Original Article

Prospective Study on Metabolic Factors and Risk of Prostate Cancer

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BACKGROUND: There are inconsistent data regarding the association between metabolic factors, separately and combined, and the risk of prostate cancer and death from prostate cancer. **METHODS:** In the Metabolic Syndrome and Cancer Project (Me-Can), data on body mass index (BMI); blood pressure; and blood levels of glucose, cholesterol, and triglycerides were collected for 289,866 men. Cox proportional hazard models were used to calculate relative risks (RRs) by exposures in quintiles as well as for z scores (with a mean of 0 and a standard deviation of 1) together with a composite sum of scores to assess the combined effect of metabolic factors. RRs were corrected for random errors in measurement. **RESULTS:** During a mean follow-up of 12 years, 6673 men were diagnosed with prostate cancer and 961 died of the disease. Men with high levels of glucose and triglycerides were found to have a decreased risk of prostate cancer: top versus bottom quintile of glucose: RR, 0.82 (95% confidence interval [95% CI], 0.62-1.08; *P* value for trend = .03) and top versus bottom quintile of triglycerides: RR, 0.88 (95% CI, 0.74-1.04; *P* value for trend = .001). High BMI, elevated blood pressure, and a high composite z score were found to be associated with an increased risk of death from prostate cancer: top versus bottom quintile of BMI: RR, 1.36 (95% CI, 1.08-1.71); systolic blood pressure: RR, 1.62 (95% CI, 1.07-2.45); and per 1-unit increase of the composite z score: RR, 1.13 (95% CI, 1.03-1.25). **CONCLUSIONS:** The authors found no evidence of an association between high levels of metabolic factors and the risk of prostate cancer, but high BMI, elevated blood pressure, and a composite score of all metabolic factors were associated with an increased risk of death from prostate cancer. ***Cancer*** **2012;118:6199-206.** © *2012 American Cancer Society.*

KEYWORDS: epidemiology, metabolic factors, prostate cancer, metabolic syndrome, cohort study, body mass index, blood pressure.

INTRODUCTION

The etiology of prostate cancer is largely unknown and there are no established modifiable risk factors.[1] However, the geographical distribution, demonstrating a high incidence in Western Europe and North America,[2] suggests that prostate cancer is related to a "Western" lifestyle or environment. In these areas, there is a high prevalence of metabolic syndrome, which is comprised of insulin resistance, obesity, hypertension, and high levels of blood glucose and lipids.[3,4] There are several different definitions of this state of multiple metabolic aberrations, but regardless of the definition used, metabolic syndrome has consistently been associated with an increased risk of cardiovascular disease and diabetes mellitus type 2.[5,6]

Large studies on overweight, most often measured as high body mass index (BMI), have generally demonstrated a modest positive association with prostate cancer[7-9] and a stronger association with death from prostate cancer.[10-12] Less is known about the relation between high levels of other metabolic factors such as blood glucose, lipids, and blood pressure and the risk of prostate cancer because the majority of studies have been limited in size with a few exceptions.[9,13,14] Studies

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investigating the joint effects of these metabolic aberrations have reported inconsistent results; 1 meta-analysis reported an increased risk,[15] a few reported no association,[16-18] and still others have found a reduced risk[19,20] of prostate cancer.

Metabolic factors, with the exception of BMI, are measured with random error because of inexact measurement methods and long-term fluctuations, which may dilute an association by regression dilution bias.[21,22] To minimize such bias, random error in the exposures needs to be accounted for but this has not been done in previous reports.

The objective of the current study was to investigate the association between BMI, blood pressure, glucose, cholesterol, and triglycerides, both separately and combined, with the risk of prostate cancer and death from prostate cancer in a large pooled prospective study taking measurement error into account.

MATERIALS AND METHODS

Study Population

This study was conducted within the Metabolic Syndrome and Cancer (Me-Can) project, which has been previously described in detail elsewhere.[23] In brief, the Me-Can project is comprised of 7 subcohorts in Norway, Sweden, and Austria. In total 289,866 men were included in the current study with prospectively collected data regarding weight; height; systolic and diastolic blood pressure; and circulating levels of glucose, cholesterol, and triglycerides from 1 or several health examinations. The study was approved in each country by the respective Research Ethics Committee and informed consent had been obtained from all participants.

