariate with predicted values from an estimated regression model, the regression calibration. We used RDR in analysis of quintiles, in the first approach using z-scores and for WHO categories.

In our data set, the values used for RDR and regression calibration had minimal differences between studies. In paper I, only data from men with repeated measurements were used; in paper III and IV, data from both men and women were used. In paper III and IV, RDR for BMI was 0.90, for systolic blood pressure, 0.53, for diastolic blood pressure, 0.51, for glucose (log) 0.28, for cholesterol, 0.66, and for triglycerides, (log) 0.51. Thus, measurements of BMI had a much smaller random error than the other exposures in accordance with previous observations [54-56]. The correction was applied by dividing the regression coefficient computed by the Cox model with RDR for the exposure, $HR_{corrected}=e^{\log(HRoriginal)/RDR}$. RDR was estimated as the regression coefficient in the regression models with the repeated health examination as a dependent variable and the baseline health examination as an independent variable. Age at baseline, fasting time, smoking status, sex, birth year, BMI, and time from date of baseline examination were included as fixed effects in the model and cohort was included as random effect. In the mutually adjusted model, we replaced the original z-score with the predicted z-score calculated in a similar mixed linear model [57]. RDR and regression calibration were predicted at half of the mean follow-up time – six years after baseline health examination.

Alternative methods

Time dependent HRs (paper I)

We considered using a flexible parametric model [58] for paper I to evaluate the time-dependency for the covariates not satisfying the assumption of proportional hazards.

Conditional probability (paper II)

Previously published papers using competing risk analysis have calculated conditional probability of prostate cancer, defined as the probability that the main event has occurred given that a participant has not experienced the competing event at a given time. This was computed as $p_{cp}(t) = p_{main}(t)/(1-p_{competing}(t))$ [59, 60], where p_{main} and $p_{competing}$ were defined as the cumulative incidence of main and competing event, which we analysed in paper II. We also calculated Pepe and Mori's test of equality for cumulative incidence and conditional probability curves [60] but this was not used in the final manuscript.

Multi-state models (paper II)

An extension of competing risk is to add more states to the model and create a multi-state model. One of the most common multi-state models is a three state model, one state with healthy, one state with diseased and one state with dead individuals, also called the illness-death-model [61]. This was considered to be included in paper II and similar covariates as in that study were included in these models.

Software

Most of calculations were performed with STATA MP/2 version 11.2 (StataCorp LP, College Station, Texas). Random error calculations and predictions of multi-state models were performed in R version 2.7.2 and quintile analysis of bladder cancer were performed in SAS version 9.1 (SAS Institute Inc., Cary, NC, USA).

Main results

General results

Table 1 lists the characteristics of the participants included in the Me-Can project. Participants had undertaken the baseline health examination at mean age of 44 years and mean follow-up time was 12 years.

Table 1. Characteristics for participants in the Me-Can project measured at baseline health examination.

		Men N (%)	Women N (%)
Participants		289,866 (50.1)	288,834 (49.9)
Cohort	Norway:		
	Oslo	16,760 (5.8)	0 (0)
	NCS	25,952 (9.0)	25,072 (8.7)
	CONOR	52,181 (18.0)	57,687 (20.0)
	40-y	60,676 (20.9)	68,211 (23.6)
	Austria:		
	VHM&PP	73,213 (25.3)	86,671 (30.0)
	Sweden:		
	VIP	38,843 (13.4)	40,669 (14.1)
	MPP	22,241 (7.7)	10,524 (3.6)
Smoking status	Never smoker	113,496 (39.2)	144,815 (50.1)
	Ex-smoker	86,086 (29.7)	72,600 (25.1)
	Smoker	89,419 (30.9)	70,721 (24.5)
BMI (kg/m^2)*	Normal	131,167 (45.3)	170,535 (59.0)
	Overweight	127,846 (44.1)	82,869 (28.7)
	Obese	30,853 (10.6)	35,430 (12.3)
Blood pressure (mmHg)**	Normal	179,497 (61.9)	212,968 (73.7)
	Hypertension	110,369 (38.1)	75,866 (26.3)
Glucose levels (mmol/l) and fasting status	Fasting ≤8 hours	151,279 (52.2)	149,121 (51.6)
	Fasting >8 hours, Normal levels	122,841 (42.4)	127,524 (44.2)
	Fasting > 8 hours, Impaired fasting glucose	10,594 (3.7)	8,149 (2.8)
	Fasting > 8 hours, Diabetes	5,152 (1.8)	4,040 (1.4)

* Definitions according to WHO: overweight 25-30 kg/m^2, obese >30 kg/m^2

** Systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90mmHg

*** Impaired fasting glucose ≥ 6.1 mmol/l, diabetes ≥ 7.0 mmol/l

In this thesis, only results using metabolic factors transformed to z-score have been presented. For backward calculations, we used the mean and standard deviation for metabolic factors among men and women found in **Table 2**. There might be minor changes between papers due to further exclusion of participants.

Table 2. Mean and standard deviation (SD) of metabolic factors at baseline health examination.

	Men		Women	
Metabolic factor	**Mean**	**(SD)**	**Mean**	**(SD)**
BMI (kg/m^2)	25.7	(3.5)	24.9	(4.4)
Systolic blood pressure (mm Hg)	132.6	(16.9)	126.9	(19.4)
Diastolic blood pressure (mm Hg)	81.2	(10.9)	76.8	(11.3)
Glucose (mmol/L)*	5.1	(1.3)	5.0	(1.1)
Cholesterol (mmol/L)*	5.6	(1.2)	5.6	(1.2)
Triglycerides (mmol/L)*	1.6	(1.2)	1.3	(0.8)

* Calculated among participants fasting >8 hours before health examination

Prostate cancer (paper I)

During follow-up, 6,673 men were diagnosed with prostate cancer (mean age at diagnosis 68 years) and 961 men died from prostate cancer (mean age at death 72 years).

For prostate cancer diagnosis, high levels of glucose, HR=0.90 (0.82-0.98), and triglycerides, HR=0.94 (0.89-0.99), were associated with decreased risk in univariate analysis, but after adjustment for the other metabolic factors, these associations were no longer significant (**Figure 4A**). For death from prostate cancer, we found that BMI, blood pressure, and the composite score were associated with risk, but after adjustment for the other metabolic factors, only the association for blood pressure remained significant, HR=1.17 (1.04-1.32) (**Figure 4B**).

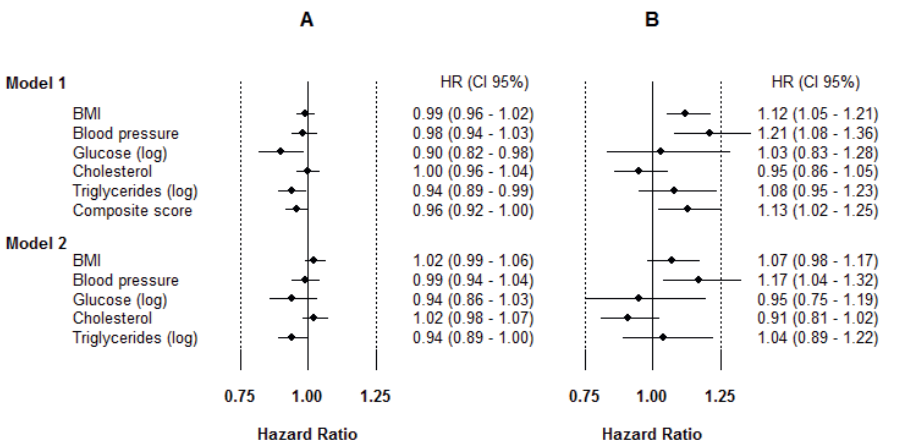

Figure 4. Risk of A) diagnosis and B) death from prostate cancer by exposures in z-scores. Model 1: Cox regression models were adjusted for smoking and stratified for categories of birth year, age at health examination, and cohort. Model 2: Mutually adjusted model. Both models were corrected for random errors.

