uicc
global cancer control

IJC
International Journal of Cancer

Metabolic syndrome and risk of bladder cancer: prospective cohort study in the metabolic syndrome and cancer project (Me-Can)

Christel Häggström[1], Tanja Stocks[1,2], Kilian Rapp[3], Tone Bjørge[4,5], Björn Lindkvist[6], Hans Concin[7], Anders Engeland[4,5], Jonas Manjer[8], Hanno Ulmer[9], Randi Selmer[5], Steinar Tretli[10], Göran Hallmans[11], Håkan Jonsson[12] and Pär Stattin[1]

[1] Department of Surgical and Perioperative sciences, Urology and Andrology, Umeå University, Umeå, Sweden
[2] Institute of Health Sciences, VU University, Amsterdam, The Netherlands
[3] Institute of Epidemiology, Ulm University, Ulm, Germany
[4] Department of Public Health and Primary Health Care, University of Bergen, Bergen, Norway
[5] Norwegian Institute of Public Health, Oslo/Bergen, Norway
[6] Department of Medicine, Sahlgrenska Academy, Gothenburg, University of Gothenburg, Sweden
[7] Agency for Preventive and Social Medicine, Bregenz, Austria
[8] Department of Surgery, Malmö University Hospital, Malmö, Sweden
[9] Department of Medical Statistics, Informatics and Health Economics, Innsbruck Medical University, Innsbruck, Austria
[10] Institute of Population-based Cancer Research, The Cancer Registry of Norway, Oslo, Norway
[11] Department of Public Health and Clinical Medicine, Nutritional Research, Umeå University, Umeå, Sweden
[12] Department of Radiation Sciences, Oncology, Umeå University, Umeå, Sweden

There are little data on the putative association between factors in the metabolic syndrome (MetS) and risk of bladder cancer. In the Metabolic Syndrome and Cancer project (Me-Can), measurements of height, weight, blood pressure and circulating levels of glucose, cholesterol, and triglycerides had been collected from 578,700 subjects in cohorts in Norway, Austria, and Sweden. We used Cox proportional hazard models to calculate relative risks (RRs) of bladder cancer by exposures divided into quintiles, in categories according to the World Health Organisation (WHO) and as a continuous standardized variable (z-score with mean = 0 and standard deviation = 1) for each separate component and its standardized sum, a composite MetS score. RRs were corrected for random error in measurements. During a mean follow-up of 11.7 years (SD = 7.6), 1,587 men and 327 women were diagnosed with bladder cancer. Significant associations with risk were found among men per one unit increment of z-score for blood pressure, RR = 1.13 (95% CI 1.03–1.25), and the composite MetS score, RR = 1.10 (95% CI 1.01–1.18). Among women, glucose was nonsignificantly associated with risk, RR = 1.41 (95% CI 0.97–2.06). No statistically significant interactions were found between the components in the MetS in relation to bladder cancer risk. Hypertension and a composite MetS score were significantly but modestly associated with an increased risk of bladder cancer among men and elevated glucose was associated with a nonsignificant increase in risk among women.

Epidemiology

Every year, around 360,000 men and women are diagnosed with bladder cancer, and the highest incidence is found in Europe and North America,[1] continents with high prevalence of the metabolic syndrome (MetS).[2,3] MetS is a constellation of factors related to insulin resistance including obesity, impaired glucose tolerance, dyslipidemia, and hypertension[4] and has consistently been associated with an increased risk of cardiovascular diseases and diabetes type 2[5,6] and also recently to risk of cancer at some sites.[7–10]

There are little data on the association between the MetS and risk of bladder cancer, for separate components as well as for MetS factors combined.[7,9,11–28] The association between

Key words: epidemiology, bladder cancer, metabolic syndrome, cohort study

Abbreviations: BMI: body mass index; CONOR: cohort of Norway; ICD: international statistical classification of diseases; 40-y: age 40-program; Me-Can: metabolic syndrome and cancer project; MetS: metabolic syndrome; MPP: Malmö preventive project; NCS: Norwegian counties study; Oslo: Oslo study I cohort; RDR: regression dilution ratio; RR: relative risk; SD: standard deviation; VHM&PP: Vorarlberg health monitoring and prevention programme; VIP: Västerbotten intervention project; WHO: World Health Organization

Grant sponsor: The World Cancer Research Fund; **Grant number:** 2007/09; **Grant sponsor:** The Swedish Cancer Foundation; **Grant number:** 2007/693

DOI: 10.1002/ijc.25521

History: Received 5 Mar 2010; Accepted 27 May 2010; Online 21 Jun 2010

Correspondence to: Christel Häggström, Department of Surgical and Perioperative Sciences, Urology and Andrology, Umeå University, 901 85 Umeå, Sweden, Fax: +46-90-125396, E-mail: christel.haggstrom@urologi.umu.se

body mass index (BMI) and bladder cancer has been inconsistent. Some studies have shown an increased risk for high levels of BMI,[16,18,24] one study reported a decreased risk[16] and several studies have reported no significant association.[7,11,12,17,19,21,23,24,27] A few smaller studies (n cases < 500) on hypertension,[14,22] cholesterol,[15,20,25] and bladder cancer risk have reported inconsistent associations. Two large studies have investigated glucose levels in relation to risk of bladder cancer, one reported an association with fatal bladder cancer among men (no data reported for women),[9] whereas a recent a study from the Me-Can project showed an association between high glucose and risk of bladder cancer among women.[10]

The aim of this study was to investigate the association between components in the MetS, in single and jointly, with risk of bladder cancer in a large prospective cohort.