Endpoints

Men diagnosed with prostate cancer were identified by linkage to each National Cancer Register by use of code 177 in The International Classification of Diseases, 7th edition (ICD-7). The cause of death was obtained by linkage to the National Cause of Death Registers and in Norway and Sweden, data were also linked to the Register of Total Population and Population Changes for assessment of vital status.

Statistical Analysis

Hazard ratios were calculated using Cox proportional hazard regression models with age as the time scale and are denoted as relative risks (RRs). Participants were followed until the date of the event (ie, prostate cancer diagnosis or death from prostate cancer), or until censoring at the date of other cancer diagnoses (for analysis of prostate cancer diagnosis), death, emigration, or end of follow-up (for analysis of prostate cancer diagnosis: December 31, 2003 in Austria, December 31, 2005 in Norway, and December 31, 2006 in Sweden; for analysis of prostate cancer death: December 31, 2003 in Austria and December 31, 2004 in Norway and Sweden), whichever occurred first. To reduce the probability of reverse causation, follow-up began 1 year after the first health examination.

The proportional hazards assumption was checked graphically and tested with Schoenfeld residuals for all exposures and covariates including birth cohort (before 1927, 1927-1929, 1930-1932, 1933-1938, 1939 and later), smoking (current, nonsmoker, or former smoker), and age at measurement (aged $\leq$ 42 years, 43 years-48 years, 49 years-54 years, 55 years-60 years, and $\geq$ 61years). For age at measurement and birth cohort, we found violations of the proportionality assumption and tested with the likelihood ratio test interaction between those covariates and the separate exposures, but no interaction was found in our data. Therefore we decided to stratify within the models for categories of age at measurement and birth cohort in addition to subcohort.

We calculated the RRs for each exposure divided into quintiles and transformed to a standardized score (z score). BMI and blood pressure were divided into quintiles and transformed into z scores separately for subcohort, while glucose, cholesterol, and triglycerides were divided into quintiles and transformed into z scores separately for subcohort and fasting time ($<$ 1 hour, 1 hour-2 hours, 2 hours-4 hours, 4 hours-8 hours, and $>$ 8 hours). Because the distributions of glucose and triglycerides were skewed, a natural logarithm was applied before the z score transformation.

In an analysis of exposures in quintiles, smoking status and quintiles of BMI (except for BMI) were included in the models. The mean value within each quintile was used as a continuous variable to test for linear trend across quintiles. In the Cox models with z scores, we defined mid-blood pressure[24] as (systolic + diastolic blood pressure)/2 to avoid collinearity and a composite metabolic z score was defined as the sum of all separate z scores to analyze the joint effect of the metabolic factors. In addition to analyzing the exposures separately in the models, we constructed a Cox model mutually adjusted for all separate exposures.

To investigate whether associations differed according to calendar period at the time of diagnosis, we performed subgroup analyses for follow-up ending on December 31, 1996 and beginning on January 1, 1997, respectively. This cut point was chosen because an

increase in the incidence of prostate cancer was noted in Sweden at approximately that date,[25,26] and an ongoing increase was noted in Norway[27] and Austria.[28]

We investigated 2-way interactions for pairwise exposures in z scores and for the exposures, subcohort, smoking status, and fasting time using the likelihood ratio test for both diagnosis and death from prostate cancer. In total, $>$ 15 tests of interactions were performed for each endpoint and we adjusted the significance level for multiple testing using the Bonferroni correction.[29]