From start of follow-up until December 31, 1996 (the pre-PSA era), there were 1,345 prostate cancer cases and 268 deaths; after that date to end of follow-up in the PSA era, there were 5,328 cases and 698 deaths. All metabolic factors and the composite score were more strongly associated with risk among men in the pre-PSA era, but not in the PSA era (**Figure 5A**). For death from prostate cancer, we found similar risk estimates for the two periods (**Figure 5B**). No multiplicative interactions between any of the exposures on risk of prostate cancer were found.

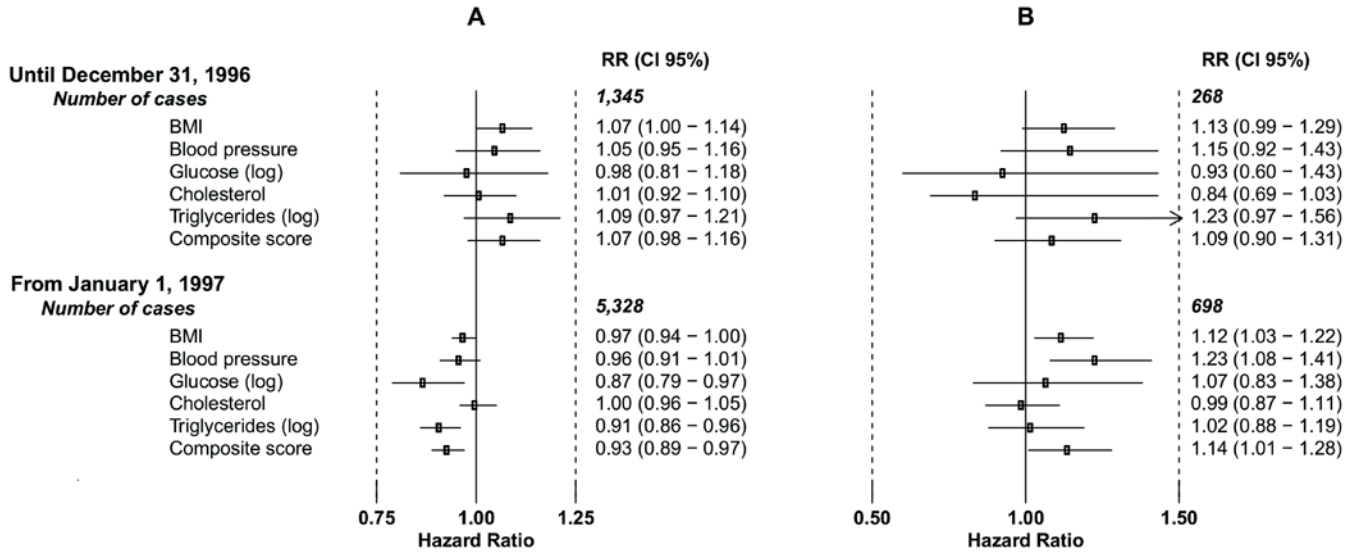

Figure 5. Risk of A) diagnosis and B) death from prostate cancer by exposures in z-scores for two periods of follow-up. Cox regression models were adjusted for smoking and stratified for categories of birth year, age at health examination, and cohort. The results were corrected for random errors.

Prostate cancer with competing risk analysis (paper II)

This study consisted of 285,040 men and during follow-up, 5,893 men were diagnosed with prostate cancer and 1,013 men died of prostate cancer (**Figure 6**). Of these, 1,366 men were diagnosed with prostate cancer in the pre-PSA era with end of follow-up at December 31, 1996 and 4,527 men were diagnosed in the PSA era with start of follow-up at January 1, 1997.

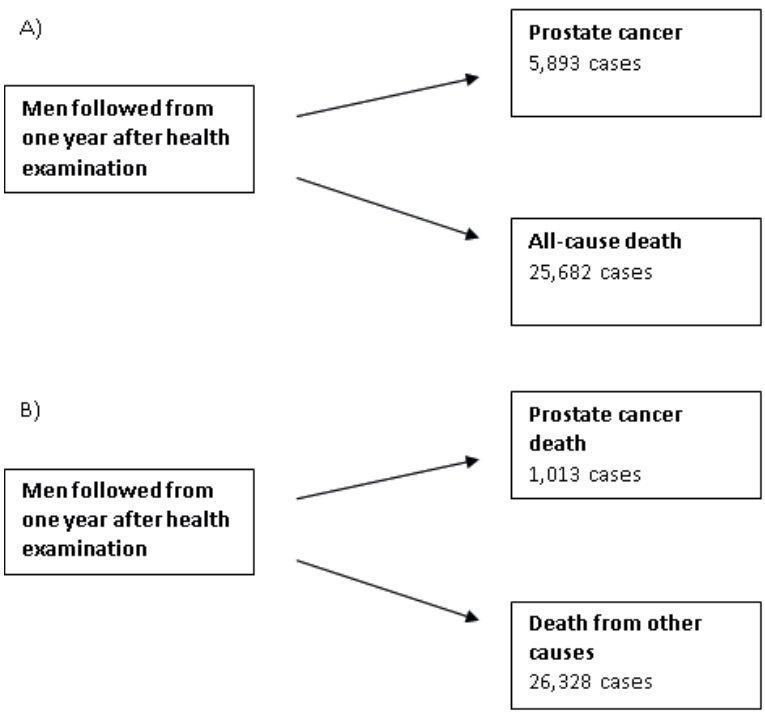

Figure 6. Main and competing events in analysis of A) prostate cancer and B) prostate cancer death. Men were followed until the first point in time of main or competing event or until censoring due to migration or end of follow up in each analysis. The number of cases in the competing event in A) is smaller than in B) because many of men followed to date of prostate cancer diagnosis in A) have died from both prostate cancer and other causes in B).

In the pre-PSA era, men below age 80 with normal levels of the composite score had 6% probability of prostate cancer and men with high levels had 5% probability. In the PSA era, corresponding probabilities were twice as high,

13% and 11%, respectively (**Figure 7**). In the PSA era, men below 80 years with normal levels of BMI, blood pressure, glucose, cholesterol, and triglycerides had approximately 13% probability of prostate cancer and approximately 37% probability of the competing event, all-cause death. For men with high levels of these metabolic factors, corresponding probabilities were 12% and 47% (**Figure 8**).