Material and Methods

Study population

This study was conducted within the Metabolic syndrome and Cancer project (Me-Can), which has recently been described in detail.[29] In brief, the Me-Can project consists of seven different cohorts, from Norway; the Oslo study I cohort (Oslo), Norwegian Counties Study (NCS), Cohort of Norway (CONOR) and Age 40-program (40-y), Sweden; Västerbotten Intervention Project (VIP) and Malmö Preventive Project (MPP) and Austria; Vorarlberg Health Monitoring and Prevention Programme (VHM & PP). In total, 578,700 subjects were included in the study with prospectively collected data on body mass index (BMI, weight/height^2; kg/m^2), systolic and diastolic blood pressure, and circulating levels of glucose, cholesterol, and triglycerides from one or several health examination(s). The study was approved by a Research Ethics Committee in each country.

Endpoints

Incident cancers were identified through linkages with each National Cancer Registry. The International Classification of Diseases, seventh revision (ICD-7) code 181 was used for identification of bladder cancer. The cause of death was obtained by linkage to each National Cause of Death Registry. In Norway and Sweden, data were also linked to the Registry of Total Population and Population Changes for assessment of vital status (data not available in Austria). To reduce the probability of reverse causation, we excluded subjects with a cancer diagnosis before the baseline examination, and follow-up in all risk calculations started at the date of 1 year after baseline examination.

Statistical methods

Risk was analysed with Cox proportional hazards regression with age as time scale. Subjects were followed until the date of event, that is, cancer diagnosis or cancer death, or until censoring at the date of death from any cause, emigration, or end of follow-up, whichever occurred first. Hazard ratios calculated from the regression analysis are denoted as relative risks (RRs).

We calculated RRs for quintiles of exposure, for predefined categories according to the World Health Organisation (WHO)[30,31] as well as for exposures transformed to standard scores (z-scores).

BMI and blood pressure were divided into quintiles separately for cohort and sex, whereas glucose, triglycerides, and cholesterol were divided into quintiles separately for cohort, sex, and fasting time. Fasting time before the health examination was categorized into the following groups; less than 1 hour, 1–2 hours, 2–4 hours, 4–8 hours, and more than 8 hours. RRs for each exposure in quintiles were calculated with the lowest quintile as reference. We used the mean value within each quintile in tests of linear trend and treated the means as a continuous variable in the Cox model. Quintile analyses were stratified by cohort and adjusted for smoking status (current, non, or exsmoker), five categories of birth date (before 1927, 1927–1929, 1930–1932, 1933–1938, 1939 and later), age at measurement and BMI in quintiles (except for BMI).

We also calculated RRs in groups according to cut-offs as defined by WHO[32,33] for BMI (overweight $\geq$ 25 kg/m^2, obesity $\geq$ 30 kg/m^2), systolic blood pressure (hypertension $\geq$ 140 mmHg), and diastolic blood pressure (hypertension $\geq$90 mmHg). We assessed the proportion of subjects who had glucose levels defined as impaired fasting glucose (6.1–6.9 mmol/l) and diabetes ($\geq$ 7.0 mmol/l) among subjects who had fasted $>$ 8 hours prior to blood draw, and subsequently selected the same proportions of subjects among those who had shorter fasting time, to use the full data set. In this analysis, and the analyses of WHO categories, we stratified and adjusted the Cox models as in the quintile analysis.

To convert the exposures to the same scale, we transformed the original values to standardized variables (z-scores) with zero as mean and one as standard deviation. The z-score was 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. BMI and blood pressure were transformed into z-scores separately for cohort and sex, and glucose, triglycerides, and cholesterol were transformed to z-scores separately for cohort, sex, and fasting time. As the distribution of glucose and triglycerides was skewed, natural logarithm was applied before z-score transformation. We stratified the Cox model by cohort and adjusted for smoking status, five categories of birth date and age at measurement. As a second approach we analysed a model additionally adjusted for all individual z-scores. Blood pressure was calculated by (systolic + diastolic blood pressure)/2, to avoid colinearity in the model. A composite MetS variable was finally computed, separately within each cohort, sex, and fasting time, as the transformed sum of all z-scores. The MetS variable was used in a separate Cox model stratified for cohort and adjusted for smoking, five categories of birth date, and age at measurement.

The proportional hazard assumption was tested with Schoenfeld residuals for all covariates including date of birth

(five categories, before 1927, 1927–1929, 1930–1932, 1933–1938, 1939 and later), categories of smoking (current/non/exsmoker) and age at measurement in addition to all exposure variables as z-scores, and we found no violation of the assumption.

