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ORIGINAL PAPER

Components of the metabolic syndrome and risk of prostate cancer: the HUNT 2 cohort, Norway

Richard M. Martin · Lars Vatten · David Gunnell · Pål Romundstad · Tom I. L. Nilsen

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Abstract
Background The metabolic syndrome has been suggested as a unifying link between a "western" lifestyle and an increased prostate cancer risk.
Methods We assessed the associations of components of the metabolic syndrome with prostate cancer in a prospective cohort based on 29,364 Norwegian men followed up for prostate cancer incidence and mortality from 1995–1997 to the end of 2005 in the second Nord Trøndelag Health Study (HUNT 2).
Results During a mean 9.3 years follow-up, 687 incident prostate cancers were diagnosed, and 110 men died from prostate cancer. There was little evidence that baseline BMI, waist circumference, waist–hip ratio, total or HDL-cholesterol, triglycerides, presence of the metabolic syndrome, diabetes, antihypertensive use, or cardiovascular disease were associated with incident or fatal prostate cancer. There was weak evidence that raised blood pressure was associated with an increased risk: for each SD (12 mm) increase in diastolic blood pressure, there was an 8% (95% CI = 1–17%; $p = 0.04$) increased risk of incident prostate cancer.
Conclusions We found little evidence to support the hypothesis that the metabolic syndrome or its components explains higher prostate cancer mortality rates in countries with a "western" diet and lifestyle. The positive association of blood pressure with prostate cancer warrants further investigation.

Keywords Prostate cancer · Metabolic syndrome · Blood pressure · Waist circumference · Waist:hip ratio · Body mass index · Obesity · Total cholesterol · High density lipoprotein cholesterol · Triglycerides

R. M. Martin (✉) · D. Gunnell
Department of Social Medicine, University of Bristol, Bristol BS8 2PR, UK
e-mail: Richard.Martin@bristol.ac.uk

L. Vatten · P. Romundstad
Department of Public Health, Norwegian University of Science and Technology, Trondheim, Norway

L. Vatten
International Agency for Research on Cancer, Lyon, France

T. I. L. Nilsen
Human Movement Science Program, Norwegian University of Science and Technology, Trondheim, Norway

Introduction

Prostate cancer mortality varies widely across the world, being 26-fold greater in the USA compared with China [1]. Identification of any modifiable environmental risk factors that might underlie these large mortality variations [2–5] could point to potentially effective prevention strategies [1]. Since prostate cancer mortality is high in countries characterized as having "westernized" lifestyles, diet and related behavioral exposures have been implicated as key factors [6]. The metabolic syndrome (a clustering of the metabolic risk factors hyperinsulinemia, hypertension, hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol, and abdominal adiposity [7, 8]) has been suggested as a unifying link between a "western" lifestyle and hormonal risk factors for prostate cancer [9, 10], perhaps via the IGF-I signaling pathway [11, 12]. The syndrome affects 25% of adults in the USA and is increasing [13], highlighting the potential growing importance of this exposure.

Hyperinsulinemia and measures of general and central adiposity have been positively associated with aggressive and fatal prostate cancer [10, 14–18], but fewer studies have investigated the other features of the metabolic syndrome. Hypertension [14, 19], lower HDL-cholesterol and raised triglycerides [14, 20], and combinations of metabolic syndrome components [21] have been positively associated with prostate cancer. Knowledge of associations of specific metabolic factors with prostate cancer could suggest novel prevention strategies [22, 23] and alternative biological pathways in prostate carcinogenesis [24, 25]. However, there are null or inconsistent findings with blood pressure [24, 26], total- and HDL-cholesterol [27, 28], central adiposity (waist circumference or waist–hip ratio [29, 30]), triglycerides [28], and other markers of insulin resistance [31, 32]. The limited number of positive studies many of which are based on small datasets suggests the possibility that some observed associations may have been due to chance findings or that publication bias has distorted the literature. We investigated the hypothesis that the following components of the metabolic syndrome are prospectively associated with prostate cancer in the second wave of the Nord Trøndelag Health Study (HUNT 2) (http://www.hunt.ntnu.no/): systolic and diastolic blood pressure, triglycerides, total and high-density lipoprotein (HDL) cholesterol, body mass index, and waist circumference. In secondary analyses, we investigated the hypothesis that the metabolic syndrome (defined, with modification, by the National Cholesterol Education Program's Adult Treatment Panel (ATP) III criteria [33]) is associated with prostate cancer, assessed whether associations differed for advanced and fatal prostate cancer compared with localized disease, and investigated metabolic syndrome components in relation to survival amongst men diagnosed with prostate cancer.

Methods

Study population

Between 1995 and 1997, all residents in Nord-Trøndelag County in Norway aged 20 years or older were invited to participate in the second wave of the Nord-Trøndelag Health Study (HUNT 2). Among 92,936 eligible individuals, 64,943 (69.9%) accepted the invitation, completed questionnaires and attended a clinical examination (30,425 men and 34,518 women). Among the 30,425 men who participated, we excluded 882 men with prevalent cancer at baseline, 126 were excluded due to incomplete information on height or weight, 52 were excluded due to incomplete data on marital status, and one was excluded due to unknown date of participation. This study is therefore based on the follow-up for cancer of 29,364 men. The population in Nord-Trøndelag County (127,000 residents) is stable, with a net out-migration of 0.3% per year (1996–2000) and is ethnically homogenous (less than 3% non-Caucasian).