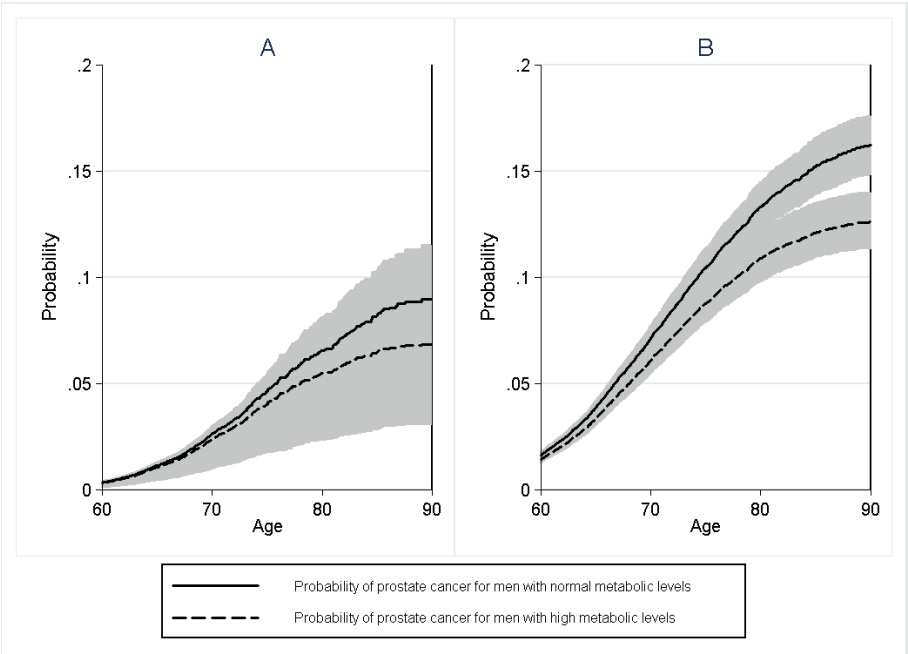

Figure 7. Competing risk analysis of prostate cancer, with cumulative incidence of prostate cancer for men with high and normal levels of the composite score in A) the pre-PSA era and in B) the PSA era. Solid lines correspond to normal levels of metabolic factors, dashed line to high levels, and shaded areas are 95% confidence intervals.

In the analysis of p-values from Fine and Gray regression, high levels of BMI, triglycerides, glucose, and the composite score were associated with a decreased probability of prostate cancer in the PSA era. High levels of all single metabolic factors and the composite score, in both periods were associated with increased probability of all-cause death.

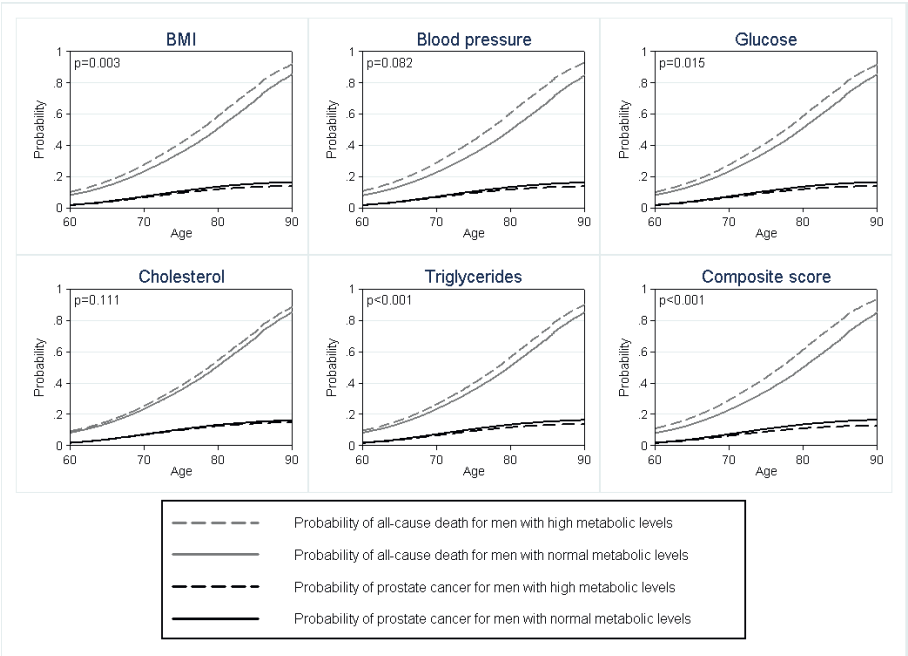

Figure 8. Competing risk analysis of prostate cancer, with cumulative incidence of prostate cancer (black lines) and of the competing event, all-cause death (grey lines) in the PSA era. The curves are stacked for each level of exposure and the remaining area above the curves corresponds to the probability of no event. Solid lines correspond to normal levels and dashed line to high levels of metabolic factors. P-values are from Fine and Gray regression for prostate cancer in the figures, and p-values for the competing event were all <0.001.

In analysis of p-values from Fine and Gray regression, men with high blood pressure had an increased probability of prostate cancer death, and men with high cholesterol levels had a decreased probability (**data not shown**).

In the cumulative incidence functions, men below 80 years with high levels of blood pressure had 2.4% probability of prostate cancer death and 43% probability of competing event, death from other causes. For men with normal levels of blood pressure, corresponding probabilities were 2.0% and 30%. Men below 80 years with high levels of cholesterol had 1.8% probability of prostate cancer death and 37% probability of competing event; for men with normal levels of cholesterol, the corresponding probabilities were 2.1% and 30%. High levels of all single metabolic factors and the composite score were associated with increased probability of death from other causes.

Kidney cancer (renal cell carcinoma, paper III)

Participants with complete data of all metabolic factors were selected which resulted in that the study consisted of 278,920 men and 281,468 women. During follow-up, 592 men and 263 women were diagnosed with RCC at a median age of 62 years and 244 men and 84 women died from RCC.

Among men, high levels of BMI, blood pressure, glucose, triglycerides, and composite score were associated with increased risk of RCC (**Figure 9A, model 1**). After including other exposures to the model, some of the associations were attenuated, and in the mutually adjusted model, the associations for mid blood pressure, HR= 1.37 (1.18-1.59) and triglycerides, HR=1.22 (1.00-1.50) and risk of RCC remained significant (**Figure 9A, model 2**). Among women, high levels of BMI and triglycerides (borderline) were associated with risk of RCC (**Figure 9B, model 1**). In the mutually adjusted model the association between BMI were still significant, HR=1.23 (1.04-1.45) (**Figure 9B, model 2**).

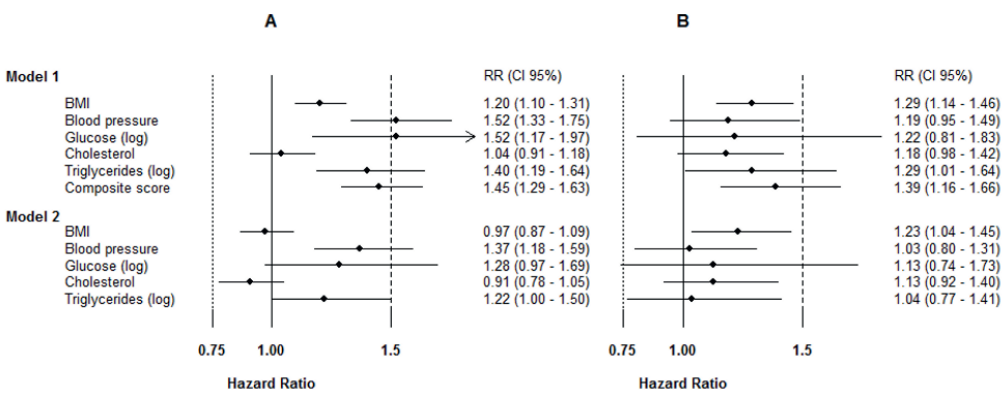

Figure 9. Risk of RCC by exposures in z-scores among A) men and B) women. Model 1: Cox regression models were adjusted for smoking, categories of birth year, age at health examination and stratified for cohort. Model 2: Mutually adjusted model. Both models were corrected for random errors.