We used the Wald test to test for interaction between pair wise exposures and between exposures and smoking, for both incident and fatal bladder cancer as endpoint. In these tests, we adjusted the significance level for multiple testing with the Bonferroni correction.[32] To further investigate smoking as an effect modifier, we analysed z-scores in strata of smoking status.

Correction for random errors

We corrected RRs for random error, that is, measurement error and within-person variability, by use of methods based on regression dilution ratio (RDR), similar to those described by Wood *et al.*[33] We used two methods for correction; direct adjustment of the estimated parameter using the estimated RDR and regression calibration. The calculations were based on data from subjects who had undergone repeated measurements in Me-Can, in total data from 133,820 subjects and 406,364 health examinations.

RDR was estimated as the regression coefficient in the regression models with the repeated measurement as dependent variable and the baseline measurement as independent variable. Age at baseline, fasting time, smoking status, sex, birth year, BMI, time from date of baseline examination were included as fixed effects in the model and cohort was included as random effect. We used RDR in analysis of quintiles, WHO categories and for univariate analysis of z-scores. In our data set, RDR was for BMI 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.[34–36] The correction was applied by dividing the regression coefficient computed by the Cox model with RDR for the exposure, $RR_{corrected} = e^{\log(RRoriginal)/RDR}$.

In the multivariate analysis of z-scores, we replaced the original z-score with a calibrated z-score calculated by regression calibration in a similar mixed linear model.[37] As the Cox model included adjustment for all individual z-scores, except the composite MetS z-score, the model used for prediction was additionally adjusted for these z-scores as fixed independent variables. RDR and regression calibration were predicted at half of the mean follow up time, that is, 6 years after baseline examination.

All statistical tests in the study were two-sided, and p-values lower than 0.05 were considered as statistically significant. Calculations were performed with STATA version 10.1, and R version 2.7.2 was used for random error calculations.

Results

Mean age at baseline examination was 44 years (SD = 11.7), 11% of the study subjects were obese (BMI $\geq$ 30kg/m^2) and 32% had hypertension (systolic blood pressure $\geq$ 140 mmHg or diastolic blood pressure $\geq$ 90 mmHg) (**Table 1**). Half of the subjects had fasted more than 8 hours prior to blood draw (n = 278,300), 8% of men and 6% of women among those subjects had impaired fasting glucose according to the WHO definition (6.1–6.9 mmol/l), 4% of men and 3% of women had glucose levels in the diabetic range ($\geq$ 7.0 mmol/l). The percentages of current smokers were 30% among men and 25% among women. During a mean follow up time of 12 years (SD = 7.6), bladder cancer was diagnosed in 1,587 men and 327 women, and 216 men and 58 women died of bladder cancer.

In analyses of the exposures in quintiles, we found a significant trend for an increase in risk by increasing levels of systolic blood pressure among men, top vs. bottom quintile RR = 1.31 (95% CI 0.95–1.80, p_{trend} = 0.02) and diastolic blood pressure RR = 1.29 (95% CI 0.90–1.85, p_{trend} = 0.03) (**Table 2**). Among women, no statistically significant association with risk for any of the exposures was found (**Table 3**).

In analyses of the exposures in categories according to the WHO, increases in risk were found among men for systolic blood pressure, above vs. below 140 mmHg, RR = 1.42 (95% CI 1.15–1.74), and diastolic blood pressure, above vs. below 90 mmHg, RR = 1.29 (95% CI 1.04–1.60). We also found an association with risk for men with impaired fasting glucose levels, RR = 1.96 (95% CI 1.14–3.36), uncorrected RR = 1.22 (95% CI 1.04–1.43) but no increased risk for men with diabetic levels of glucose, RR = 0.58 (95% CI 0.24–1.43). Among women, we found an increase in risk for diabetic levels of glucose, RR = 6.94 (95% CI 1.67–28.75), that uncorrected was RR = 1.77 (95% CI 1.16–2.68). In contrast, a nonsignificant decrease was observed for women with impaired glucose levels, RR = 0.55 (95% CI 0.12–2.54).

In analyses for exposures transformed to z-scores, calculated per one unit increase, blood pressure, RR = 1.13 (95% CI 1.03–1.25) and the composite MetS score, RR = 1.09 (95% CI 1.01–1.18) were associated with risk among men, and among women the strongest risk factor was glucose, RR = 1.41 (95% CI 0.97–2.06), in the multivariate approach taking all single factors into account in the model (**Table 4**).

In analysis, the 274 cases of fatal bladder cancer as endpoint, the multivariate approach of z-scores resulted in a significant association among men for blood pressure with risk, RR = 1.34 (95% CI 1.06–1.69). No other factor was significantly associated with the risk of fatal bladder cancer.