Baseline data

The study has been described in detail elsewhere (www.hunt.ntnu.no/forskning/metodeartikkel.pdf). Briefly, information was collected on a range of lifestyle and health-related factors, including past medical history, measures of physical activity, smoking, alcohol consumption, marital status, and education. At the clinical examination, standardized anthropometric measurements were conducted by the trained nurses: height was measured to the nearest centimeter; weight to the nearest half kilogram; and waist and hip circumference to the nearest centimeter. Additionally, blood pressure was measured automatically three times at 2-min intervals using a Dinamap 845XT (Critikon). The mean of the second and third reading was used in the analysis of diastolic, systolic, and mean arterial pressure. Finally, a blood sample (non-fasting) was drawn from all the participants, centrifuged at the research clinic, and sent in a cooler to the laboratory, usually on the same day. Serum samples were analyzed for glucose, total cholesterol, HDL-cholesterol, and triglycerides on a Hitachi 911 Auto-analyzer, applying reagents from Boehringer Mannheim. The data were used to derive a binary variable for the presence or absence of the metabolic syndrome in each man, as defined by the ATP III criteria, i.e., men who were above the threshold value for three or more of the following components were classified as having the metabolic syndrome: waist circumference ($\geq$103 cm), triglycerides [$\geq$150 mg/dl ($\geq$1.7 mmol/l)], HDL-cholesterol [<40 mg/dl (<1.04 mmol/l)], and blood pressure (systolic $\geq$ 130 mmHg and/or diastolic $\geq$ 85 mmHg) [33]. Since we did not have fasting glucose levels, we replaced the glucose criteria (fasting glucose $\geq$ 110 mg/dl) with a non-fasting (random) glucose threshold of $\geq$200 mg/dl ($\geq$11.1 mmol/l), which was defined as a positive screen in the health survey. This cut-off for random glucose has also been used in previous studies [34]. Obesity was defined as BMI $\geq$ 30 kg/m^2.

Follow up

The unique 11-digit identity number of Norwegian citizens was used to link individuals from the HUNT Study to information on cancer incidence at the Cancer Registry of Norway. Prostate cancer was registered according to the International Classification of Diseases, seventh edition

(ICD-7, code 177). We also used information from the Cancer Registry on metastasis at the time of diagnosis to classify men, who presented with either localized prostate cancer (defined as no invasion to surrounding tissues/organs, lymph nodes, or distant organs) or advanced prostate cancer (defined as regional or distant metastases) at diagnosis.

Information on deaths, where prostate cancer was registered as the underlying cause, was obtained by linkage to the Cause of Death Registry at Statistics Norway (ICD-9 code: 185; and ICD-10 code: C61).

For the analyses of prostate cancer incidence, each participant contributed person-time from the date of clinical examination until the date of any cancer diagnosis (of any site, not just prostate cancer), death, emigration, or to the end of follow-up till December 31, 2005, whichever occurred first. For the analysis of prostate cancer mortality, participants contributed person-years until death, emigration, or to the end of December 31, 2004. The use of different dates to define the end of follow-up for incidence (2005) and mortality (2004) is because the Cause of Death Registry linkage was not updated as recently as the Cancer Registry linkage at the time of obtaining the linked data for this study.

The study was approved by the Norwegian Data Inspectorate, the Norwegian Board of Health, and by the Regional Committee for Ethics in Medical Research.

Statistical analysis

We used Cox proportional hazards models to compute hazard ratios (HRs) with 95% confidence intervals (CI) for prostate cancer incidence and mortality, where men within quartiles 2–4 of each exposure variable were compared to the reference group of men in the lowest quartile (quartile cut-points were based on the distribution among all men in the study who had available data on a specific variable). Additionally, we calculated standard deviation (SD) scores for the exposure variables and estimated the HR associated with an increase in one SD. Since age is a strong determinant of prostate cancer risk, and individuals entered the study at different ages, we very closely controlled for current age in all models using age as the follow-up time scale in the Cox model [35]. In addition, we adjusted for height in quintiles (since height is independently associated with prostate cancer [36]), smoking status (never, former, current, and unknown), marital status (married, unmarried, widower, and divorced/separated), education (<10, 10–12, and ≥13 years), a recreational physical activity variable [37] (based on responses to questions on hours spent on light and hard activity during 1 week (averaged over a year): no activity; <3 h light activity; 3+ h light or <1 h hard activity; ≥1 h hard activity; unknown), and the International Prostate Symptom Score (no, mild, moderate, severe, and unknown lower urinary tract symptoms). Results for blood pressure were also controlled for the concurrent use of blood pressure medication, although this adjustment made little difference to affect estimates. Trend tests across quartiles of exposure level were calculated using the median value within each category in the Cox model. We examined the associations of the metabolic syndrome and its components with the following outcomes: all incident prostate cancers; whether prostate cancers were localized or advanced at diagnosis; and prostate cancer mortality. We also undertook an analysis restricted to those with incident prostate cancer to assess the associations of the metabolic syndrome and its components with survival (deaths from all causes).