RRs were corrected for random error (ie, measurement error and within-person variability) by the use of methods based on the regression dilution ratio (RDR) for analysis of quintiles and univariate analysis of z scores and regression calibration for multivariate analysis of z scores, similar to those described by Wood et al.[30] In brief, calculations were based on data from repeated measurements in Me-Can from a total of 62,031 men with 174,212 health examinations and were predicted at approximately one-half of the mean follow-up time (ie, 6 years after baseline examination). The RDR was estimated as the regression coefficient in the regression models with the repeated measurement as a dependent variable and the baseline measurement as an independent variable in which age at baseline, fasting time, smoking status, birth year, BMI, and time from date of baseline examination were included as fixed effects in the model and subcohort was included as a random effect. The RDR was used in analysis of quintiles and for univariate analysis of z scores. Similar to previous reports, measurements of BMI had a much smaller random error than the other exposures[21,22,31]: the RDR was 0.90 for BMI, 0.51 for systolic blood pressure, 0.48 for diastolic blood pressure, 0.30 for glucose, 0.64 for cholesterol, and 0.46 for triglycerides. The correction was applied by dividing the regression coefficient computed by the Cox model with the RDR for the exposure: $RR_{corrected} = e^{\log(RR original)/RDR}$.

All statistical tests were 2-sided, and P values $< .05$ were considered to be statistically significant. Calculations were performed using STATA MP/2 software (version 11.2; StataCorp LP, College Station, Tex) and R statistical software (version 2.7.2; R Foundation, Vienna, Austria).

RESULTS

Of the 289,866 men in the study cohort, 127,846 (44%) were overweight (BMI of 25 kg/m^2-30 kg/m^2) and 30,853 (11%) were obese (BMI $\geq$ 30 kg/m^2), 110,369 (38%) had hypertension (systolic or diastolic blood pressure $\geq$ 140 or 90 mm Hg), and 113,496 (39 %) were nonsmokers on the date of recruitment (Table 1). The mean age of the participants at the time of recruitment was 44 years (standard deviation [SD], 11 years); during follow-up, 6673 men were diagnosed with prostate cancer as their first cancer at a mean age of 68 years (SD, 7 years) and 961 men died of prostate cancer at a mean age of 72 years (SD, 8 years). The prostate cancer incidence rate in the cohort was 202 per 100,000 person-years and the prostate cancer mortality rate was 33 per 100,000 person-years. Until December 31, 1996, there were 1345 prostate cancer cases and 268 deaths, and after that date there were 5328 cases and 698 deaths.

In an analysis using prostate cancer as an endpoint, no increase in risk was found for any of the exposures, but high levels of glucose and triglycerides were associated with a decreased risk: top versus bottom quintile and trends over quintiles: RR, 0.82 (95% confidence interval [95% CI], 0.62-1.08), P value for trend = .03 and RR, 0.88 (95% CI, 0.74-1.04), P value for trend = .001, respectively (Table 2). Similarly, in the univariate analysis of per-unit increase of z score, we found a decreased risk for high levels of glucose (RR, 0.90 [95% CI, 0.82-0.98]) and triglycerides (RR, 0.94 [95% CI, 0.89-0.99]), but after adjustment for the other metabolic factors, these associations were no longer found to be significant (Fig. 1a). In subgroup analysis according to calendar period at the time of prostate cancer diagnosis, all metabolic factors and the composite score were found to be more strongly associated with risk in men diagnosed until December 31, 1996 than for men diagnosed after January 1, 1997 (Fig. 2a).

In an analysis using prostate cancer death as an endpoint, we found an increased risk for top versus bottom quintile and trends over quintiles of BMI (RR, 1.36 [95% CI, 1.08-1.71]; P value for trend = .01), systolic blood pressure (RR, 1.62 [95% CI, 1.07-2.45]; P value for trend = .001), and a trend over quintiles for diastolic blood pressure (P value for trend = .001) (Table 2). In univariate analysis of z scores we found the same risk pattern, but after adjustment for the other metabolic factors, only the association for mid-blood pressure remained statistically significant (RR, 1.17 [95% CI, 1.04-1.32]) (Fig. 1b). We also found an association between the composite score and prostate cancer death (RR, 1.13 [95% CI,1.03-1.25]). In a subgroup analysis according to calendar time, we found similar risk estimates for the 2 time periods (Fig. 2b).