Current smokers had a strongly increased risk compared to nonsmokers, both for men, uncorrected RR = 2.74 (95% CI 2.38–3.17) and for women, RR = 3.51 (95% CI 2.67–4.61). The risk was also increased for ex-smokers, among men RR = 2.56 (95% CI 1.33–1.83), and among women RR = 2.38 (95% CI 1.69–3.34). We found no difference in risk for the single exposures or the composite MetS score in strata of smoking status and formal test showed no significant interaction across strata. Among separate exposures, we

Table 1. Baseline characteristics for subjects in metabolic syndrome and cancer project (Me-Can)

	Men N (%)	Women N (%)
Subjects	289,866 (50.1)	288,834 (49.9)
Person-years (incident cancer)	3,325,710	2,892,451
Cohort		
Norway:		
Oslo	1,676 (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)
Age at measurement (years)		
<40	82,913 (28.6)	85,92 (29.8)
40–44	101,476 (35.0)	101,609 (35.2)
45–49	43,136 (14.9)	27,661 (9.6)
50–54	18,521 (6.4)	21,262 (7.4)
≥55	43,82 (15.1)	52,382 (18.1)
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)[1]		
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)[2]		
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[3]		
Fasting ≤8 hours	151,279 (52.2)	149,121 (51.6)
Fasting >8 hours, Normal	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)
Follow-up (years)		
1–4	37,814 (13.1)	37,673 (13.1)
5–9	113,016 (39.2)	123,798 (43.1)
10–14	65,677 (22.8)	74,278 (25.9)
15–20	18,888 (6.6)	22,853 (8.0)
>20	52,675 (18.3)	28,718 (10.0)

[1]Definitions according to WHO overweight 25–30 kg/m^2, obese >30 kg/m^2. [2]Systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg. [3]Impaired fasting glucose ≥ 6.1 mmol/l, diabetes ≥ 7.0 mmol/l.

Table 2. Relative risks of bladder cancer for quintiles of exposures among **men** in the metabolic syndrome and cancer project (Me-Can)

Exposure	Quintile	Mean (SD)	*n* cases	RR (95% CI)	P_{trend}
BMI	1	21.5 (1.3)	269	1.00	0.35
	2	23.8 (0.8)	302	1.06 (0.89–1.28)	
	3	25.4 (0.8)	316	1.06 (0.88–1.26)	
	4	27.1 (0.9)	303	0.97 (0.80–1.16)	
	5	30.8 (2.8)	334	1.13 (0.94–1.35)	
Systolic Blood Pressure	1	112.2 (6.2)	225	1.00	0.02
	2	122.8 (3.5)	205	0.88 (0.62–1.27)	
	3	129.7 (4.0)	325	0.94 (0.68–1.31)	
	4	138.7 (3.9)	307	1.04 (0.74–1.45)	
	5	157.1 (13.3)	458	1.31 (0.95–1.80)	
Diastolic Blood Pressure	1	66.4 (5.2)	211	1.00	0.03
	2	74.3 (3.4)	283	0.99 (0.69–1.41)	
	3	80.2 (2.7)	320	0.99 (0.69–1.41)	
	4	86.2 (3.4)	338	1.26 (0.88–1.81)	
	5	97.0 (7.7)	370	1.29 (0.90–1.85)	
Glucose	1	4.2 (0.5)	268	1.00	0.22
	2	4.8 (0.3)	280	1.18 (0.65–2.17)	
	3	5.1 (0.3)	260	1.02 (0.55–1.90)	
	4	5.5 (0.4)	355	1.45 (0.81–2.59)	
	5	6.9 (2.0)	359	1.36 (0.76–2.45)	
Cholesterol	1	4.3 (0.5)	212	1.00	0.93
	2	5.1 (0.3)	315	1.23 (0.94–1.60)	
	3	5.7 (0.3)	288	0.92 (0.70–1.20)	
	4	6.3 (0.3)	326	0.99 (0.76–1.29)	
	5	7.4 (0.8)	382	1.08 (0.83–1.40)	
Triglycerides	1	0.8 (0.2)	238	1.00	0.36
	2	1.2 (0.2)	290	1.09 (0.78–1.54)	
	3	1.5 (0.3)	317	1.15 (0.82–1.62)	
	4	2.1 (0.4)	321	1.15 (0.82–1.62)	
	5	3.7 (1.7)	323	1.20 (0.85–1.70)	

Cox regression models were adjusted for smoking, five categories of birth year, age at measurement and quintiles of BMI (except for BMI) and stratified for cohort. Regression dilution ratio was used for random error correction, could be transformed back to original data by: $RR_{original} = e^{log(RRcorrected)*RDR}$. RDR for BMI = 0.902, systolic blood pressure = 0.525, diastolic blood pressure = 0.513, glucose (log) = 0.278, cholesterol = 0.657, and triglycerides (log) = 0.505.

found no significant pair-wise interactions after Bonferroni adjustment of the significance level.

Discussion

In this prospective cohort with almost 2,000 incident bladder cancer cases, high blood pressure and a composite MetS score including BMI, blood pressure, glucose, cholesterol, and triglycerides, were significantly although modestly associated with an increased risk among men. Among women, our data suggested that high levels of glucose levels were associated with risk. We found no evidence for synergy between factors in the MetS on the association with bladder cancer.