Trend tests over quintiles and analyses using cubic spline models indicated approximately linear associations for all metabolic factors in relation to RCC risk (**data not shown**). We found no biological interaction between metabolic factors or multiplicative statistical interactions between the exposures or between exposure and smoking on risk of RCC after applying the Bonferroni correction.

Bladder cancer (paper IV)

During follow up, bladder cancer was diagnosed in 1,587 men and 327 women, and 216 men and 58 women died of bladder cancer.

For diagnosis of bladder cancer, we found that blood pressure, HR=1.15 (1.05-1.26) and the composite score, HR=1.10 (1.01-1.18) were associated with risk among men (**Figure 10, model 1**), and in the mutually adjusted model, blood pressure were still significant. Among women, in both approaches, the strongest risk factor was glucose, HR=1.41 (0.97-12.06), (**Figure 10**).

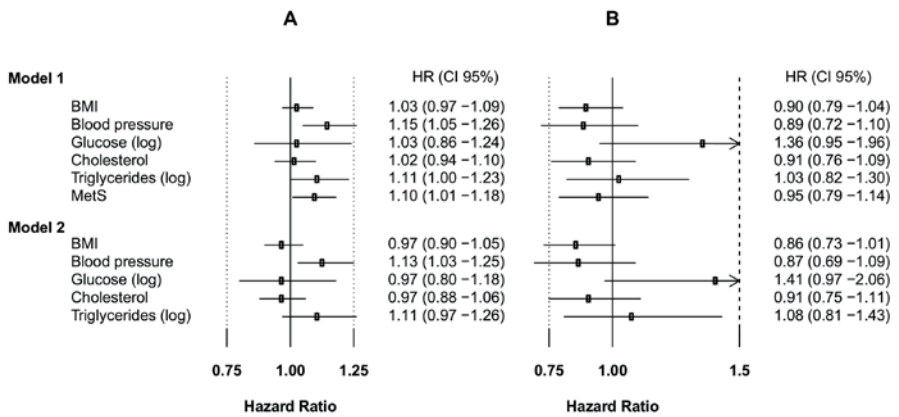

Figure 10. Hazard ratios of bladder cancer for exposures in z-scores among A) men and B) women. Model 1: Cox regression models were adjusted for smoking, categories of birth year, age at health examination and stratified for cohort. Model 2: Mutually adjusted model. Both models were corrected for random errors.

For death from bladder cancer, we found that blood pressure was associated with risk among men, HR=1.34 (95% CI 1.06-1.69), in the mutually adjusted model, calculated per one unit increase of z-score (**data not shown**). No other metabolic factor was associated with the risk of death from bladder cancer among men or women.

We found no difference in risk for the any of the exposures in strata of smoking status and formal testing showed no interaction across strata. No interactions between metabolic factors on risk of bladder cancer after Bonferroni adjustment of the significance level were found.

Results from alternative statistical methods

Time dependent HRs (paper I)

Because some of the covariates in paper I did not satisfy the proportional hazards assumption for the Cox model, we further investigated calendar time and age using the flexible parametric model and calculated time-dependent HRs. In these models, we used WHO categories of BMI, with normal levels of BMI as baseline corresponding to HR=1, solid lines for HR of overweight and dashed lines for HR of obese men and risk of prostate cancer (**Figure 11**).

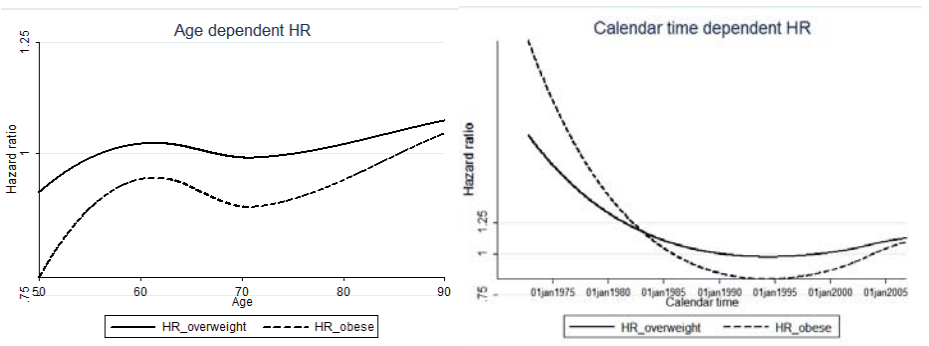

Figure 11. Time-dependent hazard ratios for prostate cancer calculated per age (left) and calendar time (right) for overweight (solid line) and obese (dashed line) men according to WHO categories. The baseline is men with BMI below 25 which corresponds to HR=1. In both these models, five knots were used in the flexible parametric models, and the models were adjusted for five categories of birth date and age at health examination, cohort and categories of smoking.

Although we have not investigated time dependent HRs fully with confidence intervals or p-values, our results suggest that obese and overweight men had a lower risk of prostate cancer along the full age-span, and that there was a shift in association between overweight and obese men and prostate cancer risk over calendar time.

Conditional probability (paper II)

Using competing risk analysis, we also calculated conditional probability with p-values from the Pepe and Mori test (**Figure 12**). We found that there were no differences in conditional probability of prostate cancer and prostate cancer death for men with normal and high levels of the composite score. However, in subgroup analyses in categories of age, we found that older men (>80 years) with high blood pressure had a higher conditional probability of prostate cancer death than men with normal levels (**data not shown**).

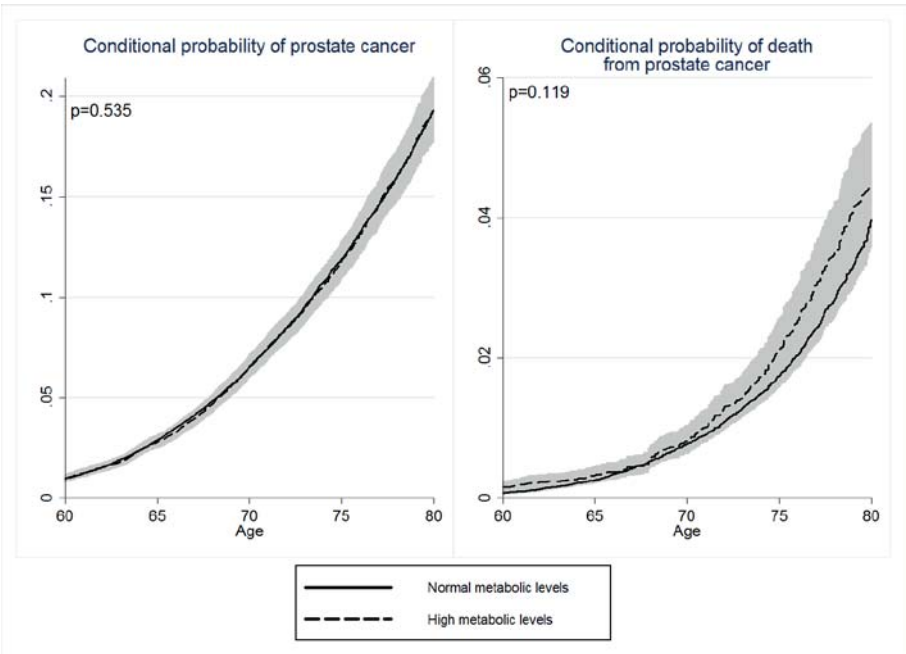

Figure 12. Conditional probability of prostate cancer (left) and death from prostate cancer (right) for normal and high levels of composite score. P-values in the figures correspond to Pepe and Mori test of differences between conditional probabilities.

