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Original article

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Metabolic risk score and cancer risk: pooled analysis of seven cohorts

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Abstract

Background: There are few data on the joint influence of metabolic factors on risk of separate cancers.

Methods: We analysed data on body mass index, blood pressure and plasma levels of glucose, total cholesterol and triglycerides from seven European cohorts comprising 564 596 men and women with a mean age of 44 years. We weighted those factors equally into a standardized metabolic risk score [MRS, mean = 0, standard deviation (SD) = 1], with an individual's level indicated as SDs from the sex- and cohort-specific means. Cancer hazard ratios were calculated by Cox regression with age as timescale and with relevant adjustments including smoking status. All statistical tests were two-sided.

Results: During a mean follow-up of 12 years, 21 593 men and 14 348 women were diagnosed with cancer. MRS was linearly and positively associated with incident cancer in total and at sites ($P < 0.05$). In men, risk per SD MRS was increased by 43% (95% confidence interval: 27–61) for renal cell cancer, 43% (16–76) for liver cancer, 29% (20–38) for colon cancer, 27% (5–54) for oesophageal cancer, 20% (9–31) for rectal cancer, 19% (4–37) for leukaemias, 15% (1–30) for oral cancer and 10% (2–19) for bladder cancer. In

women, risk increases per SD MRS were 56% (42–70) for endometrial cancer, 53% (29–81) for pancreatic cancer, 40% (16–67) for renal cell cancer, 27% (9–47) for cervical cancer and 17% (3–32) for rectal cancer.

Conclusion: This largest study to date on the joint influence of metabolic factors on risk of separate cancers showed increased risks for several cancers, in particular renal cell and liver cancer in men and endometrial and pancreatic cancer in women.

Key words: cohort studies, metabolic syndrome x, neoplasms

Key messages

- In this pooled study of seven European cohorts, high levels of a metabolic risk score of five components—BMI, blood pressure and plasma levels of glucose, total cholesterol and triglycerides—were related to increased overall risks of cancer incidence and mortality in men and in women.
- The highest risk increases were found for renal cell and liver cancer in men, and for endometrial and pancreatic cancer in women.
- The strongest individual risk factors for total incident cancer were in men high levels of blood pressure and triglycerides, and in women high plasma glucose.

Introduction

There is substantial evidence that obesity increases the risk of many cancers.[1] The risk is particularly increased for oesophageal adenocarcinoma, renal cell carcinoma, colorectal cancer, endometrial cancer and postmenopausal breast cancer.[1–6] Much less is known about the association between other metabolic aberrations and the risk of cancer. However, recent years have shown an increased interest in a putative association between cancer and the metabolic syndrome: a constellation of obesity and insulin resistance, hypertension and dyslipidaemia.[7] Studies of common cancers have shown that individuals with the metabolic syndrome have an increased risk of cancer of the colorectum, pancreas and endometrium.[5,6,8,9] However, the analytical approach to the metabolic syndrome has been very heterogeneous between studies,[8] so the strength of associations with various cancers remains unclear and data on rare cancers are lacking.

To date, most studies of the metabolic syndrome have dichotomized ingoing factors into low-risk and high-risk groups, which finds little support in the literature for cardiovascular disease.[10] Also, in our analyses of more than 500 000 individuals, we found linear associations between cancer risk and both blood glucose[11] and blood pressure,[12] which is unsupportive to the use of dichotomization. By use of a continuous metabolic risk score (MRS) comprising equal weights from body mass index (BMI), blood pressure and plasma levels of glucose, triglycerides and total cholesterol, we have assessed the risks of several separate cancers (see e.g. references 3, 5, 6, 9, 13, 14, 19, 28, 29 and 30).

In this study, we report the association between MRS and the risk of cancer overall and at separate sites. We assess the strength and shape of association between MRS and total cancer incidence and cancer mortality, and with a large number of separate cancers for a direct comparison of their strength of associations with the MRS.

Methods

The Me-Can cohort

The Me-Can project pools data from seven cohorts in Norway, Sweden and Austria. A detailed description and the inclusion criteria for the 578 700 participants are reported elsewhere.[13] In brief, cohort health examinations performed between 1975 and 2005 (see Table 1) include measurements of height, weight, blood pressure and circulating levels of glucose, total cholesterol and triglycerides. In the present study with MRS as the primary exposure, we excluded 14 104 (2%) individuals because of incomplete data for one or more variable in the MRS, leaving 564 596 participants (281 193 men and 283 403 women) in the study. The study was approved by research ethical committees in Norway, Austria and Sweden.