Among men, high blood pressure was consistently associated with risk in all three statistical approaches. Previous studies were based on much smaller study populations,[14,22,38] the largest study to date was based on 69 cases and reported no association.[14] Little is known about possible pathways between hypertension and cancer.[39]

Among women, the strongest risk factor was elevated glucose levels, although our findings were borderline significant. Previous cohort studies have investigated the association between glucose levels and risk,[9,10,40] one study did not report results for women,[9] another study found a significant increase in risk for diabetic women.[40] The third study was conducted within the Me-Can project and

Table 3. Relative risks of bladder cancer for quintiles of exposures among **women** in the metabolic syndrome and cancer project (Me-Can)

Exposure	Quintile	Mean (SD)	*n* cases	RR (95% CI)	P_{trend}
BMI	1	20.0 (1.2)	51	1.00	0.34
	2	22.3 (0.8)	60	1.00 (0.66–1.51)	
	3	24.1 (0.8)	70	1.00 (0.67–1.50)	
	4	26.4 (1.0)	56	0.67 (0.44–1.03)	
	5	31.7 (3.6)	72	0.87 (0.58–1.32)	
Systolic Blood Pressure	1	103.9 (5.7)	30	1.00	0.94
	2	114.2 (3.3)	47	1.14 (0.48–2.74)	
	3	122.5 (3.0)	64	1.46 (0.63–3.36)	
	4	133.2 (4.8)	66	1.11 (0.47–2.60)	
	5	155.7 (16.1)	101	1.12 (0.48–2.60)	
Diastolic Blood Pressure	1	61.3 (4.8)	42	1.00	0.85
	2	70.1 (3.1)	48	0.77 (0.33–1.78)	
	3	77.1 (3.5)	72	0.78 (0.35–1.71)	
	4	82.8 (4.7)	71	0.93 (0.42–2.05)	
	5	92.8 (8.4)	75	0.81 (0.37–1.81)	
Glucose	1	4.1 (0.5)	47	1.00	0.19
	2	4.6 (0.3)	44	0.90 (0.21–3.98)	
	3	5.0 (0.3)	58	0.82 (0.21–3.29)	
	4	5.3 (0.3)	68	1.94 (0.50–7.46)	
	5	6.5 (1.6)	91	1.86 (0.51–6.77)	
Cholesterol	1	4.2 (0.4)	38	1.00	0.80
	2	4.9 (0.2)	43	0.77 (0.39–1.50)	
	3	5.5 (0.3)	55	0.76 (0.40–1.45)	
	4	6.1 (0.3)	69	0.78 (0.42–1.45)	
	5	7.3 (0.9)	103	0.92 (0.50–1.67)	
Triglycerides	1	0.6 (0.1)	51	1.00	0.55
	2	0.9 (0.1)	39	0.26 (0.11–0.60)	
	3	1.1 (0.1)	60	0.48 (0.22–1.01)	
	4	1.5 (0.2)	64	0.42 (0.20–0.90)	
	5	2.5 (1.1)	89	0.62 (0.30–1.31)	

Cox regression models were adjusted for smoking, five categories of birth year, age at measurement and quintiles of BMI (except for BMI) and stratified for cohort. Regression dilution ratio was used for random error correction, could be transformed back to original data by: $RR_{original} = e^{log(RRcorrected)*RDR}$. RDR for BMI = 0.902, systolic blood pressure = 0.525, diastolic blood pressure = 0.513, glucose (log) = 0.278, cholesterol = 0.657, triglycerides (log) = 0.505.

reported a statistically significantly increased risk among women, RR = 1.45 (1.05–2.01) per mmol increment of glucose.[10] Compared to our current data set, a slightly different selection of data was used in that study, as one of the Norwegian cohorts was entirely excluded because of restrictions of the Norwegian data. Previously, a meta-analysis[41] and some cohort studies[13,19,27,42] have investigated the association between prevalent diabetes and bladder cancer. All these studies reported an increased risk for both men and women, but only in some of these studies did the results reach statistical significance. A possible pathway between diabetes and bladder cancer risk is the increased incidence of urinary tract infections among diabetic subjects, in particular among women.[43,44]

We found no significant associations between serum levels of cholesterol and triglycerides and risk. These exposures have previously been studied in much smaller cohorts.[15,20,25] The largest study to date (303 cases) reported a small nonsignificant decrease in risk for high cholesterol levels.[15] To the best of our knowledge, no previous studies have examined triglyceride levels in relation to bladder cancer risk, but triglyceride levels have been linked to risk of cancer at other sites in some studies, for example, colon and breast.[45]

Table 4. Relative risks of bladder cancer for z-scores of exposures separately and combined among **men** and **women** in the metabolic syndrome and cancer project (Me-Can)