Multi-state models (paper II)

In paper II, we initially considered expanding the competing risk analysis to include more states – i.e., a multi-state analysis with three states, also called an illness-death model (**Figure 13**). In this setting, all participants start at state 1, alive and free of prostate cancer. Participants either stay in state 1 or are diagnosed with prostate cancer or die. If they receive a diagnosis of prostate cancer, they are moved to state 2; if they die, they are moved to state 3. Rates between states and probability for being in each state can be calculated. The probability for being in each state could be interpreted as prevalence, in contrast to paper II, where lifetime probability of prostate cancer was calculated.

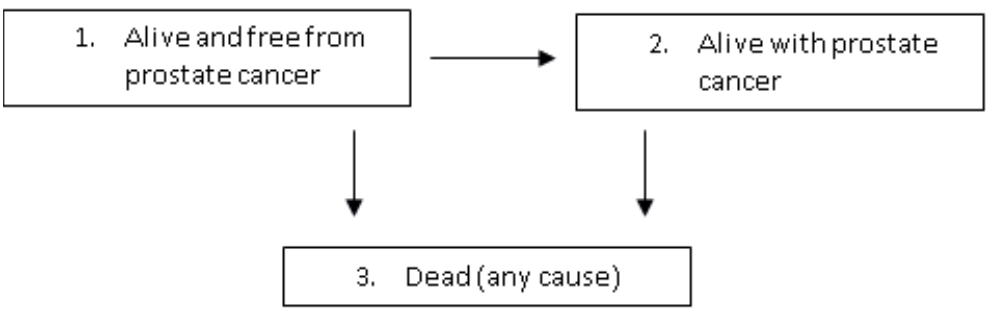

Figure 13. Multi-state model with three states, illness-death model.

We calculated the probability for being in each state with age as timescale for normal and high levels of blood pressure and stacked those probabilities (**Figure 14**). Probability of being in state 2, alive with prostate cancer, is highest around 78-80 years of age and highest for men with normal blood pressure, approximately 5%. Men with high blood pressure had a prevalence of 4% for prostate cancer in the same age-span. For men around 55 years of age, the probability of being alive and free from prostate cancer is almost 1.0, 100%. For men around 95 years of age, the probability of being dead is almost 100% for men with high blood pressure and about 90% for men with normal blood pressure.

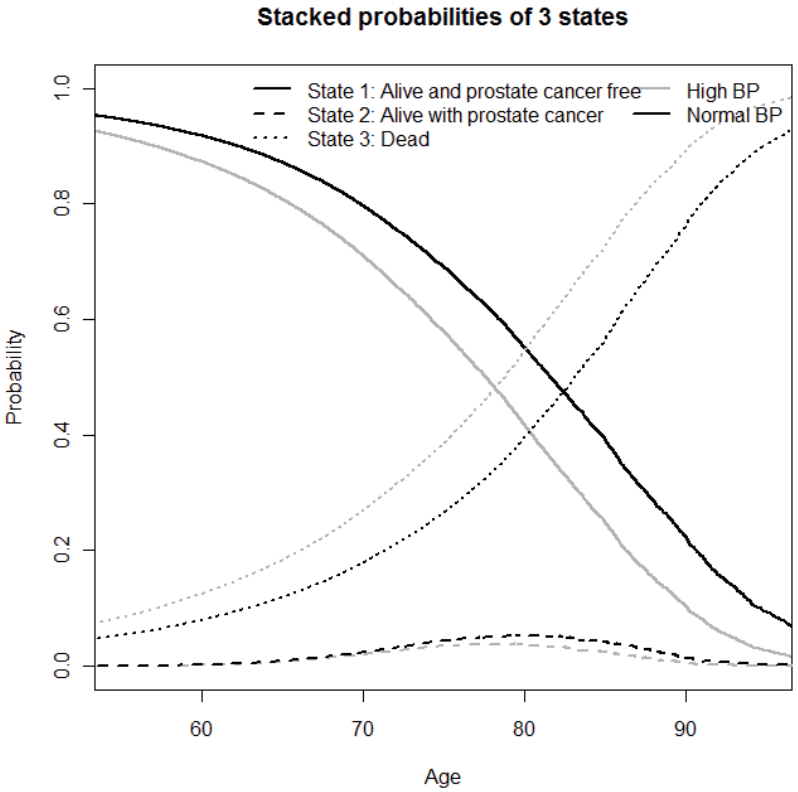

Figure 14. Stacked probabilities for being in any of the three states in a multi-state model. The solid lines correspond to the probability of being in state 1 (alive and free of disease), the dashed line, the probability of being in state 2 (alive with prostate cancer), and the dotted line, the probability of being in state 3 (dead). Black lines represent men with normal levels and grey lines represent men with high levels of blood pressure. The model includes similar covariates as in paper II.

Discussion

Study design

To draw conclusions valid for the general population, we assumed that our data represent the general population. Me-Can is a population-based project and the proportions of smokers [62] and obese individuals [63-65] were similar to background populations within the same calendar period. In the VIP cohort, a validity check was performed, comparing participants that have undertaken a health examination to the background population; only minimal differences were found [66].

To draw unbiased conclusions, we assumed our data captured all diagnoses and deaths due to prostate, kidney (RCC), and bladder cancer from participants in Me-Can. Validity studies within the Swedish [67], Norwegian [68], and Vorarlberg State Cancer Register [69] have concluded that the capture of cancer diagnoses is accurate and close to complete. The Swedish cause of death register has shown to have high quality, at least for prostate cancer patients [70].

To avoid biased estimates, we assumed that the metabolic factors measured at baseline were not going to change unevenly at follow-up. If all participants, regardless of their baseline metabolic status, were changing in the same direction, this would not substantially bias our results. If participants with metabolic aberrations at baseline changed their lifestyle and improved their health, the results would be underestimated. If the opposite happened, participants with metabolic aberrations become even more extreme at follow-up, results would be overestimated. Differences in BMI between baseline and repeated health examination within 2.5-7.5 years have been calculated in preliminary data including VHM&PPP, MPP, and VIP. BMI was divided into categories at baseline; in the repeated health examinations, all those categories had slightly higher mean BMI (Wirén, unpublished).

The Me-Can project dataset consists of participants from seven cohorts, measured at different dates using slightly different measurement methods and under different fasting status. Although the inconsistency is a weakness in the project, we have tried to overcome these differences by calculating cohort and fasting time (for glucose, cholesterol, and triglycerides) specific cut points when dividing exposures into quintiles and transformed exposures to z-scores separately for cohort and fasting time (for glucose, cholesterol, and triglycerides). In all Cox regression analyses, we have stratified within the model to allow for different baseline hazards for each cohort.

The metabolic syndrome is a state of multiple metabolic aberrations including obesity, insulin resistance, hypertension, and high levels of glucose and lipids. There exist several different definitions of this state with defined cut off levels on each of the included factors [71]. In paper IV, the composite score was called the metabolic syndrome (MetS) score, a label that reflects that the variable could be compared with the metabolic syndrome, although we did not use any of the definitions. In later papers (I-III), we called the variable composite score to avoid confusion.

There is no evidence that metabolic factors have cut offs or threshold levels where the risk is increased [72]. We assumed a linear association between increasing level of metabolic factor and risk of cancer and cancer death, and the metabolic factors were analysed as continuous variables if allowed in the models. We investigated this assumption by performing trend tests over quintiles and tested the assumption in paper III by plotting cubic splines.