We tested whether age at baseline could modify the association of exposure level with prostate cancer risk by constructing product terms between the exposure categories and age and testing for interaction using the likelihood ratio test. A cut-off value of 70 years of age was chosen to maximize numbers in each stratum. We also checked that the associations were similar in those with and without a history of cardiovascular disease or diabetes at baseline using the likelihood ratio test. In addition, we examined the association of the metabolic syndrome with prostate cancer risk across tertiles of BMI, given the findings of Pischon et al., who observed stronger associations of abdominal adiposity with prostate cancer in men with the lowest BMI tertile [18].

Departure from the proportional hazards assumption was evaluated by Schoenfeld residuals. All statistical tests were two-sided and all analyses were performed using Stata for Windows (Version 10© StataCorp LP, 1985–2007).

Results

The characteristics of the study participants at baseline are presented in Table 1. During a median follow-up of 9.3 years (258,359 person-years), 687 prostate cancers were diagnosed among the 29,364 studied men. We were able to classify 217 of these prostate cancer cases as localized and 136 as advanced at the time of diagnosis (334 were classified as unknown stage). Overall, 2,898 men died during the follow-up period, and of these, 110 (3.8%) men were registered with prostate cancer as the underlying cause of death. There was no evidence of departure from the proportional hazards assumption in the analyses described below.

There was no evidence that BMI, waist circumference, waist–hip ratio, total or HDL-cholesterol, triglyceride levels, random glucose levels, presence of the metabolic syndrome, number of metabolic factors present, or related factors (diabetes, being on blood pressure medication, or a history of cardiovascular disease) were associated with

Table 1 Baseline characteristics of the study population ($n = 29,364$)[a]

Characteristic	Without metabolic syndrome[b] ($n = 22,659$) Mean (SD) or percent (as indicated)	With metabolic syndrome[b] ($n = 6,595$) Mean (SD) or percent (as indicated)
Mean age (years) (SD)	48.0 (16.4)	53.4 (16.3)
Mean height (cm) (SD)	177.3 (6.8)	177.2 (6.8)
Mean body mass index (kg/m^2) (SD)	25.7 (3.0)	29.1 (3.7)
Mean waist circumference (cm) (SD)	89.7 (8.0)	99.4 (9.8)
Mean waist:hip ratio (SD)	0.9 (0.05)	0.9 (0.06)
Mean systolic blood pressure (mmHg) (SD)	137.4 (18.6)	148.3 (17.9)
Mean diastolic blood pressure (mmHg) (SD)	80.5 (11.7)	86.9 (11.2)
Mean arterial pressure (mmHg) (SD)	98.4 (14.2)	106.6 (13.7)
Mean total cholesterol (mmol/l) (SD)	5.7 (1.1)	6.1 (1.1)
Mean HDL-cholesterol (mmol/l) (SD)	1.3 (0.3)	0.9 (0.2)
Mean triglycerides (mmol/l) (SD)	1.6 (0.9)	3.1 (1.5)
Mean non-fasting glucose (mmol/l) (SD)	5.4 (1.2)	6.1 (2.4)
Percent obese[c]	7.7	36.6
Percent on blood pressure medication	9.3	21.3
Percent with diabetes	1.8	6.7
Percent with previous CVD[d]	7.9	14.9
Percent physically inactive[e]	6.7	9.8
Percent married	60.6	65.0
Percent with higher education[f]	20.2	15.1
Percent current smokers	28.9	27.2
Percent with moderate or severe LUTS[g]	10.7	13.2

SD standard deviation, *LUTS* lower urinary tract symptoms

[a] The number with and without metabolic syndrome does not add up to 29,364 due to missing data on 110 men

[b] Metabolic syndrome defined according to the ATP-III criteria [31] [using random glucose ≥200 mg/dl (≥11.1 mmol/l) instead of fasting glucose ≥110 mg/dl]

[c] Obesity defined as body mass index ≥30 kg/m^2

[d] Cardiovascular disease defined as angina pectoris, myocardial infarction, and stroke

[e] Inactivity defined as no leisure time physical activity in an average week

[f] Higher education defined as more than 12 years of education

[g] Moderate or severe level defined as International Prostate Symptom Score of 8–35

incident prostate cancer (Table 2). There was evidence that raised blood pressure levels were associated with an increased risk of prostate cancer. For example, for each SD increase in diastolic blood pressure (i.e., per 12 mmHg), there was an 8% (95% CI = 1–17%) increased risk of incident prostate cancer. Stratifying the outcomes by localized or advanced cancers (Table 3), also suggested largely null associations with prostate cancer by stage. However, there was evidence that for an SD increase in waist circumference (i.e., per 9.4 cm) there was a 16% increased risk of localized prostate cancer (95% CI = 1–32%), whereas there was no association of waist circumference with advanced cancers.

Table 4 suggested little evidence of associations of metabolic risk factors with death from prostate cancer and only a history of previous cardiovascular disease was associated with all-cause mortality in men with prostate cancer (Table 5).