Follow-up

The cohorts were linked to their respective national register for identification of cancer incidence, migration (except for the Austrian cohort, for whom there was no information),

Table 1. Baseline characteristics of study participants in the Metabolic Syndrome and Cancer project (Me-Can)

Characteristics	Men	Women
Cohort (year of baseline measurement), *n* (%)		
Oslo (1972–73)	16 760 (6)	
NCS (1974–83)	25 952 (9)	25 072 (9)
CONOR (1995–2003)	52 181 (18)	57 687 (20)
40-y (1994–99)	60 676 (22)	68 211 (24)
VHM&PP (1988–2002)	72 858 (26)	86 132 (30)
VIP (1986–2005)	30 699 (11)	35 871 (13)
MPP (1974–92)	22 067 (8)	10 430 (4)
Total (1972–2005)	281 193	283 403
Baseline age, years		
Mean (SD)	43.9 (11.1)	44.1 (12.3)
Categories, *n* (%)		
<30	26 744 (9)	32 751 (11)
30–44	153 479 (55)	152 321 (54)
45–59	73 219 (26)	65 464 (23)
≥60	27 751 (10)	32 867 (12)
Fasting time, h, *n* (%)[a]		
<4	119 927 (43)	121 874 (43)
4–7	29 468 (10)	25 760 (9)
≥8	131 798 (47)	135 769 (48)
Smoking status, *n* (%)		
Never smoker	108 662 (39)	141 502 (50)
Ex-smoker	84 154 (30)	71 759 (25)
Current smoker	87 778 (31)	69 628 (25)
Not known	599 (0)	514 (0)
BMI, kg/m^2		
Mean (SD)	25.7 (3.5)	24.9 (4.4)
Category,[b] *n* (%)		
<25	127 066 (45)	167 173 (59)
25–29.9	124 030 (44)	81 341 (29)
≥30	30 097 (11)	34 889 (12)
Blood pressure, mmHg		
Mean (SD) systolic blood pressure	132.8 (16.9)	126.9 (19.4)
Mean (SD) diastolic blood pressure	81.3 (11.0)	76.8 (11.3)
Mean (SD) mid blood pressure[c]	107.0 (12.7)	101.8 (14.2)
Category,[b] systolic/diastolic, *n* (%)		
<140/90	173 824 (62)	209 385 (74)
140/90–159/99	77 382 (27)	49 792 (18)
≥160/100	29 987 (11)	24 226 (8)
Glucose, mmol/l		
Mean (SD)[d]	5.1 (1.3)	5.0 (1.2)
Category,[b] *n* (%)[e]		
<6.1 in serum/plasma or <5.6 in whole blood	115 966 (88)	123 643 (91)
6.1–6.9 in serum/plasma or 5.6–6.0 in whole blood	10 719 (8)	8233 (6)
≥7.0 in serum/plasma or ≥6.1 in whole blood	5113 (4)	3893 (3)
Cholesterol, mmol/l		
Mean (SD)	5.6 (1.2)	5.6 (1.2)
Category,[b] *n* (%)[e]		
<5.2	48 768 (37)	56 050 (41)
5.2–6.1	44 165 (34)	43 418 (32)
≥6.2	38 865 (29)	36 301 (27)
Triglycerides, mmol/l		
Mean (SD)	1.6 (1.2)	1.3 (0.8)

(Continued)

Table 1. Continued

Characteristics	Men	Women
Category,[b] *n* (%)[e]		
<1.7	89 262 (68)	112 183 (83)
1.7–2.2	20 481 (15)	14 072 (10)
≥2.3	22 055 (17)	9514 (7)
Follow-up, years		
Mean (SD)	12.8 (8.7)	11.2 (6.9)
Category, *n* (%)		
<5	36 488 (13)	35 325 (12)
5–14	172 479 (61)	196 029 (69)
15–24	23 158 (8)	27 586 (10)
≥25	49 068 (18)	24 463 (9)

Oslo, Oslo study I; NCS, Norwegian Counties Study; CONOR, Cohort of Norway; 40-y, Age 40-Programme; VHM&PP, Vorarlberg Heath Monitoring and Prevention Programme; VIP, Västerbotten Intervention Project; MPP, Malmö Preventive Project; SD, standard deviation; BMI, body mass index.