When creating the composite score, each single factor was given equal weight. However, using weighted z-score where weights had been selected to maximize the risk of cancer could have been another solution [73]. If the aim would have been to find the combination of metabolic factors that predict the highest risk of cancer, a similar model could have been used.

Prostate cancer (paper I)

We found that high levels of glucose and triglycerides were associated with a decreased risk of prostate cancer and that the association between metabolic factors and risk of prostate cancer differed between calendar periods. For cases diagnosed during the pre-PSA era, the associations were stronger than for cases diagnosed in the PSA era. One study on cases diagnosed before 1998 also found an association between the metabolic syndrome and prostate cancer [14], but another study on cases diagnosed 1995 to 2005 found no such association [74]. Previous studies on glucose or triglyceride levels and risk of prostate cancer found inverse [24, 75] or no associations to risk [24, 33, 37]. In our data, high levels of BMI and blood pressure were associated with increased risk of death from prostate cancer, findings that agree with large studies on BMI [25, 76-79] and support the hypothesis that high BMI is not related to prostate cancer risk, but that it is related to an increased risk of progression and prostate cancer death [25, 76, 80, 81]. For blood pressure, the largest previous study found a non-significant association to prostate cancer death [76] although smaller studies reported null associations [82, 83].

The introduction of PSA for detection of prostate cancer was noticed as a period effect in our data. We speculate that the differences in association depending on calendar period were due to a different case mix during the two periods with a larger proportion of low-risk cases diagnosed in the PSA era. Conversely, a larger proportion of advanced cases were diagnosed in the pre-PSA era, for which there was a stronger association to metabolic risk factors. No effect of calendar time was found on risk of death from prostate cancer.

Detection bias could explain the divergent association between metabolic factors and risk of diagnosis and death from prostate cancer. That is, obese men might be diagnosed at a later stage because of lower PSA levels and a larger prostate, which makes rectal examinations more difficult [80]. Other possible explanations are decreased levels of hormones and growth factors among diabetics and obese men and the protective effect of diabetes medication on prostate cancer [84].

Hormone levels (mainly testosterone) and growth factors (mainly insulin-growth factor 1, IGF-1) have been discussed as key mediators for prostate cancer initiation [85]. Insulin resistance may result in higher levels of free IGF-1 and also may impact the cycle of fat cells (adipocytes) in a way that disturbs hormonal balance. Both hormones and IFG-1 are connected with cell proliferation [86]. High levels of IGF-1 have been associated with prostate

cancer [87-89] and with an increased risk of prostate cancer mortality among those that are diagnosed with aggressive tumours [89].

A healthy lifestyle is associated with higher levels of serum testosterone [90] and high levels have previously been associated to risk of prostate cancer [91], but this association has not been confirmed in later studies [92-94]. Men diagnosed with benign enlargement of the prostate are often prescribed 5-alpha reductase inhibitors (5ARI) to inhibit the transformation of testosterone to a more active form of testosterone. This active form of testosterone is used in the prostate and has the effect of reducing the size of the prostate. Two large randomized placebo-controlled clinical trials have investigated 5ARI and risk of prostate cancer. The first trial compared the risk of prostate cancer at biopsy in men given 5ARI for seven years with the risk for men given a placebo. The first trial concluded that men with 5ARI had a decreased risk of low-risk prostate cancer, but found an increased risk of high-risk prostate cancer [95]. The second trial found similar results after four years [96]. There are discussions in the literature whether the medication drives the aggressiveness of the actual tumour or whether there is a detection bias due to higher probability of finding the cancer tumour in a smaller prostate [97]. One recent large case-control study investigated men treated with 5ARI for urinary tract symptoms and found no indication of increased risk of high-risk prostate cancer, and a decreased risk of low-risk prostate cancer [98].

After paper I was published in October 2012, some new studies have been published in this field, most of them confirming our findings. There are two recent meta-analyses. One study, investigating clustered metabolic factors and prostate cancer risk, found no association with prostate cancer diagnosis, but did find an association with death from prostate cancer [99]. The other study, investigating BMI and prostate cancer in risk categories, found an inverse association between high BMI and localized prostate cancer and an association with advanced disease [100]. A large case-control study (almost 45,000 cases of prostate cancer) found that diabetic men had a reduced risk of prostate cancer [19]. One study has used offspring BMI as an instrumental variable for own BMI, and found no association with risk of prostate cancer death [101].

Prostate cancer with competing risk analysis (paper II)

In paper I, we investigated metabolic factors as putative etiological factors for prostate cancer using Cox proportional hazards model. This approach found no association with risk of prostate cancer but did find an association with prostate cancer death, a finding that confirms several other large studies. Paper II had another purpose: to study whether a man with high levels of metabolic factors has a different probability of prostate cancer compared to men with normal levels of metabolic factors. There are mainly two reasons why the results from these two types of analyses differ. First, prostate cancer is mainly diagnosed at an age when many men might already have died (mean age at prostate cancer diagnosis in Scandinavia is between 70-75 years) [10]. In conventional survival analysis, this may affect calculations towards overestimation of the absolute risk [102]. The cumulative incidence of prostate cancer in the current study was lower than Kaplan-Meier failure estimates (1 - S(t)) using conventional survival analysis when censoring for all endpoints other than prostate cancer (**Figure 15**) in accordance with simulated data [103] and previous studies [104, 105].

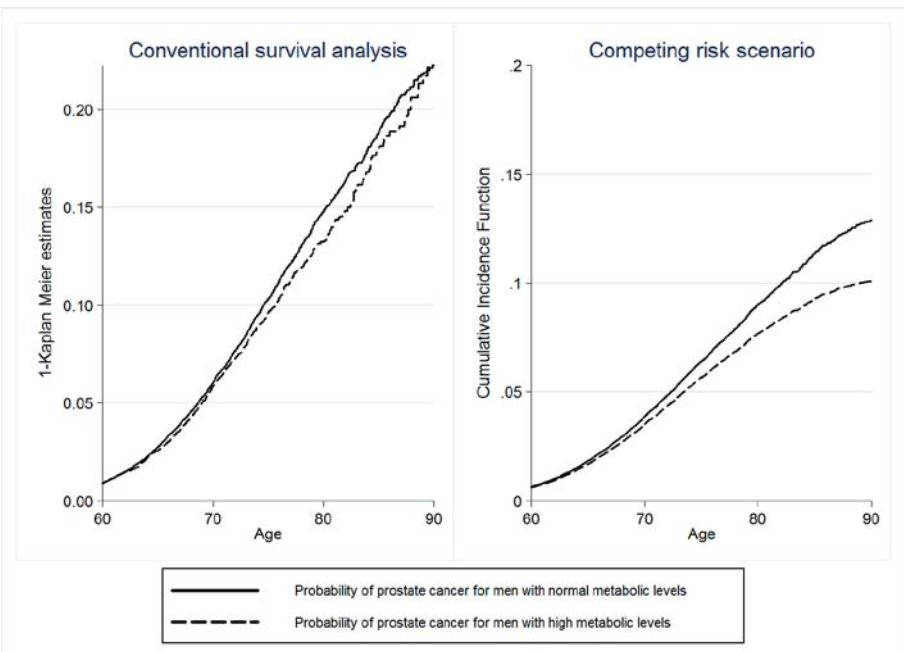

Figure 15: Calculated probabilities for prostate cancer for men with normal and high levels of the composite score in a comparison with conventional survival analysis (left) and competing risk scenario (right).