	RR (95% CI)[1]	RR (95% CI)[2]
Men		
BMI	1.03 (0.97–1.09)	0.97 (0.90–1.05)
Blood pressure	1.15 (1.05–1.26)	1.13 (1.03–1.25)
Glucose (log)	1.03 (0.86–1.24)	0.97 (0.80–1.18)
Cholesterol	1.02 (0.94–1.10)	0.97 (0.88–1.06)
Triglycerides (log)	1.11 (1.00–1.23)	1.11 (0.97–1.26)
MetS	1.10 (1.01–1.18)	
Women		
BMI	0.90 (0.79–1.04)	0.86 (0.73–1.01)
Blood pressure	0.89 (0.72–1.10)	0.87 (0.69–1.09)
Glucose (log)	1.36 (0.95–1.96)	1.41 (0.97–2.06)
Cholesterol	0.91 (0.76–1.09)	0.91 (0.75–1.11)
Triglycerides (log)	1.03 (0.82–1.30)	1.08 (0.81–1.43)
MetS	0.95 (0.79–1.14)	

[1]Cox regression models were adjusted for smoking, five categories of birth year, age at measurement, and stratified for cohort. Regression dilution ratio was used for random error correction, could be transformed back to original data by: $RR_{original} = e^{log(RRcorrected)*RDR}$. RDR for BMI = 0.902, Blood Pressure = 0.544, Glucose (log) = 0.278, Cholesterol = 0.657, Triglycerides (log) = 0.505, MetS = 0.688. [2]Cox regression models were adjusted for all single exposures, smoking, five categories of birth year, age at measurement, and stratified for cohort using z-scores corrected for random errors by regression calibration.

No association was found between increasing levels of BMI and risk. Previous studies on BMI and bladder cancer risk have yielded inconsistent results, some studies have shown an increased risk,[16,18,24] one study reported a decreased risk[28] and several studies have reported no significant association.[7,11,12,17,19,21,23,24,27] The largest study to date, a cohort of US male veterans with 20,000 cases of bladder cancer, reported a significantly but modestly increased risk among white obese men but not among black obese men. However, in that study no adjustment was done for smoking.[24] Studies on the association between obesity and risk of fatal bladder cancer have reported no statistically significant associations.[7,11]

We found a significantly increased risk of bladder cancer for men with a high score of the composite variable MetS, whereas no such association was observed among women. Our study includes 30 times as many cases as the previous study on MetS and bladder cancer risk[26] and that study included 60 cases and compared incidence rates for subjects with the MetS defined by use of antihypertensive, serum lipid lowering, and antidiabetic drugs, and reported nonsignificantly increased risk among men, and no increased risk among women.

Smoking is an established risk factor for bladder cancer and we found a more than two-fold increase in risk for smokers in line with previous findings,[46] but formal test of interaction indicated no differences across strata of smoking status. We also adjusted for smoking status in our multivariate analyses of metabolic factors and bladder cancer risk. However, as a result of the crude classification of smoking, which was grouped as current, ex-smokers, or never-smokers, some residual confounding likely remained.[47]

We corrected risk estimates for random errors in analysis of exposures in quintiles, in categories defined by the WHO, and in z-scores. BMI is measured with a small random error whereas blood pressure, glucose, cholesterol, and triglycerides all have high random error in measurements.[34,36] If random errors are not accounted for, risk estimates will be underestimated for these factors because of regression dilution. By transforming the exposures to z-scores, we were able to compare them with each other on the same scale. We used the z-scores as continuous variables assuming a linear increase in risk for increasing metabolic dysregulation, and also to take advantage of the full spectrum of each exposure. By taking all factors into account in the model, we could analyse which single exposure that made the largest contribution to risk.

The main strength of our study is the large data set from seven prospective cohorts, repeated measurements of exposures in a large proportion of the subjects, data from high quality cancer registries with almost complete coverage of cases,[40,48,49] and data from cause of death registries that gave us high power to detect even quite modest associations. We tested our hypothesis using three different statistical models; in quintiles, in categories according to definitions by the WHO, and by use of standard scores with the same range for all exposures. Analyses included adjustment for smoking status and the large number of repeated measurements allowed us to correct for random error for each exposure. Our study also had some weaknesses. The slight differences in measurement methods in the cohorts[29] is a limitation that we tried to overcome by using cohort specific cut-points in analysis of exposures by quintiles and by standardization with z scores, and we also stratified for cohort in our analyses. The crude classification of smoking status is another limitation that likely resulted in some residual confounding.

In conclusion, in this large prospective study, a composite score of the MetS was associated with a significant although modest increase in risk of bladder cancer in men. Among separate components in MetS, high blood pressure was significantly associated with risk among men and for high glucose there was a nonsignificant increase in risk among women. Our data suggest that metabolic aberrations related to the MetS, which are known to increase risk of several other types of cancer, also modestly increase the risk of bladder cancer. We found no indication of a synergetic effect between factors in the MetS on risk of bladder cancer.

Acknowledgements

The author thank the screening team at the former National Health Screening Service of Norway, now the Norwegian Institute of Public Health, the contributing research centers delivering data to CONOR; in the VHM&PP, Elmar Stimpfl, data base manager, Karin Parschalk at the cancer registry, and Elmar Bechter and Hans-Peter Bischof, physicians at the Health Department of the Vorarlberg State Government; in the VIP, Åsa Ågren, database manager at the Medical Biobank, Umeå University, Sweden; and in the MPP, Anders Dahlin, data base manager.