[a]Proportion of participants with fasting time ≥8 h: 5% in the Norwegian cohorts, 92% in the VIP and 100% in the VHM&PP and MPP.

[b]Source for categories: BMI[20], blood pressure[21], glucose[22], cholesterol and triglycerides[23].

[c](Systolic + diastolic blood pressure)/2.

[d]Includes 109 731 men and 125 339 women with fasting plasma or serum samples. Participants in MPP, with glucose measured in whole blood, are not included.

[e]Includes 131 798 men and 135 769 women with fasting plasma/serum/blood samples.

vital status and cause of death. Follow-up for cancer incidence/mortality included the year 2005/04 in Norway, 2006/04 in Sweden and 2003/03 in Austria. We categorized incident cancers according to the International Classification of Diseases, 7th revision (ICD-7). ICD-7 was used during the first years of follow-up for the older cohorts so, for consistency, we used it for all cohorts.

Statistical analysis

We investigated the associations of cancer incidence and mortality with BMI, blood pressure and blood levels of glucose, total cholesterol and triglycerides by quintiles, and with MRS by quintiles and as a continuous Z-distributed variable. We constructed the MRS based on these five components, which we first converted to a Z-distribution by (level, mean)/SD within the corresponding cohort and sex, and also within categories of fasting time for measures of glucose, cholesterol and triglycerides. We used mid blood pressure [(systolic blood pressure + diastolic blood pressure)/2],[15] and we log-transformed glucose and triglyceride levels before standardization because their distributions were skewed. We standardized the sum of Z-scores of single factors within each cohort, sex and fasting time. This resulted in an MRS with a mean value of zero and an SD of one, with equal weight from each factor. Quintile cut-points were calculated separately within each cohort and sex, and also within categories of fasting time for measures of glucose, cholesterol and triglycerides.

We used Cox proportional hazards regression to calculate cancer hazard ratios (HRs) for MRS and its ingoing factors. To reduce the probability of reverse causation, follow-up started at 1 year after the baseline examination and ended at the date of the event—i.e. the date of the first cancer diagnosis or cancer death or of death from any cause or of emigration or until end of follow-up, whichever occurred first. We used age as time variable and stratified all models by cohort and by birth year category (before 1923, 1923–30, 1931–38, 1939–46, 1947–54, 1955 and later), and analyses of men and women combined were also stratified by sex. We adjusted all analyses for age at measurement (continuous), smoking status (never smoker, ex-smoker, current smoker, unknown), and quintile analysis for BMI (quintiles). We performed separate analyses for men and women when the number of cases for either sex was at least 50. We tested for potential differences between the sexes and cohorts, respectively, regarding HRs of cancer by the MRS and its components. We used likelihood ratio tests in which a model with the continuous MRS, or quintiles of MRS components, was compared with a model additionally including a product term of these exposures and sex or cohort.

To investigate the shape of the association between MRS and cancer risk we used restricted cubic spline regression[16] with knots placed at percentiles 5, 35, 65 and 95. We also performed a formal test for linearity of the association by comparing the fit of the linear model with the fit of the cubic spline model using likelihood-ratio tests in which the linear model was nested in a model that additionally included cubic splines.

We adjusted HRs for random error in the measurement of exposure factors by dividing the regression coefficient in the Cox model by the estimated regression dilution ratio (RDR) of exposure,[17] as previously described in detail.[5] We based these calculations on data from 133 820

participants for whom two or more observations with the same fasting time before measurements were available, 406 364 observations in total. We based RDR calculations on linear mixed effect models[17,18] and obtained RDR values of 0.90 for BMI, 0.53 for systolic blood pressure, 0.50 for diastolic blood pressure, 0.28 for log(glucose), 0.66 for cholesterol, 0.51 for log(triglycerides) and 0.69 for MRS. We corrected all HRs for random error using the equation $HR_{corrected} = \exp(\log(HR)/RDR)$.

Proportional hazards assumptions of the Cox model for total cancer incidence and cancer mortality were tested by Schoenfeld residuals statistics, and proportionality of MRS was additionally evaluated by inclusion of MRS as a time-dependent variable in the model. There were indications of violation for smoking status in relation to incident cancer in women, but inclusion of smoking status as stratum in the Cox model did not affect HRs, so it was not retained in the model. Proportionality was also indicated to be violated for MRS and incident cancer in women. This observation was largely driven by breast cancer for which we have previously reported results in detail for MRS and its components in relation to breast cancer risk in groups of attained age.[19] In analyses of total incident cancer in women, proportional hazards were no longer violated after exclusion of breast cancers.