Interaction tests between the exposures were performed with prostate cancer and death from prostate cancer as endpoints, but no statistically significant interactions were found. Without using Bonferroni correction, an interaction between BMI and triglycerides was found for a decreased risk of prostate cancer.

Table 1. Baseline Characteristics of Men in the Prostate Cancer Study in the Metabolic Syndrome and Cancer Project (Me-Can)

Characteristic		Incident No. Of Cases (%)	Total Cohort, No. (%)
Total		6673	289,866
Subcohort	Norway		
	Oslo (1972-1973)	1051 (16)	16,760 (6)
	NCS (1974-1988)	1140 (17)	25,952 (9)
	CONOR (1994-2003)	666 (10)	52,181 (18)
	40-y (1985-1999)	65 (1)	60,676 (21)
	Austria		
	VHM and PP (1985-2005)	1511 (23)	73,213 (25)
	Sweden		
	VIP (1985-2006)	841 (13)	38,843 (13)
	MPP (1974-1992)	1399 (21)	22,241 (8)
Age at measurement, y	<45	1716 (26)	184,387 (64)
	≥45	4957 (74)	105,479 (36)
BMI, kg/m^2[a]	Normal weight	3143 (47)	131,167 (45)
	Overweight	2979 (45)	127,846 (44)
	Obese	551 (8)	30,853 (11)
Blood pressure, mm Hg[b]	Normotension	3212 (48)	179,497 (62)
	Hypertension	3461 (52)	110,369 (38)
Fasting status	Fasting ≤8 h	2996 (45)	151,279 (52)
	Fasting >8 h	3677 (55)	138,587 (48)
Glucose levels, mmol/L[c]	Normal fasting glucose	3284 (89)	122,841 (89)
	Impaired fasting glucose	247 (7)	10,594 (8)
	Diabetic levels of glucose	146 (4)	5152 (4)
Cholesterol levels, mmol/L[d]	Normal cholesterol	2492 (68)	108,379 (78)
	Hypercholesterolemia	1185 (32)	30,208 (22)
Triglyceride levels, mmol/L[e]	Normal triglycerides	2681 (73)	90,359 (65)
	Hypertriglyceridemia	996 (27)	48,228 (35)
Smoking status	Never smoker	2538 (38)	113,496 (39)
	Former smoker	1850 (28)	86,086 (30)
	Smoker	2263 (34)	89,419 (31)

Abbreviations: BMI, body mass index; Oslo; Oslo study I; NCS, Norwegian Counties Study; CONOR, Cohort of Norway; 40-y, Age 40 Programme; VHM and PP, Vorarlberg Health Monitoring and Prevention Programme; VIP, Västerbotten Intervention Project; MPP, Malmä Preventive Project.

[a] Overweight was defined as a BMI ≥25 kg/m^2; obesity was defined as a BMI ≥30 kg/m^2.

[b] Hypertension was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg.

[c] Impaired fasting glucose ≥6.1 mmol/L and diabetes ≥7.0 mmol/L for men who had fasted >8 hours.

[d] Hypercholesterolemia ≥6.50 mmol/L for men who had fasted >8 hours.

[e] Hypertriglyceridemia ≥1.71 mmol/L for men who had fasted >8 hours.

DISCUSSION

In this large prospective cohort, high levels of BMI, blood pressure, blood glucose, triglycerides, and cholesterol as well as a high composite score of these metabolic factors were not found to be associated with an increased risk of prostate cancer. In contrast, high BMI, elevated blood pressure, and a high composite metabolic score were associated with a modest increase in the risk of prostate cancer death.

The main strengths of the current study are the large sample size with subjects from 7 prospective subcohorts with a virtually complete follow-up[32-34] and data from repeated health examinations to correct for regression dilution bias. The main limitation of the current study is the lack of tumor characteristics and other covariates that could affect the association such as heredity, comorbidity, medication, and socioeconomic status.