There was no evidence of interaction by age at baseline (<70 or ≥70 years) of associations of components of the metabolic syndrome with prostate cancer risk (e.g., for systolic blood pressure, p for interaction = 0.33; BMI, $p = 0.98$; and for total cholesterol, $p = 0.55$). Associations were similar in those with and without a history of cardiovascular disease at baseline (e.g., for systolic blood pressure, p for interaction = 0.74; BMI, $p = 0.56$; and for total cholesterol, $p = 0.59$). Sensitivity analyses excluding men with baseline diabetes did not materially alter the results, and there was no evidence for interaction with baseline diabetes (e.g., for metabolic syndrome, p for interaction = 0.31; systolic blood pressure, $p = 0.86$; and for total cholesterol, $p = 0.81$). However, there was some

Table 2 Hazard ratios (HR) of incident prostate cancer associated with metabolic risk factors

Variable	No. of person-years	No. of cases	Age-adjusted HR	Fully adjusted[a] HR (95% CI)	*p*-Value[b]
Body mass index (kg/m^2)					
<18.5	879	4	1.44	1.43 (0.53–3.87)	–
18.5–24.9	91,686	220	1.00	1.00 (Reference)	–
25.0–29.9	129,368	362	0.93	0.92 (0.77–1.09)	–
≥30.0	36,426	101	0.87	0.87 (0.69–1.11)	0.19
Body mass index (per SD, 3.5 kg/m^2)	258,359	687	0.98	0.98 (0.91–1.06)	0.64
Waist circumference (cm)					
<87	76,351	120	1.00	1.00 (Reference)	–
87–91	59,900	145	1.08	1.06 (0.83–1.35)	–
92–97	61,665	178	1.02	0.99 (0.79–1.26)	–
≥98	60,034	239	1.07	1.05 (0.83–1.32)	0.77
Waist circumference (per SD, 9.4 cm)	257,950	682	1.00	0.99 (0.92–1.08)	0.87
Waist:hip ratio					
<0.87	68,039	87	1.00	1.00 (Reference)	–
0.87–0.89	66,180	137	1.04	1.03 (0.78–1.34)	–
0.90–0.93	64,754	200	1.07	1.05 (0.82–1.36)	–
≥0.94	58,969	258	1.03	1.02 (0.80–1.31)	0.91
Waist:hip ratio (per SD, 0.06)	257,942	682	0.99	0.99 (0.92–1.07)	0.84
Systolic blood pressure (mmHg)					
<128	68,992	94	1.00	1.00 (Reference)	–
128–137	67,083	123	1.23	1.27 (0.97–1.66)	–
138–150	64,253	150	1.04	1.07 (0.82–1.38)	–
≥151	57,697	319	1.12	1.20 (0.95–1.52)	0.29
Systolic blood pressure (per SD, 19.0 mmHg)	258,025	686	1.03	1.06 (0.99–1.13)	0.11
Diastolic blood pressure (mmHg)					
<75	71,033	99	1.00	1.00 (Reference)	–
75–81	64,690	144	1.09	1.10 (0.85–1.42)	–
82–89	62,456	186	1.16	1.20 (0.94–1.53)	–
≥90	59,844	257	1.18	1.25 (0.99–1.58)	0.05
Diastolic blood pressure (per SD, 11.9 mmHg)	258,023	686	1.06	1.08 (1.01–1.17)	0.04
Mean arterial pressure (mmHg)					
<90	67,167	83	1.00	1.00 (Reference)	–
90–98	68,285	121	1.09	1.13 (0.85–1.49)	–
99–109	63,931	191	1.22	1.28 (0.99–1.66)	–
≥110	57,840	289	1.18	1.27 (0.99–1.63)	0.06
Mean arterial pressure (per SD, 14.5 mmHg)	257,223	684	1.05	1.08 (1.01–1.16)	0.03
Total cholesterol (mmol/l)					
<5.0	69,445	99	1.00	1.00 (Reference)	–
5.1–5.8	69,058	171	1.03	1.03 (0.80–1.31)	–
5.9–6.6	62,270	202	1.10	1.11 (0.88–1.42)	–
≥6.7	57,093	214	1.07	1.10 (0.87–1.40)	0.39
Total cholesterol (per SD, 1.2 mmol/l)	257,866	686	1.03	1.05 (0.97–1.14)	0.24
HDL cholesterol (mmol/l)					
<1.1	78,341	212	1.00	1.00 (Reference)	–
1.1–1.2	69,137	167	0.99	0.99 (0.81–1.22)	–
1.3–1.4	53,170	147	1.12	1.13 (0.91–1.39)	–
≥1.5	57,191	160	0.93	0.93 (0.76–1.14)	0.66
HDL cholesterol (per SD, 0.3 mmol/l)	257,839	686	0.98	0.98 (0.91–1.05)	0.56