We performed statistical analyses in Stata (version 10.0) and R (version 2.7.2 for RDR calculations). All statistical tests were two-sided.

Results

Table 1 shows the characteristics of the study participants at baseline. Mean age was 44.0 years (SD = 11.7); 44% of men and 29% of women were overweight (BMI 25–29.9 kg/m^2), and 11% of men and 12% of women were obese (BMI $\geq$ 30 kg/m^2). Mean follow-up time was 12.8 years (SD = 8.7) among men and 11.2 years (SD = 6.9) among women. Calculations of HRs for cancer included 3 230 484 person-years and 21 593 incident cancers in men and 2 828 417 person-years and 14 348 incident cancers in women. The corresponding numbers for cancer mortality were 3 041 384 person-years and 8572 cancer deaths in men, and 2 653 234 person-years and 4405 cancer deaths in women. Mean levels of metabolic risk factors, and number of incident cases in each cohort, are shown in SupplementaryTable 1, available as Supplementary data at *IJE* online).

In men, the risk for any cancer for top vs bottom quintile of metabolic factors was increased by 28% [95% confidence interval (CI): 17–41%] for diastolic blood pressure ($P_{trend} < 0.001$), 23% for systolic blood pressure (95% CI: 12–33%, $P_{trend} < 0.001$), 20% for triglycerides (95% CI: 10–32%, $P_{trend} = 0.01$) and 17% for MRS (95% CI: 9–25%, $P_{trend} < 0.001$) (Table 2). These factors and glucose levels were also related to increased cancer mortality in men. BMI and cholesterol were related to neither cancer incidence nor cancer mortality. There were no interactions between metabolic factors in quintiles and cohort in relation to cancer incidence or mortality in men (P_{het} all $\geq$0.05), except for systolic blood pressure and cancer mortality ($P_{het} = 0.02$), for which HRs in the top quintile ranged between 0.37 (95% CI: 0.14–0.94, $P_{trend} = 0.07$) in the Age 40-Programme to 1.96 (95% CI: 1.32–2.90, $P_{trend} < 0.001$) in the Vorarlberg Health Monitoring and Prevention Programme.

In women, there was a 46% increased risk for any cancer for the top vs bottom quintiles of blood glucose (95% CI: 21–76%, $P_{trend} < 0.001$), 18% for triglycerides (95% CI: 6–32%, $P_{trend} = 0.001$), 12% for BMI (95% CI: 5–19%, $P_{trend} < 0.001$) and 26% for MRS (95% CI: 15–38%, $P_{trend} < 0.001$) (Table 3). A positive trend was also shown for systolic blood pressure ($P_{trend} = 0.04$). The top cholesterol quintile was related to an 11% decreased risk of incident cancer in women (95% CI: 2–18%, $P_{trend} = 0.01$). Top quintiles of systolic and diastolic blood pressure were not related to incident cancer risk in women. All factors except cholesterol showed a positive trend for cancer mortality in women. There were no interactions between metabolic factors and cohort, except for glucose and incident cancer ($P_{het} = 0.03$) that showed HRs for the top quintile ranging from 0.83 (95% CI: 0.49–1.42, $P_{trend} = 0.6$) in the Age 40-Programme to 2.11 (95% CI: 1.21–3.67, $P_{trend} = 0.002$) in the Västerbotten Intervention Project. HRs for quintile analyses differed between men and women for BMI and glucose in relation to cancer incidence ($P_{interaction} = 0.03$ and 0.001) and for glucose, triglycerides and MRS in relation to cancer mortality ($P_{interaction} = 0.02$, 0.046 and 0.01). In both men and women, results from quintile analyses of MRS, blood pressure, glucose and triglycerides showed stronger associations with cancer mortality than with cancer incidence, though confidence intervals were overlapping. Exclusion of the first 5 years of follow-up did not affect HRs in quintiles for cancer incidence or mortality in men or in women.