We first calculated RRs in quintile levels of exposure to be able to compare our results with those of previous reports. Second, we transformed the exposures to z scores and used them as continuous variables assuming a linear increase in risk for increasing levels of metabolic aberration and to take advantage of the full range of each exposure. Because all z scores are on the same scale, we could compare the RRs for different exposures with each other. Third, by including all factors in the same model, we analyzed which separate exposures had the strongest association with risk, taking all exposures into account. To assess associations for all metabolic factors combined, we created a continuous composite score by adding data for the 5 metabolic factors and to avoid diluted risk estimates caused by random error in the measurement of these factors, we corrected RRs by RDR and regression calibration.[21,22]

Table 2. Relative Risk of Prostate Cancer and Death From Prostate Cancer in Me-Can According to Quintile Levels of Exposures[a]

Exposure	Quintile	Mean (SD)	Total No.	No. of Incident Cases	Prostate Cancer Diagnosis RR (95% CI)	No. of Fatal Cases	Death From Prostate Cancer RR (95% CI)
BMI	1	21.47 (1.32)	57,800	1023	1.00	143	1.00
	2	23.80 (0.76)	57,672	1302	1.09 (0.99-1.19)	184	1.20 (0.94-1.53)
	3	25.37 (0.77)	58,293	1459	1.09 (1.00-1.20)	191	1.16 (0.92-1.47)
	4	27.13 (0.91)	58,076	1475	1.03 (0.94-1.12)	219	1.26 (1.00-1.58)
	5	30.82 (2.75)	58,025	1414	1.02 (0.93-1.12)	224	1.36 (1.08-1.71)
					P_{trend}=.431		P_{trend}=.013
Systolic blood pressure	1	112.15 (6.23)	54,343	920	1.00	125	1.00
	2	122.84 (3.51)	54,344	961	1.04 (0.87-1.24)	121	0.85 (0.53-1.39)
	3	129.71 (4.04)	63,755	1458	0.97 (0.82-1.14)	202	1.12 (0.72-1.72)
	4	138.72 (3.87)	56,078	1388	0.99 (0.84-1.17)	170	0.90 (0.58-1.42)
	5	157.12 (13.34)	60,934	1934	0.95 (0.81-1.12)	342	1.62 (1.07-2.45)
					P_{trend}=.440		P_{trend}=.001
Diastolic blood pressure	1	66.38 (5.22)	45,959	750	1.00	114	1.00
	2	74.30 (3.44)	59,341	1264	1.20 (0.99-1.45)	173	1.05 (0.65-1.72)
	3	80.19 (2.70)	68,506	1563	1.10 (0.91-1.32)	220	1.00 (0.62-1.61)
	4	86.16 (3.38)	60,247	1519	1.13 (0.93-1.37)	218	1.22 (0.75-1.96)
	5	97.00 (7.66)	55,401	1565	1.06 (0.87-1.28)	235	1.24 (0.77-2.00)
					P_{trend}=.857		P_{trend}=.001
Glucose	1	4.17 (0.53)	55,600	1200	1.00	177	1.00
	2	4.77 (0.34)	55,752	1263	1.12 (0.84-1.48)	191	1.30 (0.63-2.69)
	3	5.13 (0.35)	56,207	1263	1.14 (0.86-1.52)	186	1.25 (0.60-2.60)
	4	5.54 (0.41)	61,526	1459	0.93 (0.71-1.23)	186	0.67 (0.32-1.41)
	5	6.87 (1.99)	60,361	1478	0.82 (0.62-1.08)	219	1.05 (0.52-2.14)
					P_{trend}=.034		P_{trend}=.936
Cholesterol	1	4.28 (0.49)	57,036	940	1.00	131	1.00
	2	5.12 (0.28)	57,457	1172	0.93 (0.81-1.07)	180	1.06 (0.75-1.49)
	3	5.68 (0.28)	58,166	1434	1.03 (0.91-1.18)	223	1.22 (0.88-1.70)
	4	6.29 (0.31)	57,934	1500	0.99 (0.87-1.12)	198	0.89 (0.63-1.25)
	5	7.43 (0.82)	58,680	1609	0.96 (0.85-1.10)	226	0.96 (0.69-1.34)
					P_{trend}=.711		P_{trend}=.387
Triglycerides	1	0.80 (0.18)	55,538	1087	1.00	159	1.00
	2	1.17 (0.20)	56,246	1394	1.24 (1.06-1.45)	189	1.07 (0.72-1.62)
	3	1.54 (0.26)	56,859	1396	1.10 (0.94-1.29)	192	0.98 (0.65-1.48)
	4	2.07 (0.37)	56,788	1364	1.03 (0.88-1.21)	220	1.21 (0.81-1.82)
	5	3.71 (1.71)	56,661	1205	0.88 (0.74-1.04)	189	1.03 (0.68-1.58)
					P_{trend}=.001		P_{trend}=.888