References

1. Parkin D, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005;55:74–108.
2. Cameron A, Shaw J, Zimmet P. The metabolic syndrome: prevalence in worldwide populations. *Endocrinol Metab Clin North Am* 2004;33:351–75.
3. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. *JAMA* 2002;287:356–9.
4. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet* 2005;365: 1415–28.
5. Lakka HM, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J, Salonen JT. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA* 2002;288: 2709–16.
6. Ninomiya JK, L'Italien G, Criqui MH, Whyte JL, Gamst A, Chen RS. Association of the metabolic syndrome with history of myocardial infarction and stroke in the Third National Health and Nutrition Examination Survey. *Circulation* 2004;109: 42–6.
7. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med* 2003;348:1625–38.
8. Bergstrom A, Pisani P, Tenet V, Wolk A, Adami H. Overweight as an avoidable cause of cancer in Europe. *Int J Cancer* 2001;91:421–30.
9. Jee SH, Ohrr H, Sull JW, Yun JE, Ji M, Samet JM. Fasting serum glucose level and cancer risk in Korean men and women. *JAMA* 2005;293:194–202.
10. Stocks T, Rapp K, Bjorge T, Manjer J, Ulmer H, Selmer R, Lukanova A, Johansen D, Concin H, Tretli S, Hallmans G, Jonsson H, et al. Blood glucose and risk of incident and fatal cancer in the metabolic syndrome and cancer project (Me-Can): analysis of six prospective cohorts. *PLoS Med* 2009;6:e1000201.
11. Batty GD, Shipley MJ, Jarrett RJ, Breeze E, Marmot MG, Smith GD. Obesity and overweight in relation to organ-specific cancer mortality in London (UK): findings from the original Whitehall study. *Int J Obes* 2005;29:1267–74.
12. Cantwell MM, Lacey JV, Jr., Schairer C, Schatzkin A, Michaud DS. Reproductive factors, exogenous hormone use and bladder cancer risk in a prospective study. *Int J Cancer* 2006;119:2398–401.
13. Coughlin SS, Calle EE, Teras LR, Petrelli J, Thun MJ. Diabetes mellitus as a predictor of cancer mortality in a large cohort of US adults. *Am J Epidemiol* 2004;159: 1160–7.
14. Grove JS, Nomura A, Severson RK, Stemmermann GN. The association of blood pressure with cancer incidence in a prospective study. *Am J Epidemiol* 1991; 134:942–7.
15. Hiatt RA, Fireman BH. Serum cholesterol and the incidence of cancer in a large cohort. *J Chronic Dis* 1986;39:861–70.
16. Holick CN, Giovannucci EL, Stampfer MJ, Michaud DS. Prospective study of body mass index, height, physical activity and incidence of bladder cancer in US men and women. *Int J Cancer* 2007;120:140–6.
17. Jee SH, Yun JE, Park EJ, Cho ER, Park IS, Sull JW, Ohrr H, Samet JM. Body mass index and cancer risk in Korean men and women. *Int J Cancer* 2008;123:1892–6.
18. Koebnick C, Michaud D, Moore SC, Park Y, Hollenbeck A, Ballard-Barbash R, Schatzkin A, Leitzmann MF. Body mass index, physical activity, and bladder cancer in a large prospective study. *Cancer Epidemiol Biomarkers Prev* 2008;17: 1214–21.
19. Larsson SC, Andersson SO, Johansson JE, Wolk A. Diabetes mellitus, body size and bladder cancer risk in a prospective study of Swedish men. *Eur J Cancer* 2008;44: 2655–60.
20. Morris DL, Borhani NO, Fitzsimons E, Hardy RJ, Hawkins CM, Kraus JF, Labarthe DR, Mastbaum L, Payne GH. Serum cholesterol and cancer in the Hypertension Detection and Follow-up Program. *Cancer* 1983;52:1754–9.
21. Reeves GK, Pirie K, Beral V, Green J, Spencer E, Bull D. Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study. *BMJ* 2007;335:1134.
22. Rosengren A, Himmelmann A, Wilhelmsen L, Branehog I, Wedel H. Hypertension and long-term cancer incidence and mortality among Swedish men. *J Hypertens* 1998;16: 933–40.
23. Samanic C, Chow WH, Gridley G, Jarvholm B, Fraumeni JF, Jr. Relation of body mass index to cancer risk in 362,552 Swedish men. *Cancer Causes Control* 2006; 17:901–9.
24. Samanic C, Gridley G, Chow WH, Lubin J, Hoover RN, Fraumeni JF, Jr. Obesity and cancer risk among white and black United States veterans. *Cancer Causes Control* 2004;15:35–43.
25. Schatzkin A, Hoover RN, Taylor PR, Ziegler RG, Carter CL, Albanes D, Larson DB, Licitra LM. Site-specific analysis of total serum cholesterol and incident cancer in the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study. *Cancer Res* 1988;48: 452–8.
26. Russo A, Autelitano M, Bisanti L. Metabolic syndrome and cancer risk. *Eur J Cancer* 2008;44:293–7.
27. Tripathi A, Folsom AR, Anderson KE. Risk factors for urinary bladder carcinoma in postmenopausal women. The Iowa Women's Health Study. *Cancer* 2002;95: 2316–23.
28. Goldbohm R, Balder H, van de Bosch L, Preller L, Schouten L, van den Brandt P. Is body weight associated with risk of bladder cancer? *Proc Am Assoc Cancer Res* 2006; 2006:B226.
29. Stocks T, Borena W, Strohmaier S, Bjorge T, Manjer J, Engeland A, Johansen D, Selmer R, Hallmans G, Rapp K, Concin H, Jonsson H, et al. Cohort Profile: the metabolic syndrome and cancer project (Me-Can). *Int J Epidemiol* 2010;39:660–7.
30. World Health Organisation. Definition, diagnosis and classification of diabetes mellitus and its complications. Report of a WHO consultation. Part 1: Diagnosis and classification of diabetes mellitus. Geneva: World Health Organisation; 1999.
31. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser* 2000;894:i–xii, 1–253.
32. Bland JM, Altman DG. Multiple significance tests: the Bonferroni method. *BMJ* 1995;310:170.
33. Wood AM, White I, Thompson SG, Lewington S, Danesh J. Regression dilution methods for meta-analysis: assessing long-term variability in plasma fibrinogen among 27,247 adults in 15 prospective studies. *Int J Epidemiol* 2006;35:1570–8.
34. Clarke R, Shipley M, Lewington S, Youngman L, Collins R, Marmot M, Peto R. Underestimation of risk associations due to regression dilution in long-term follow-up of prospective studies. *Am J Epidemiol* 1999;150:341–53.
35. Emberson JR, Whincup PH, Morris RW, Walker M, Lowe GD, Rumley A. Extent of regression dilution for established and novel coronary risk factors: results from the British Regional Heart Study. *Eur J Cardiovasc Prev Rehabil* 2004;11: 125–34.
36. Whitlock G, Clark T, Vander Hoorn S, Rodgers A, Jackson R, Norton R, MacMahon S. Random errors in the measurement of 10 cardiovascular risk factors. *Eur J Epidemiol* 2001;17:907–9.
37. Fibrinogen Studies Collaboration. Correcting for multivariate measurement error by regression calibration in meta-analyses of epidemiological studies. *Stat Med* 2009;28:1067–92.