Table 2 continued

Variable	No. of person-years	No. of cases	Age-adjusted HR	Fully adjusted[a] HR (95% CI)	*p*-Value[b]
Triglycerides (mmol/l)					
<1.18	66,353	140	1.00	1.00 (Reference)	–
1.18–1.66	63,388	181	1.07	1.07 (0.86–1.34)	–
1.67–2.41	64,033	174	0.98	0.99 (0.79–1.23)	–
≥2.42	64,082	191	1.14	1.16 (0.93–1.45)	0.21
Triglycerides (per SD, 1.3 mmol/l)	257,856	686	1.03	1.04 (0.97–1.12)	0.29
Random blood glucose (mmol/l)					
<4.9	75,757	119	1.00	1.00 (Reference)	–
4.9–5.2	61,387	142	1.04	1.04 (0.81–1.33)	–
5.3–5.8	60,267	186	1.08	1.09 (0.87–1.38)	–
≥5.9	60,455	239	1.01	1.03 (0.82–1.28)	0.95
Random blood glucose (per SD, 1.6 mmol/l)	257,866	686	0.99	0.99 (0.93–1.06)	0.77
Number of metabolic factors present					
0	37,486	50	1.00	1.00 (Reference)	–
1	89,183	232	0.97	1.00 (0.74–1.36)	–
2	72,407	218	1.08	1.14 (0.83–1.55)	–
3	45,365	146	0.99	1.04 (0.75–1.44)	–
4–5	11,729	35	0.71	0.75 (0.47–1.16)	0.58
Metabolic syndrome[c]					
No	199,075	487	1.00	1.00 (Reference)	
Yes	58,355	194	0.91	0.91 (0.77–1.09)	0.31
Diabetes					
No	251,482	648	1.00	1.00 (Reference)	
Yes	6,447	39	0.97	0.98 (0.70–1.36)	0.89
Blood pressure medication					
No	230,027	526	1.00	1.00 (Reference)	
Yes	27,855	160	0.97	0.95 (0.79–1.14)	0.57
Previous cardiovascular disease[d]					
No	237,804	530	1.00	1.00 (Reference)	
Yes	20,094	157	1.05	1.03 (0.85–1.23)	0.79

CI confidence interval, *HDL* high density lipoprotein

[a] Adjusted for age, height (quarters), smoking (never, former, current, and unknown), marital status (married, unmarried, widower, and divorced/separated), education (<10, 10–12, and ≥13 years), physical activity (no activity, <3 h light, ≥3 h light or <1 h hard, ≥1 h hard, and unknown), International Prostate Symptom Score (none, mild, moderate, and severe lower urinary tract symptoms); and blood pressure measures also adjusted for the use of blood pressure medication

[b] For polychotomous variables, the *p*-value is computed from a trend test over the median category value

[c] Metabolic syndrome defined according to the ATP-III criteria [31] [using random glucose ≥200 mg/dl (≥11.1 mmol/l) instead of fasting glucose ≥110 mg/dl]

[d] Cardiovascular disease defined as angina pectoris, myocardial infarction, or stroke

evidence of an interaction of metabolic syndrome with thirds of BMI ($p = 0.03$) [i.e., there was no association of metabolic syndrome with prostate cancer in the lowest third of BMI (HR = 1.03; 95% CI = 0.65–1.64), a positive association in the middle third (HR = 1.32; 95% CI = 0.98–1.77), and an inverse association in the highest third (HR = 0.77; 95% CI = 0.59–0.99)].

Discussion

Major findings

In this large population-based cohort study, we found little evidence that BMI, obesity, waist circumference, waist–hip ratio, total or HDL-cholesterol, triglycerides, presence of

Table 3 Hazard ratios (HR) for localized, advanced, and unstaged prostate cancer associated with metabolic risk factors

Variable	No. of person-years	Localized		Advanced		Unstaged	
		No. of cases	HR[a] (95% CI)	No. of cases	HR[a] (95% CI)	No. of cases	HR[a] (95% CI)
Body mass index (per SD, 3.5 kg/m^2)	258,359	217	1.09 (0.96–1.25)	136	0.98 (0.81–1.17)	334	0.91 (0.82–1.03)
Waist circumference (per SD, 9.4 cm)	257,950	217	1.16 (1.01–1.32)	135	0.98 (0.82–1.18)	330	0.90 (0.80–1.01)
Waist:hip ratio (per SD, 0.06)	257,942	217	1.11 (0.97–1.27)	135	0.99 (0.83–1.18)	330	0.92 (0.82–1.03)
Systolic blood pressure (per SD, 19.0 mmHg)	258,025	217	1.02 (0.90–1.15)	134	1.13 (0.97–1.32)	334	1.05 (0.96–1.16)
Diastolic blood pressure (per SD, 11.9 mmHg)	258,023	217	1.07 (0.93–1.22)	134	1.10 (0.93–1.30)	334	1.09 (0.98–1.21)
Mean arterial pressure (per SD, 14.5 mmHg)	257,223	216	1.07 (0.94–1.21)	134	1.06 (0.90–1.24)	333	1.09 (0.99–1.20)
Total cholesterol (per SD, 1.2 mmol/l)	257,866	217	1.05 (0.91–1.21)	135	0.94 (0.78–1.13)	334	1.09 (0.98–1.22)
HDL cholesterol (per SD, 0.3 mmol/l)	257,839	217	0.92 (0.80–1.05)	135	1.08 (0.92–1.25)	334	0.98 (0.89–1.09)
Triglycerides (per SD, 1.3 mmol/l)	257,856	217	1.07 (0.96–1.20)	135	0.89 (0.72–1.10)	334	1.07 (0.96–1.18)
Random blood glucose (per SD, 1.6 mmol/l)	257,866	217	0.98 (0.87–1.11)	135	0.94 (0.79–1.12)	334	1.01 (0.92–1.11)
Metabolic syndrome[b] (yes versus no)	257,430	217	0.96 (0.71–1.30)	134	0.96 (0.66–1.42)	330	0.87 (0.68–1.12)
Blood pressure medication (yes versus no)	257,882	217	1.06 (0.77–1.46)	135	1.05 (0.70–1.56)	334	0.85 (0.65–1.10)
Previous CVD[c] (yes versus no)	257,898	217	1.05 (0.75–1.48)	136	0.83 (0.53–1.29)	334	1.10 (0.85–1.42)