Abbreviations: 95% CI, 95% confidence interval; BMI, body mass index; P_{trend}, *P* value for trend; RR, relative risk; SD, standard deviation.

[a] Cox regression models were adjusted for smoking and quintiles of BMI (except for BMI) and stratified for subcohort, 5 birth cohorts, and 5 categories of age at measurement. The regression dilution ratio (RDR) was used for random error correction; corrected values can be transformed back to original data using the equation $RR_{original}=e^{log(RRcorrected)*RDR}$. The RDRs for the following characteristics were as follows: BMI, 0.899; systolic blood pressure, 0.513; diastolic blood pressure, 0.478; glucose, 0.298; cholesterol, 0.644; and triglycerides, 0.461.

We found no association between high levels of BMI, blood pressure, and cholesterol and the risk of prostate cancer. In what to our knowledge was the largest cohort study on BMI (33,314 cases), the authors reported an association with prostate cancer in obese versus normal-weight men (RR, 1.09 [95% CI, 1.04-1.15])[8] and a large meta-analysis reported an RR of 1.05 (95% CI, 1.01-1.08) for each 5-kg/m^2 increment in BMI,[7] whereas other larger studies of BMI have shown no associations.[9,35-37] Our results are in keeping with what to our knowledge are the largest studies on blood pressure (10,002 cases)[9] and cholesterol (5 011 cases),[18] which reported no association with prostate cancer.

In the current study, high levels of glucose and triglycerides were associated with a decreased risk of prostate cancer, in accordance with previous reports. Previous studies have consistently reported an inverse association between diabetes and prostate cancer,[13,38-41] and 2 studies also reported an inverse association between glucose levels and prostate cancer[18,42] whereas others have found no evidence of an association.[13,14] In what is the largest previous study on triglycerides reported to date, no association with risk was noted.[18]

To the best of our knowledge, the current study is the largest study published to date regarding combinations of metabolic factors; for a composite score of 5 metabolic factors we found no associations with prostate