38. Hole DJ, Hawthorne VM, Isles CG, McGhee SM, Robertson JW, Gillis CR, Wapshaw JA, Lever AF. Incidence of and mortality from cancer in hypertensive patients. *BMJ* 1993;306:609–11.
39. Stumpe KO. Hypertension and the risk of cancer: is there new evidence? *J Hypertens* 2002;20:565–7.
40. Rapp K, Schroeder J, Klenk J, Ulmer H, Concin H, Diem G, Oberaigner W, Weiland SK. Fasting blood glucose and cancer risk in a cohort of more than 140,000 adults in Austria. *Diabetologia* 2006;49:945–52.
41. Larsson SC, Orsini N, Brismar K, Wolk A. Diabetes mellitus and risk of bladder cancer: a meta-analysis. *Diabetologia* 2006; 49:2819–23.
42. Inoue M, Iwasaki M, Otani T, Sasazuki S, Noda M, Tsugane S. Diabetes mellitus and the risk of cancer: results from a large-scale population-based cohort study in Japan. *Arch Intern Med* 2006;166:1871–7.
43. Joshi N, Caputo GM, Weitekamp MR, Karchmer AW. Infections in patients with diabetes mellitus. *N Engl J Med* 1999;341: 1906–12.
44. Kantor AF, Hartge P, Hoover RN, Narayana AS, Sullivan JW, Fraumeni JF, Jr. Urinary tract infection and risk of bladder cancer. *Am J Epidemiol* 1984;119: 510–5.
45. Cowey S, Hardy RW. The metabolic syndrome: a high-risk state for cancer? *Am J Pathol* 2006;169:1505–22.
46. Alberg AJ, Kouzis A, Genkinger JM, Gallicchio L, Burke AE, Hoffman SC, Diener-West M, Helzlsouer KJ, Comstock GW. A prospective cohort study of bladder cancer risk in relation to active cigarette smoking and household exposure to secondhand cigarette smoke. *Am J Epidemiol* 2007;165:660–6.
47. Rothman KJ and Greenland S, eds. Modern Epidemiology. Pennsylvania: Lippincott, Williams & Wilkins, 1998. 132–134.
48. Larsen IK, Smastuen M, Johannesen TB, Langmark F, Parkin DM, Bray F, Moller B. Data quality at the Cancer Registry of Norway: an overview of comparability, completeness, validity and timeliness. *Eur J Cancer* 2009;45:1218–31.
49. Sandblom G, Dufmats M, Olsson M, Varenhorst E. Validity of a population-based cancer register in Sweden–an assessment of data reproducibility in the South-East Region Prostate Cancer Register. *Scand J Urol Nephrol* 2003;37: 112–9.