Second, high levels of metabolic factors are related to increased risk of death from all causes [22], which may influence calculations of hazard ratios [106], since men with high levels of metabolic factors are more likely to die at a younger age and therefore more likely to be censored in conventional survival analysis than men with normal levels. This is also noticeable within our data, with a gap between the curves in the competing risk scenario larger than in the conventional survival analysis approach (**Figure 15**). In other words, among men censored due to a competing event (i.e., all-cause death or death from other causes), there are more men with high levels of metabolic factors than those censored for other reasons (i.e., migration or end of follow-up).

This scenario is similar to reports on smoking as a risk factor for dementia, Alzheimer disease [107], and melanoma [108]; these studies found a decreased risk among smokers. One of these studies defined competing risk bias using directed acyclic graphs (DAGs) [108], and discussed whether the decreased risk among smokers may be due to a selection bias, since smokers have a shorter life expectancy compared to non-smokers. Accordingly, we speculate that a similar selection bias may exists due to censoring for death in etiological studies of metabolic factors and prostate cancer, since men with high levels of metabolic factors have a shorter life expectancy than men with normal levels. In the scenario of metabolic syndrome and prostate cancer, a DAG could look like **Figure 16**.

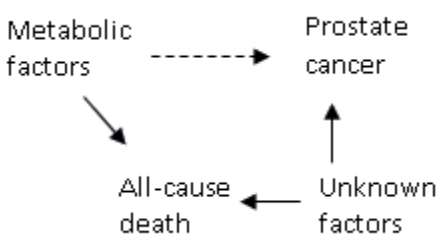

Figure 16. DAG for selection bias due to competing risks. Conditioning on a collider (i.e., only choosing those that have survived all causes of death) may bias the association between metabolic factors and prostate cancer.

Underlying assumptions are that there are common causes for both prostate cancer and the risk of death. Competing risks are a collider in this DAG, and the bias could be introduced when stratifying survivors (i.e., only including those that have survived competing events). To investigate whether such a bias exists, we would need to simulate hypothetical data, an aim outside the scope of our study. In this study, we have focused on calculating probabilities similar to the probabilities in the real world. This is also why we chose to include all

primary, secondary, and later prostate cancer diagnoses in the study: in the real world, men with a cancer diagnosis may still get prostate cancer. Also, in the data set, we have no information of other diseases (not cancer related) or medication that may affect the probability of prostate cancer.

There are only a few studies on metabolic factors and prostate cancer that have used a competing risk approach, and these studies have used different methods with inconsistent results [23-25]. In our study, men with high levels of metabolic factors had a lower probability of prostate cancer. This finding agrees with results in a Swedish cohort study (almost 37,000 men) that used Fine and Gray regression. That study found that men with high levels of BMI at age 60 had a decreased probability of low-risk prostate cancer, non-significantly increased probability of high-risk prostate cancer, and an increased probability of prostate cancer death [25]. However, our findings are in contrast with two other studies [23, 24] that calculated conditional probability of prostate cancer. The first study, which included almost 200,000 men and 5,000 prostate cancer cases, found an increased risk of prostate cancer for high levels of triglycerides and glucose at age 75 [24]. The second study, which consisted of 2,322 men, reported that men at age 50 with metabolic syndrome had an increased probability of prostate cancer at age 80 [23].

In the PSA era, we found larger differences in probability of prostate cancer for men with normal and high levels of metabolic factors than in the pre-PSA era. We speculate that more men with high socioeconomic status undergo PSA testing more often than men with lower socioeconomic status [109] and therefore these men have a higher risk of prostate cancer, in particular low-risk tumours [20, 21]. Men with high socioeconomic status have lower prevalence of the metabolic syndrome [110], obesity [111], and diabetes mellitus type 2 [112] than men with low socioeconomic status. The metabolic syndrome, obesity, diabetes, and high levels of other metabolic factors have been linked to lower risk of prostate cancer during the PSA era [19, 74, 113].

We calculated conditional probability, sub distribution hazard ratios, and p-values from Pepe and Mori test for differences between cumulative incicence curves, but decided not to include these results in the final paper. The main reason for this exclusion was that conditional probability curves and sub distribution hazards were difficult to interpret [114] and that the Pepe and Mori test used unadjusted cumulative incidence curves [115].

Kidney cancer (renal cell carcinoma, paper III)

Our results indicate that high BMI, blood pressure, glucose, and triglycerides among men and high BMI among women are associated with risk of RCC, and several of these factors may interplay on biological pathways. By adding single factors to a model to investigate which factors attenuated other factors, we found that blood pressure and triglycerides among men and BMI among women were independent risk factors. This method is similar to how previous studies have investigated independence [116]. However, this approach only reveals independence among the measured covariates, and the actual "independent" risk factor may interact or share the same pathway with other, not measured, factors. To further investigate the interplay between metabolic factors, we calculated biological interaction [50], which as stated, should test whether the covariates share the same pathway. However, we have not been convinced that this test reflects the interplay within pathways better than other statistical measures of interaction [117].

Our findings for BMI and blood pressure among men agree with results from previous studies [30, 116, 118-121]. As previous data suggests, the results for BMI were attenuated after adjustments for other metabolic factors [119] and high blood pressure was independently associated with risk of RCC [30]. Our results for glucose [31, 33], cholesterol [31, 32], and triglycerides [31], and risk of RCC also agree with previous reports. We found a stronger association between BMI and RCC in women than in men, results that are also in line with a recently published meta-analysis [122]. In contrast to several previous reports [116, 119, 120, 123], we did not observe an association between blood pressure and RCC among women.

The data did not reveal multiplicative statistical interaction or any evidence of biological interaction, thus, the interactions between metabolic factors on risk of RCC are on an additive scale, similar to previous reports [29, 31, 116, 124, 125]. Smoking is an established risk factor for RCC, but no evidence of effect modification due to smoking status was found. Two previous studies used spline functions to investigate levels of BMI and systolic and diastolic blood pressure and risk of RCC. For BMI, one study reported, in line with our data, a steady increase of RCC with increasing levels of BMI [121], although the other study reported, in contrast to our data, a positive but non-linear dose-response between blood pressure and RCC [120].

There are a few biological mechanisms that may link metabolic factors to initiation of renal cell cancer. Insulin resistance may result in higher levels of free IGF-1; this relationship has been proposed as a possible link between

BMI, abnormal glucose metabolism, and RCC [86]. Insulin resistance may also impact the cycle of adipocytes and disturb the hormonal balance [126]. It is unclear why obese women have higher risk compared to men [86]. Lipid peroxidation, which is increased in obese and hypertensive subjects, has been hypothesized to be partly responsible for the association between obesity, hypertension, and RCC [127, 128]. The mechanisms for high blood pressure and RCC risk independent of obesity are unclear, but researchers have speculated that renal injury or functional changes due to hypertension in the renal tubule could increase susceptibility for cancer cells to grow [126].

After paper III was published in January 2013, very few new findings for metabolic factors and risk of RCC and/or kidney cancer have been noted. One small case-control study reported that insulin resistance was inversely associated to risk of RCC, independent of obesity, diabetes mellitus type 2, lifestyle, and hormonal covariates [129]. Also, offspring BMI, used as a proxy for own BMI, has been associated with risk of kidney cancer death among both men and women [101].