In spline models, the MRS was linearly and positively associated with incident cancer in both men and women (Figure 1). HRs per SD increment in MRS were 1.05 (95% CI: 1.03–1.08) in men and 1.08 (95% CI: 1.05–1.11) in women. The association was also linear and positive for cancer mortality in women, whereas in men the association was non-linear with no association observed for levels below the mean MRS level, but an increased risk for increasing MRS levels above the mean MRS level (Z = 0). The associations between continuous MRS and cancer

Table 2. Hazard ratio[a] of cancer incidence and mortality in men by quintile of metabolic factors

Exposure	Quintile	Mean (SD)	Hazard ratio (95% CI)	
			Cancer incidence *n* cases = 21 593	Cancer mortality *n* cases = 8572
BMI, kg/m^2	1	21.5 (1.3)	1.00 (referent)	1.00 (referent)
	2	23.8 (0.8)	1.00 (0.95–1.05)	0.89 (0.83–0.96)
	3	25.4 (0.8)	0.99 (0.94–1.04)	0.88 (0.82–0.95)
	4	27.1 (0.9)	0.99 (0.94–1.04)	0.88 (0.81–0.94)
	5	30.8 (2.7)	1.04 (0.99–1.09)	1.02 (0.95–1.10)
			P_{trend}[b] = 0.1	P_{trend}[b] = 0.3
Systolic blood pressure, mmHg	1	112.3 (6.4)	1.00 (referent)	1.00 (referent)
	2	122.9 (3.9)	1.02 (0.93–1.11)	1.04 (0.90–1.21)
	3	129.8 (4.4)	1.10 (1.01–1.20)	1.22 (1.06–1.40)
	4	138.2 (4.4)	1.18 (1.08–1.29)	1.23 (1.07–1.42)
	5	156.5 (13.5)	1.23 (1.12–1.33)	1.51 (1.31–1.72)
			P_{trend}[b] < 0.001	P_{trend}[b] < 0.001
Diastolic blood pressure, mmHg	1	67.0 (5.0)	1.00 (referent)	1.00 (referent)
	2	75.2 (3.2)	1.06 (0.96–1.17)	0.98 (0.84–1.14)
	3	80.2 (2.7)	1.09 (0.99–1.19)	1.08 (0.94–1.25)
	4	86.3 (3.5)	1.14 (1.04–1.25)	1.15 (0.99–1.33)
	5	97.1 (7.7)	1.28 (1.17–1.41)	1.35 (1.16–1.57)
			P_{trend}[b] < 0.001	P_{trend}[b] < 0.001
Glucose, mmol/l	1	4.2 (0.5)	1.00 (referent)	1.00 (referent)
	2	4.8 (0.3)	1.06 (0.90–1.24)	0.90 (0.70–1.16)
	3	5.1 (0.4)	1.10 (0.93–1.29)	1.07 (0.83–1.38)
	4	5.5 (0.4)	1.12 (0.96–1.30)	1.06 (0.83–1.36)
	5	6.9 (2.0)	1.11 (0.95–1.30)	1.47 (1.16–1.88)
			P_{trend}[b] = 0.2	P_{trend}[b] < 0.001
Cholesterol, mmol/l	1	4.3 (0.5)	1.00 (referent)	1.00 (referent)
	2	5.1 (0.3)	0.95 (0.89–1.02)	0.96 (0.86–1.07)
	3	5.7 (0.3)	0.98 (0.91–1.05)	0.92 (0.82–1.02)
	4	6.3 (0.3)	0.96 (0.90–1.03)	0.89 (0.80–1.00)
	5	7.4 (0.8)	0.98 (0.91–1.05)	0.97 (0.87–1.09)
			P_{trend}[b] = 0.8	P_{trend}[b] = 0.9
Triglycerides, mmol/l	1	0.8 (0.2)	1.00 (referent)	1.00 (referent)
	2	1.2 (0.2)	1.16 (1.07–1.27)	1.05 (0.92–1.21)
	3	1.5 (0.3)	1.13 (1.04–1.24)	1.11 (0.96–1.27)
	4	2.1 (0.4)	1.18 (1.08–1.28)	1.14 (0.99–1.32)
	5	3.7 (1.7)	1.20 (1.10–1.32)	1.33 (1.15–1.53)
			P_{trend}[b] = 0.01	P_{trend}[b] < 0.001
Metabolic risk score	1	−1.3 (0.4)	1.00 (referent)	1.00 (referent)
	2	−0.6 (0.2)	1.08 (1.01–1.16)	1.02 (0.92–1.14)
	3	−0.1 (0.1)	1.11 (1.04–1.18)	1.07 (0.96–1.19)
	4	0.5 (0.2)	1.10 (1.03–1.17)	1.09 (0.98–1.21)
	5	1.5 (0.6)	1.17 (1.09–1.25)	1.27 (1.14–1.41)
			P_{trend}[b] < 0.001	P_{trend}[b] < 0.001

CI, confidence interval; SD, standard deviation; BMI, body mass index.