CI confidence interval, *HDL* high density lipoprotein, *CVD* cardiovascular disease

[a] Adjusted for age, height (quarters), smoking (never, former, current, and unknown), marital status (married, unmarried, widower, and divorced/separated), education (<10, 10–12, and ≥13 years), physical activity (no activity, <3 h light, ≥3 h light or <1 h hard, ≥1 h hard, and unknown), International Prostate Symptom Score (none, mild, moderate, and severe lower urinary tract symptoms); and blood pressure measures also adjusted for use of blood pressure medication

[b] Metabolic syndrome defined according to the ATP-III criteria [31] [using random glucose ≥200 mg/dl (≥11.1 mmol/l) instead of fasting glucose ≥110 mg/dl]

[c] Cardiovascular disease defined as angina pectoris, myocardial infarction, or stroke

the metabolic syndrome, or related factors (diabetes, antihypertensives, or a history of cardiovascular disease) were associated with the development of incident, advanced, or fatal prostate cancer. There was weak evidence that increasing blood pressure levels may be positively associated with incident prostate cancer.

Strengths and limitations

This analysis has several strengths, including its defined county-wide population base, prospective design, cohort size of almost 30,000 men, follow-up of nearly 10 years, large number of incident prostate cancers, and almost 100% ascertainment of outcomes amongst those with exposure information at baseline.

In many countries, the underlying cause of death is assigned by the national cause of death registries on the basis of physician-completed death certificates, which are known to be unreliable, particularly for long-latency diseases in the elderly such as prostate cancer [38–40]. In Norway, however, the unique 11-digit identity number allows close collaboration between the Cancer Registry and the Cause of Death Registry, such that the underlying cause of death is assigned on the basis of information transferred from the Cancer Registry (year of diagnosis, histology, basis for and certainty of the diagnosis, and extent of disease at time of diagnosis), as well as death certificates, autopsy reports, and queries to physicians [41]. Validation of the prostate cancer data reported to the Cancer Registry has shown over 99% completeness [42] and that there was less than a 1% discrepancy between an underlying cause of death being assigned as prostate cancer from the official mortality statistics and, based on the same information, the underlying causes of death assigned by independent expert review [41]. In this study, only three of the 687 prostate cancers had not been morphologically verified.

Another strength was the ability to undertake analyses by whether cancers were localized or advanced at diagnosis based on whether cases presented with regional or distant metastasis. Since PSA screening is not routine in Norway, the cancers are likely to be largely clinically relevant and associations will not be distorted by the detection due to screening of biologically indolent cancers, which may be etiologically distinct [43].

Limitations of the study include the fact that the numbers of advanced and fatal prostate cancers were small, so we did not obtain precise effect estimates. As in all

Table 4 Hazard ratios (HR) of death from prostate cancer associated with metabolic risk factors

Variable	No. of person-years	No. of prostate cancer deaths	Age-adjusted HR	Fully adjusted[a] HR (95% CI)	*p*-Value
Body mass index (per SD, 3.5 kg/m^2)	238,382	110	1.01	1.01 (0.83–1.24)	0.89
Waist circumference (per SD, 9.4 cm)	237,794	107	0.93	0.91 (0.74–1.12)	0.40
Waist:hip ratio (per SD, 0.06)	237,786	107	0.91	0.91 (0.75–1.11)	0.36
Systolic blood pressure (per SD, 19.0 mmHg)	237,872	109	1.09	1.11 (0.95–1.30)	0.18
Diastolic blood pressure (per SD, 11.9 mmHg)	237,872	109	1.01	1.03 (0.86–1.24)	0.83
Mean arterial pressure (per SD, 14.5 mmHg)	237,872	109	1.02	1.03 (0.88–1.22)	0.70
Total cholesterol (per SD, 1.2 mmol/l)	237,736	110	0.91	0.91 (0.75–1.12)	0.19
HDL cholesterol (per SD, 0.3 mmol/l)	237,712	110	1.03	1.03 (0.87–1.23)	0.67
Triglycerides (per SD, 1.3 mmol/l)	237,727	110	1.05	1.05 (0.86–1.29)	0.63
Random blood glucose (per SD, 1.6 mmol/l)	237,736	110	0.89	0.89 (0.73–1.08)	0.23
Metabolic syndrome[b] (yes versus no)	237,324	107	0.80	0.81 (0.52–1.25)	0.34
Diabetes (yes versus no)	237,772	110	0.65	0.64 (0.26–1.58)	0.34
Blood pressure medication (yes versus no)	237,735	109	0.87	0.87 (0.56–1.36)	0.54
Previous cardiovascular disease[c] (yes versus no)	237,762	110	1.01	1.03 (0.67–1.57)	0.91