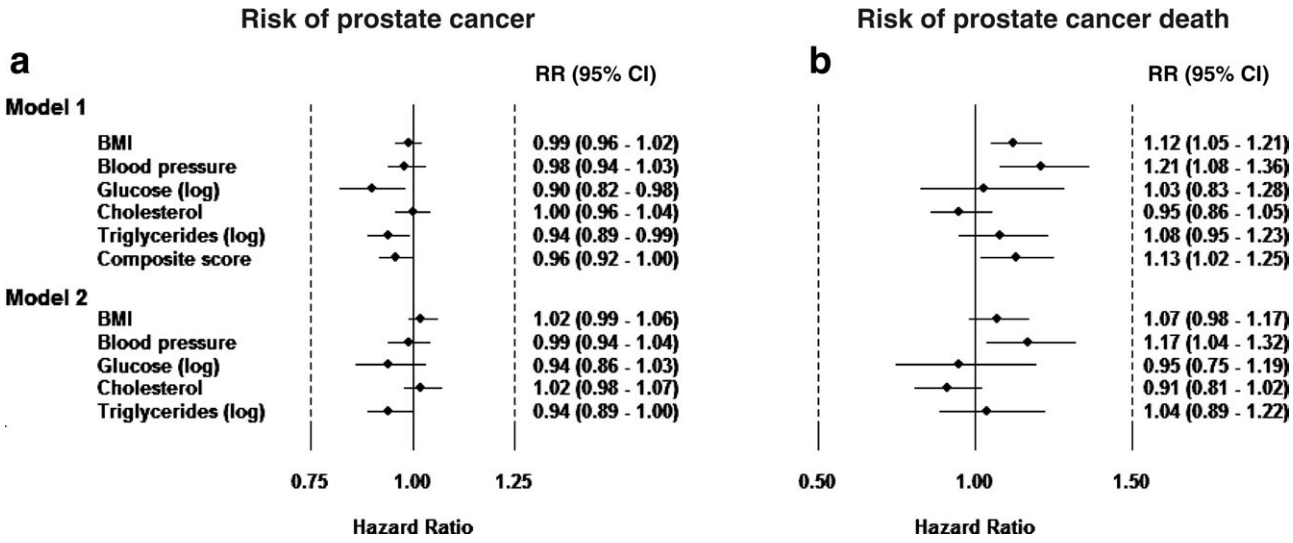

Figure 1. Relative risk of prostate cancer (a) and death from prostate cancer (b) by exposures in z scores. Model 1: Cox regression models were adjusted for smoking and stratified for subcohort, 5 birth cohorts, and 5 categories of age at measurement. Correction for random error was performed using the regression dilution ratio (RDR); the original values for each variable can be obtained using the equation $RR_{original} = e^{\log(RRcorrected)*RDR}$, in which RR indicates relative risk. The RDR for body mass index (BMI) was 0.899 and it was 0.528 for blood pressure, 0.283 for glucose (log), 0.644 for cholesterol, 0.512 for triglycerides (log) and 0.677 for the composite score. Model 2: Cox regression models were adjusted for smoking; stratified for subcohort, 5 birth cohorts, and 5 categories of age at measurement; and also adjusted for z scores of all separate metabolic exposures. Correction for random error was made by regression calibration. 95% CI indicates 95% confidence interval.

cancer risk. Previously, a meta-analysis on metabolic syndrome and risk of prostate cancer based on 8 studies with a total of 731 cases reported an increased risk for men with a combination of high levels of 3 metabolic factors[15]; however, more recent studies found no association with risk[16,18] or a decreased risk.[19,20] The majority of these studies were limited in size with < 400 cases, with the exception of 1 study that was based on 5112 cases of prostate cancer.[18]

We found that high BMI and elevated blood pressure were associated with an increased risk of death from prostate cancer. When taking all factors into account in