[a]Hazard ratio from Cox regression model, with attained age as timescale, stratified by cohort and birth year and adjusted for baseline age, smoking status and quintiles of BMI (except BMI and metabolic risk score). HRs are corrected for regression dilution ratio (RDR); conversion into uncorrected HR = exp(log($HR_{corrected}$)*RDR). RDR: BMI, 0.90; systolic blood pressure, 0.53; diastolic blood pressure, 0.50; log(glucose), 0.28; cholesterol, 0.66; log(triglycerides), 0.51; metabolic risk score, 0.69.

[b]*P*-value for the Wald test of a linear risk estimate, assigning each participant the mean cohort-specific level within the corresponding quintile.

incidence and mortality did not differ between Me-Can subcohorts in men or in women (P_{het} all ≥0.05).

Associations between continuous MRS and risk of cancer at separate sites are shown in Figure 2. A positive association was found in both sexes for renal cell, colon and rectal cancer, and several other cancers showed associations in men or in women. In men, the risk increase per SD MRS increment was 43% (95% CI: 16–76%) for renal

Table 3. Hazard ratio[a] of cancer incidence and mortality in women by quintile of metabolic factors

Exposure	Quintile	Mean (SD)	Hazard ratio (95% CI)	
			Cancer incidence *n* cases = 14 348	Cancer mortality *n* cases = 4405
BMI, kg/m^2	1	20.0 (1.2)	1.00 (referent)	1.00 (referent)
	2	22.2 (0.8)	1.01 (0.95–1.08)	0.85 (0.76–0.96)
	3	24.1 (0.8)	1.00 (0.94–1.06)	0.92 (0.82–1.03)
	4	26.4 (1.0)	0.99 (0.93–1.05)	0.83 (0.74–0.93)
	5	31.7 (3.6)	1.12 (1.05–1.19)	1.04 (0.93–1.16)
			P_{trend}[b] < 0.001	P_{trend}[b] = 0.03
Systolic blood pressure, mmHg	1	104.0 (5.7)	1.00 (referent)	1.00 (referent)
	2	114.2 (3.3)	1.01 (0.89–1.13)	1.00 (0.80–1.26)
	3	122.5 (3.0)	1.04 (0.92–1.17)	1.04 (0.83–1.31)
	4	133.1 (4.9)	0.99 (0.88–1.11)	1.18 (0.95–1.47)
	5	156.7 (16.2)	1.10 (0.98–1.24)	1.25 (1.00–1.55)
			P_{trend}[b] = 0.04	P_{trend}[b] = 0.02
Diastolic blood pressure, mmHg	1	61.3 (4.8)	1.00 (referent)	1.00 (referent)
	2	70.1 (3.1)	1.00 (0.88–1.13)	1.33 (1.05–1.69)
	3	76.8 (3.6)	0.96 (0.86–1.09)	1.23 (0.97–1.55)
	4	82.4 (4.7)	1.01 (0.90–1.14)	1.40 (1.11–1.75)
	5	92.4 (8.4)	1.08 (0.96–1.22)	1.61 (1.28–2.03)
			P_{trend}[b] = 0.08	P_{trend}[b] < 0.001
Glucose, mmol/l	1	4.1 (0.5)	1.00 (referent)	1.00 (referent)
	2	4.6 (0.3)	1.01 (0.82–1.24)	1.07 (0.73–1.58)
	3	5.0 (0.3)	1.03 (0.85–1.25)	1.24 (0.86–1.78)
	4	5.3 (0.3)	1.39 (1.14–1.69)	1.81 (1.26–2.60)
	5	6.5 (1.6)	1.46 (1.21–1.76)	2.19 (1.55–3.08)
			P_{trend}[b] < 0.001	P_{trend}[b] < 0.001
Cholesterol, mmol/l	1	4.2 (0.4)	1.00 (referent)	1.00 (referent)
	2	4.9 (0.2)	0.96 (0.88–1.05)	0.98 (0.82–1.16)
	3	5.5 (0.3)	0.94 (0.86–1.02)	0.87 (0.73–1.03)
	4	6.1 (0.3)	0.96 (0.88–1.05)	0.99 (0.84–1.16)
	5	7.3 (0.9)	0.89 (0.82–0.98)	0.95 (0.81–1.11)
			P_{trend}[b] = 0.01	P_{trend}[b] = 0.7
Triglycerides, mmol/l	1	0.6 (0.1)	1.00 (referent)	1.00 (referent)
	2	0.9 (0.1)	1.05 (0.94–1.18)	1.16 (0.93–1.46)
	3	1.1 (0.1)	1.01 (0.91–1.13)	1.23 (0.99–1.52)
	4	1.5 (0.2)	1.09 (0.98–1.22)	1.44 (1.16–1.78)
	5	2.5 (1.1)	1.18 (1.06–1.32)	1.72 (1.39–2.12)
			P_{trend}[b] = 0.001	P_{trend}[b] < 0.001
Metabolic risk score	1	−1.2 (0.3)	1.00 (referent)	1.00 (referent)
	2	−0.6 (0.1)	1.15 (1.05–1.25)	1.21 (1.01–1.45)
	3	−0.1 (0.1)	1.11 (1.01–1.21)	1.24 (1.04–1.48)
	4	0.4 (0.2)	1.12 (1.03–1.23)	1.36 (1.14–1.61)
	5	1.5 (0.6)	1.26 (1.15–1.38)	1.63 (1.37–1.93)
			P_{trend}[b] < 0.001	P_{trend}[b] < 0.001