Bladder cancer (paper IV)

Among men, we found that high blood pressure was consistently associated with risk. Previous studies on blood pressure were based on much smaller study populations and reported no association [130-132]. Among women, the strongest risk factor was high glucose levels, although our findings were of borderline significance. Previous cohort studies have investigated the association between glucose levels and risk [33, 37, 69] and between prevalent diabetes and risk [41, 133-136]. Most of these studies reported an increased risk for both men and women, but only in some of these studies did the results reach statistical significance. We found an increased risk of bladder cancer for men who had a high composite score, whereas no such association was observed among women. Our study included 30 times as many cases as a previous study on the metabolic syndrome and bladder cancer risk [137]. Smoking is an established risk factor for bladder cancer and we found a more than two-fold increase in risk for smokers, findings in line with previous studies [138], but formal tests of interaction indicated no differences across strata of smoking status. However, as a result of the crude classification of smoking, some residual confounding likely remained.

A possible pathway between high levels of glucose or diabetes and bladder cancer risk is the increased incidence of urinary tract infections, also a risk factor for bladder cancer among diabetic individuals, in particular among diabetic women [139, 140]. There are no clear pathways to why hypertension could be associated with risk of bladder cancer among men. One study of only men detected higher levels of IGF-1 in bladder cancer cases compared to controls, a finding that might suggest a higher risk of bladder cancer among men with insulin resistance [141].

After paper IV was published in June 2010, a few new studies in this field have been published. Recent meta-analyses found an association for metabolic syndrome with bladder cancer among men [142] and associations for obesity and diabetes with increased risk of bladder cancer among men and women [143] [144]. A large Taiwanese cohort study found an association between diabetes and bladder cancer [145]. Other studies have reported an association between diabetes mellitus type 2 for more than 15 years and invasive bladder cancer [146] and that diabetic postmenopausal women increased risk of bladder cancer [147].

Future perspectives

To assess causality between risk factor and outcome, randomized clinical trials (RCT) are assumed to produce the highest quality results. There are methods similar to a RCT that can analyse data collected in an observational study. These methods, which will probably be used more frequently, attempt to randomly distribute confounders, both known and unknown, within the study population. Creating a propensity score of covariates and matching participants on propensity score [148] is one way to ensure more random study selection so as to minimise bias. Other ways of avoiding unmeasured confounding is to use instrumental variables as proxies for something else such as socioeconomic background factors, which may confound associations, and be hard to measure and account for otherwise. In the cancer research field, one study has used son's BMI [101] as a proxy for own BMI and another study used health service area as proxy for a therapy option among men with prostate cancer [149]. In a comparison between adjusting for covariates, adjusting for propensity score, and instrumental variable analysis, the instrumental variable analysis was found to be the best method to reduce selection bias in a similar way as a RCT [150]. Genes can also be used as instrumental variables, also called Mendelian randomization. However, an extensive paper on the use of Mendelian randomization between nutrition and cancer risk concluded that these kinds of studies normally require a large sample size, except under certain circumstances where strong associations are involved [151].

If a study contains several possible outcomes, treatments, or something else that changes the characteristics of a study participant, multi-state models can be used in studies with only one endpoint. Large population-based studies of diseases could use this approach and calculate the rates and predict probabilities of being in each state. In a larger context and in large datasets, theories based on complex networks can be used by placing covariates as nodes in a "map" and analysing how the flow between these nodes changes over time. A large study using this method suggested that friends had higher impact for an individual's risk of obesity than siblings [152]. When studying outcomes that may depend on socioeconomic or demographic factors, methods based on network theories might add an extra dimension than traditional epidemiological study designs.

Conclusions

We found that high levels of metabolic factors were associated to diagnosis of kidney and bladder cancer and to death from prostate, kidney and bladder cancer **(Table 3)**. Results for death from kidney and bladder cancer pointed in the same direction as the results for diagnosis for these cancer sites.

Table 3. Overview of associations between high metabolic factors and the composite score and risk of prostate, kidney, and bladder cancer. A minus sign in the table corresponds to inverse association, plus sign to an increased risk, double plus to independent risk factors and zero to no multiplicative interactions.

	Prostate cancer (paper I)		**Kidney cancer (Renal cell carcinoma, paper III)**		**Bladder cancer (paper IV)**	
	MEN		Diagnosis		Diagnosis	
	Diagnosis	Death	MEN	WOMEN	MEN	WOMEN
BMI		+	+	++		
Blood pressure		+	++		+	
Glucose	-		+			+
Cholesterol						
Triglycerides	-		+	+		
Composite score	-	+	+	+	+	
Interactions	0	0	0	0	0	0

Additional conclusions for prostate cancer (paper I-II):

- The associations between high levels of metabolic factors and risk of prostate cancer in the pre-PSA era were stronger than in the PSA era. In the PSA era, inverse associations between high levels of metabolic factors and prostate cancer were found. For prostate cancer death, no changes according to calendar period were found.

- Men with high levels of metabolic factors had a decreased probability of prostate cancer, similar probability of prostate cancer death, and increased probability of competing events (all-cause death and other causes of death), compared to men with normal levels.

Additional conclusions for kidney cancer (renal cell carcinoma, RCC, paper III) and bladder cancer (paper IV):

- Blood pressure among men and BMI among women were found to be independent risk factors for RCC. Several of the other metabolic factors may interplay in biological pathways, but no biological interaction was found.

- The associations between increasing levels of metabolic factors and risk of RCC were found to be approximately linear.

- No effect modification due to smoking was found for risk of RCC or bladder cancer.

Populärvetenskaplig sammanfattning

Prostatacancer är den vanligaste cancerformen i Sverige med ca 10 000 nya fall årligen. Förekomsten av prostata-, njur- och urinblåsecancer är vanligare i Nordamerika och Västeuropa, än i utvecklingsländer, vilket antyder att risken för dessa cancerformer är kopplade till diet och livsstil.

Syftet med denna avhandling var att undersöka sambandet mellan olika metabola riskfaktorer och risk för prostata-, njur- och urinblåsecancer. De metabola faktorer vi studerade var kroppsmasseindex (Body mass index, BMI), blodtryck, blodsocker (glukos) och blodfetter (totalkolesterol och triglycerider). Vi ville också beräkna verkliga sannolikheter för diagnos och död av prostatacancer för män med normala jämfört med höga nivåer av metabola faktorer.

Denna avhandling bygger på det Metabola Syndromet och Cancerprojektet (Me-Can) där data från hälsokontroller av 578 700 män och kvinnor från Sverige, Norge och Österrike samlats in. Efter uppföljningstiden har mätdatat länkats till cancerregister och dödsorsaksregister i varje land, därefter har hela databasen analyserats med statistiska metoder inom överlevnadsanalys.

Vi hittade inget samband mellan någon av metabola riskfaktorerna och prostatacancer, däremot en ökad risk för död av prostatacancer hos män med högt BMI eller blodtryck. Sannolikheten att få prostatacancer var högre för män med normala värden på riskfaktorerna än för de med höga värden, men sannolikheten för att konkurrerande händelse (död) var mycket högre hos män med höga värden. Hos både män och kvinnor med höga värden på riskfaktorerna fann vi en ökad risk för njurcancer, där blodtryck hos män och BMI hos kvinnor var oberoende riskfaktorer. För urinblåsecancer hittade vi en förhöjd risk hos män med högt blodtryck.

Sammanfattningsvis fann vi att män och kvinnor med höga värden på metabola riskfaktorer hade en ökad risk för diagnos av njur- och urinblåsecancer och död av prostata-, njur-och urinblåsecancer.

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