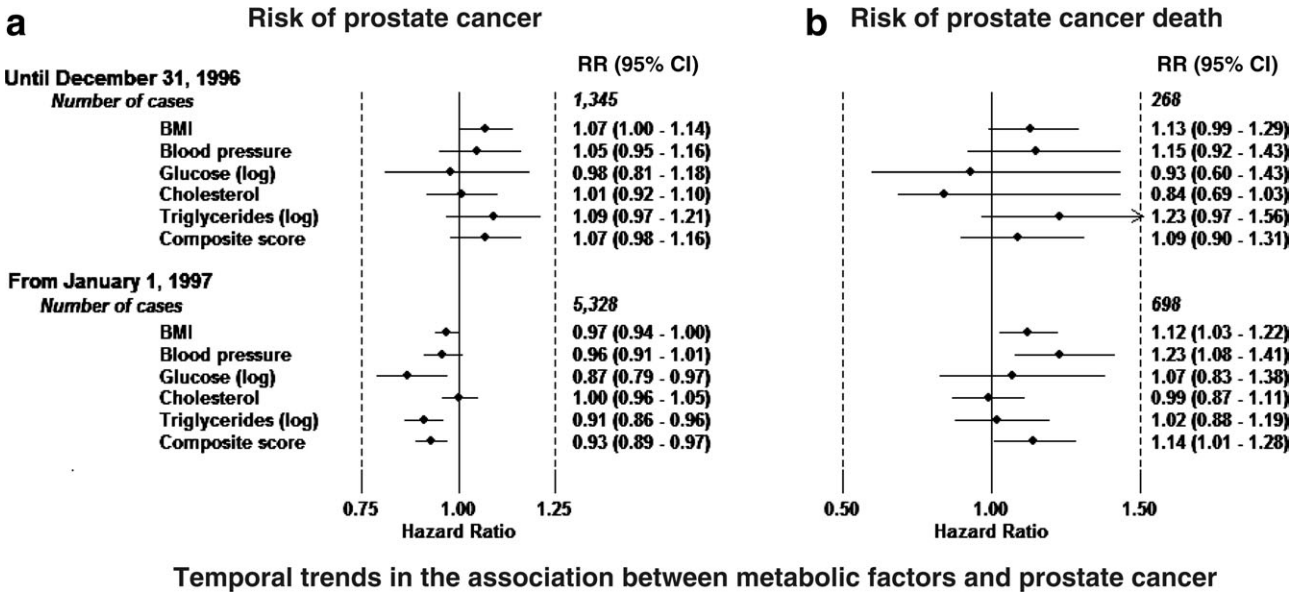

Figure 2. Relative risk of prostate cancer (a) and death from prostate cancer (b) for two periods of follow-up. Cox regression models were adjusted for smoking and stratified for subcohort, 5 birth cohorts, and 5 categories of age at measurement. The first model shows December 31, 1996 as the end of follow-up, whereas the second model shows follow-up beginning on January 1, 1997. Correction for random error was done using the regression dilution ratio (RDR).

the model, blood pressure was found to have the strongest association with risk. Our results for BMI are in keeping with previous findings in large studies,[9-12,43] and support the hypothesis that a high BMI is not related to prostate cancer risk but is associated with an increased risk of disease progression and death from prostate cancer.[9,43-45] For blood pressure, the findings of what to our knowledge is the largest previous study indicated a nonsignificant association with prostate cancer death,[9] whereas smaller studies reported a null association.[46,47] No association with risk was found for high levels of glucose, cholesterol, and triglycerides, which is in keeping with the majority of previous reports,[13,14,17,46,48] with 1 exception of a study concerning cholesterol.[46] In the current study, a composite metabolic score was found to be associated with prostate cancer death, and the only previous study on this topic was very small (total of 34 deaths from prostate cancer) and reported a nonsignificant increase in risk among men with metabolic syndrome.[49]

The association between metabolic factors and the risk of prostate cancer differed between calendar periods. We found that for those cases diagnosed before 1997, the associations were stronger than among cases diagnosed after that date. For comparison, 1 previous study regarding cases diagnosed before 1998 also found an association between metabolic syndrome and prostate cancer,[50] whereas another study on cases diagnosed between 1995 and 2005 found no such association[17]; other studies have investigated cases diagnosed both before and after 1997 with inconsistent results.[16,18-20,50,51] We chose 1997 as the cutoff date because after that date there was a distinct increase in the incidence of prostate cancer noted in Sweden,[25,26] and an ongoing increase in Norway[27] and Austria.[28] We speculate that these differences in associations are because of a different case mix during the 2 time periods (with a larger percentage of low-risk cases diagnosed after 1997), which was found with the help of improved detection methods (use of prostate-specific antigen). Conversely, a larger percentage of cases with advanced disease were diagnosed before 1997, for which there was a stronger association with metabolic risk factors. No effect for calendar time was found on the risk of death from prostate cancer.

The results of the current study add further evidence to support the hypothesis that high levels of metabolic factors separately or combined are not related to the development of prostate cancer but are related to an increased risk of disease progression, but with no evidence of synergy between the metabolic factors. Thus, from a public health perspective, the data from the current study will add some further motivation to control metabolic factors to decrease the risk of cardiovascular disease, diabetes, and, to some degree, prostate cancer death.

In conclusion, high levels of BMI, blood pressure, blood glucose, triglycerides, cholesterol, and a combination of these factors were not found to be associated with an increased risk of prostate cancer. In contrast, high levels of BMI, blood pressure, and a combination of metabolic factors were associated with a modest increase in the risk of prostate cancer death. No interaction effects between the studied factors were found on the risk of prostate cancer.

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CONFLICT OF INTEREST DISCLOSURES

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