CI, confidence interval; SD, standard deviation; BMI, body mass index.

[a]Hazard ratio from Cox regression model, with attained age as timescale, stratified by cohort and birth year and adjusted for baseline age, smoking status and quintiles of BMI (except BMI and metabolic risk score). HRs are corrected for regression dilution ratio (RDR); conversion into uncorrected HR = exp(log($HR_{corrected}$)*RDR). RDR: BMI, 0.90; systolic blood pressure, 0.53; diastolic blood pressure, 0.50; log(glucose), 0.28; cholesterol, 0.66; log(triglycerides), 0.51; metabolic risk score, 0.69.

[b]*P*-value for the Wald test of a linear risk estimate, assigning each participant the mean cohort-specific level within the corresponding quintile.

cancer, 43% (95% CI: 27–61%) for liver cancer, 29% (95% CI: 20–38%) for colon cancer, 27% (95% CI: 5–54%) for oesophageal cancer [58%, (95% CI: 17–114%) for oesophageal adenocarcinoma], 20% (95% CI: 9–31%) for rectal cancer, 19% (95% CI: 4–37%) for leukaemias, 15% (95% CI: 1–30%) for oral cancers and 10% (95% CI: 2–19%) for bladder cancer. In women, the risk increase per SD MRS was 56% (95% CI: 42–70%) for