CI confidence interval, *HDL* high density lipoprotein

[a] Adjusted for age, height (quarters), smoking (never, former, current, and unknown), marital status (married, unmarried, widower, and divorced/separated), education (<10, 10–12, and ≥13 years), physical activity (no activity, <3 h light, ≥3 h light or <1 h hard, ≥1 h hard, and unknown), International Prostate Symptom Score (none, mild, moderate, and severe lower urinary tract symptoms); and blood pressure measures also adjusted for the use of blood pressure medication

[b] Metabolic syndrome defined according to the ATP-III criteria [31] [using random glucose ≥200 mg/dl (≥11.1 mmol/l) instead of fasting glucose ≥110 mg/dl]

[c] Cardiovascular disease defined as angina pectoris, myocardial infarction, or stroke

observational studies, the possible role of uncontrolled or residual confounding must be considered, but only negative confounding could explain our null results. It seems unlikely, however, that lack of control for ethnicity or family history, the major known risk factors for prostate cancer, would produce observed effect-estimates toward the null because the cohort was ethnically homogeneous and family history of prostate cancer is not known to be associated with insulin resistance. It also seems doubtful that residual confounding by dietary, behavioral, or other factors related to a "western" lifestyle would produce negative confounding, since these variables are likely to be positively associated with both our exposures and (if anything) prostate cancer. Some prostate cancers may not have become clinically evident, given the long-latency natural history of prostate cancer [44]. In the Cancer Registry, 334 (49%) of 687 cancers had unknown metastatic status at the time of diagnosis, and we were thus unable to classify these cases as advanced or localized. However, because there was little evidence of any substantial differences across the three outcome categories compared in Table 3, it is unlikely that complete information on stage would have made much difference to our conclusions. Only non-fasting glucose measures were available, limiting the secondary analysis of the association of our binary classification of the metabolic syndrome with prostate cancer.

Comparison with existing literature

The broadly null findings are in line with several studies, showing a lack of any consistent association of prostate cancer with levels of insulin [45–47], markers of hyperinsulinemia [31] or with gene variants associated with raised insulin levels [32]. Others have found inverse relationships of insulin resistance measures [48] or metabolic syndrome and its components [49, 50] with incident prostate cancer. This is in conflict with the hypothesis that insulin resistance explains the higher prostate cancer risk in westernized versus the non-westernized countries. It has been suggested that insulin resistance may be inversely associated with prostate cancer initiation and positively associated with aggressive prostate cancer, but the evidence for this hypothesis is weak [48] and our findings are not supportive. A positive association of metabolic syndrome with prostate cancer was observed in a prospective cohort study, but the results were based on only 56 prostate cancers [51], raising the possibility of a chance finding. Another cohort study with 507 prostate cancer cases reported a 56% increased

Table 5 Hazard ratios (HR) of survival from prostate cancer associated with pre-diagnostic metabolic risk factors

Variable	No. of person-years	No. of deaths (all causes)	Age-adjusted HR	Fully adjusted[a] HR (95% CI)	*p*-Value
Body mass index (per SD, 3.3 kg/m^2)	2,312	297	1.05	1.05 (0.93–1.19)	0.40
Waist circumference (per SD, 9.1 cm)	2,300	293	1.02	1.02 (0.90–1.15)	0.81
Waist:hip ratio (per SD, 0.06)	2,300	293	1.04	1.01 (0.90–1.14)	0.86
Systolic blood pressure (per SD, 22.6 mmHg)	2,310	296	0.97	0.95 (0.84–1.06)	0.37
Diastolic blood pressure (per SD, 12.3 mmHg)	2,310	296	0.98	0.96 (0.86–1.07)	0.47
Mean arterial pressure (per SD, 16.0 mmHg)	2,310	295	0.96	0.94 (0.83–1.05)	0.26
Total cholesterol (per SD, 1.1 mmol/l)	2,310	296	0.99	0.99 (0.89–1.11)	0.92
HDL cholesterol (per SD, 0.3 mmol/l)	2,310	296	1.06	1.06 (0.94–1.20)	0.32
Triglycerides (per SD, 1.1 mmol/l)	2,310	296	0.97	0.95 (0.84–1.07)	0.39
Random blood glucose (per SD, 1.8 mmol/l)	2,310	296	0.98	1.00 (0.89–1.13)	0.98
Metabolic syndrome[b] (yes versus no)	2,299	292	1.00	0.93 (0.71–1.22)	0.60
Diabetes (yes versus no)	2,312	297	1.02	1.06 (0.65–1.74)	0.81
Blood pressure medication (yes versus no)	2,312	297	0.93	0.96 (0.73–1.26)	0.77
Previous cardiovascular disease[c] (yes versus no)	2,312	297	1.24	1.45 (1.11–1.90)	0.007

CI confidence interval, *HDL* high density lipoprotein

[a] Adjusted for age, height (quarters), smoking (never, former, current, and unknown), marital status (married, unmarried, widower, and divorced/separated), education (<10, 10–12, and ≥13 years), physical activity (no activity, <3 h light, ≥3 h light or <1 h hard, ≥1 h hard, and unknown), International Prostate Symptom Score (none, mild, moderate, and severe lower urinary tract symptoms); and blood pressure measures also adjusted for use of blood pressure medication

[b] Metabolic syndrome defined according to the ATP-III criteria [31] [using random glucose ≥200 mg/dl (≥11.1 mmol/l) instead of fasting glucose ≥110 mg/dl]

[c] Cardiovascular disease defined as angina pectoris, myocardial infarction, or stroke

risk of prostate cancer amongst men with three metabolic factors [21], but a recent review indicates that prospective data are limited [45].

Visceral fat is metabolically more active than subcutaneous or peripheral fat and abdominal adiposity is correlated with insulin resistance, glucose intolerance, dyslipidemia, and hypertension, perhaps more strongly than general adiposity measured by body mass index [52–55]. Our null findings for waist circumference, waist–hip ratio, and measures of visceral fat are in line with a meta-analysis, where the pooled effect-estimate for waist circumference was 1.03 in both prospective and case–control studies [30]. The studies included in that meta-analysis were based on incident cancers. A recent large prospective study, based on over 1 million person-years of follow-up, also found no association of waist circumference and waist–hip ratio with total prostate cancer, but these markers were positively associated with advanced prostate cancer (see also next paragraph) [18]. Our findings of no association of total and HDL-cholesterol with prostate cancer are in line with one other report [27] and with meta-analyses of trials and observational data, suggesting no association of cholesterol lowering statin therapy with prostate cancer [22]. One study reported higher HDL-cholesterol levels in men with prostate cancer (and higher total and LDL-cholesterol) [28], but this runs counter to the idea that the metabolic syndrome (characterized by low levels of HDL-cholesterol) may play a causal role in explaining international differences in prostate cancer between the western and non-western countries.

There was some evidence for an interaction of the association of metabolic syndrome with prostate cancer amongst strata defined by thirds of BMI, but the results were in the opposite direction to those of Pischon et al. [18], and these interactions probably arose by chance.

Our analysis shows no evidence of any association per standard deviation increase in body mass index, with point estimates of 0.98 for total, 0.98 for advanced, and 1.01 for fatal prostate cancers. Neither was there any strong evidence of associations of obesity with prostate cancer incidence, mortality, or survival. In contrast, a positive association of obesity with aggressive and fatal prostate cancer was a consistent finding amongst published studies recently reviewed by Hsing et al. [45] and Freedland and Platz [15], including strong evidence of a dose–response relationship of increasing degree of obesity in the Cancer Prevention Study II prospective cohort with over 4,000 cases [16]. Four large cohorts suggest a positive association of general adiposity with advanced prostate cancer: the Cancer Prevention Study I [56], Cancer Prevention Study II

[16], a Swedish study [57], and the European Prospective Investigation into Cancer and Nutrition (EPIC) [18]. The numbers of advanced and fatal prostate cancers in our study were small and the effect estimates were imprecisely measured (wide confidence intervals), so we cannot rule out a positive association of BMI with more aggressive cancers. It is possible that change in weight from early to later life is important in prostate carcinogenesis [17].

Our findings do indicate the possibility that raised blood pressure is associated with prostate cancer incidence. Although associations of systolic and diastolic blood pressure were not always consistent with each other, this finding is in line with reports that hypertension was associated with a twofold increased risk of prostate cancer in African-Americans [19], with advanced prostate cancer [14], and with a reduced risk of prostate cancer associated with anti-hypertensive treatment [23]. It has been proposed that increased central sympathetic activity (which can occur with a raised blood pressure or heart rate) may result in androgen-mediated stimulation of prostate carcinogenesis [24], and our data are in line with this hypothesis. Misclassification of long-term exposure to high blood pressure levels by recent antihypertensive treatment may have attenuated the observed effect sizes toward the null. However, antihypertensive treatment was not associated with prostate cancer in our study. This finding warrants further investigation, because reports on the blood pressure association are few, null results have also been reported [24, 26] and prostate cancer may be more likely to be diagnosed among men being seen regularly for the treatment of hypertension.

In conclusion, several key components of the metabolic syndrome were not the risk factors for prostate cancer in our population-based cohort study. Our results, however, do not exclude a role for factors acting at the tissue level that are independent of measured intermediate phenotypes. For example, endogenous lipogenesis in prostate cancer cells may play a role in the accumulation of cholesterol and other lipid products in tumor cell membranes that may in turn regulate cancer cell growth and survival [25]. Neither can we exclude the presence of differential associations in different ethnic groups [19]. There was some evidence of a positive association of blood pressure with incident prostate cancer that warrants further investigation, as it supports a previously suggested hypothesis linking increased central sympathetic nervous activity with androgen-mediated stimulation of prostate cell growth [24].

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Conflicts of interest None to declare.

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