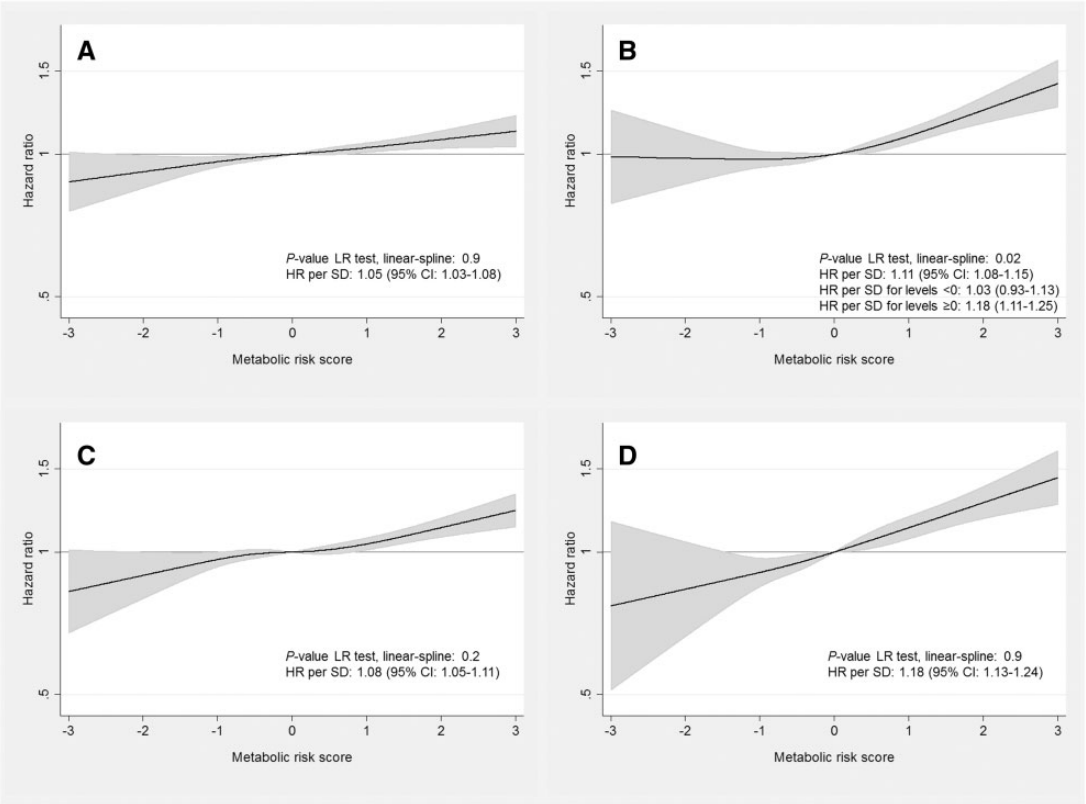

Figure 1. Hazard ratio (HR, black line) and 95% confidence interval (shaded area) of cancer incidence (A) (*n* cases = 21 593) and cancer mortality (B) (*n* cases = 8572) in men, and cancer incidence (C) (*n* cases = 14 348) and cancer mortality (D) (*n* cases = 4405) in women, by the metabolic risk score (mean = 0, SD = 1). Models were derived from restricted cubic spline regression, with knots placed at percentiles 5, 35, 65 and 95. Attained age was used as timescale, and models were stratified by cohort and birth year and adjusted for baseline age and smoking status. HRs were corrected for a regression dilution ratio of 0.69 for metabolic risk score by exp(log(HR)/0.69). Participants with values more extreme than ± 3 SD were excluded from the analyses (*n* excluded ≤ 1845). *P*-value LR test, linear-spline, refers to likelihood-ratio tests of the linear model nested in a model with addition of splines.

endometrial cancer, 53% (95% CI: 29–81%) for pancreatic cancer, 40% (95% CI: 16–67%) for renal cell cancer, 27% (95% CI: 9–47%) for cervical cancer and 17% (95% CI: 3–32%) for rectal cancer. One SD increment of the MRS was also associated with a small [5%, (95% CI: 1–9%)] decrease in breast cancer risk. This association was driven by results in women who were <50 years old (premenopausal) at the time of diagnosis [18% decreased risk (95% CI: 10%–25%)], and there was no association in women ≥60 years old (postmenopausal) at diagnosis [4% increased risk (95% CI: –3–12%)].The association between MRS and gallbladder cancer was non-significant in men and women separately but was associated with a 28% (95% CI: 3–60%) risk increment per SD of the MRS in men and women combined. There were no significant interactions between MRS and cohort in relation to risk of separate cancer forms except for pancreas and stomach cancer among men ($P_{het} = 0.01$ and 0.048, respectively) and non-Hodgkin lymphoma among women ($P_{het} = 0.01$).

Discussion

In this pooled analysis of seven European cohorts, an MRS based on equal weights from levels of BMI, blood pressure, blood glucose, triglycerides and total cholesterol was linearly, positively associated with risk of incident cancer in men and in women. In men, the strongest associations were found for renal cell cancer and liver cancer, and in women, associations were the strongest for endometrial cancer and pancreas cancer. Positive associations were found for several other cancers.

There is no consensus on the optimal definition of the metabolic syndrome but all established definitions are based on a dichotomization of the syndrome and of each component variable.[7] The relevance of such dichotomization has been questioned in the field of cardiovascular disease,[10,24] and it has not been shown relevant to cancer risk. We therefore used a continuous MRS based on equal weights from five factors in or related to the metabolic syndrome, with an individual's level expressed as SDs from the sex- and cohort-specific mean. Our previous studies have generally shown

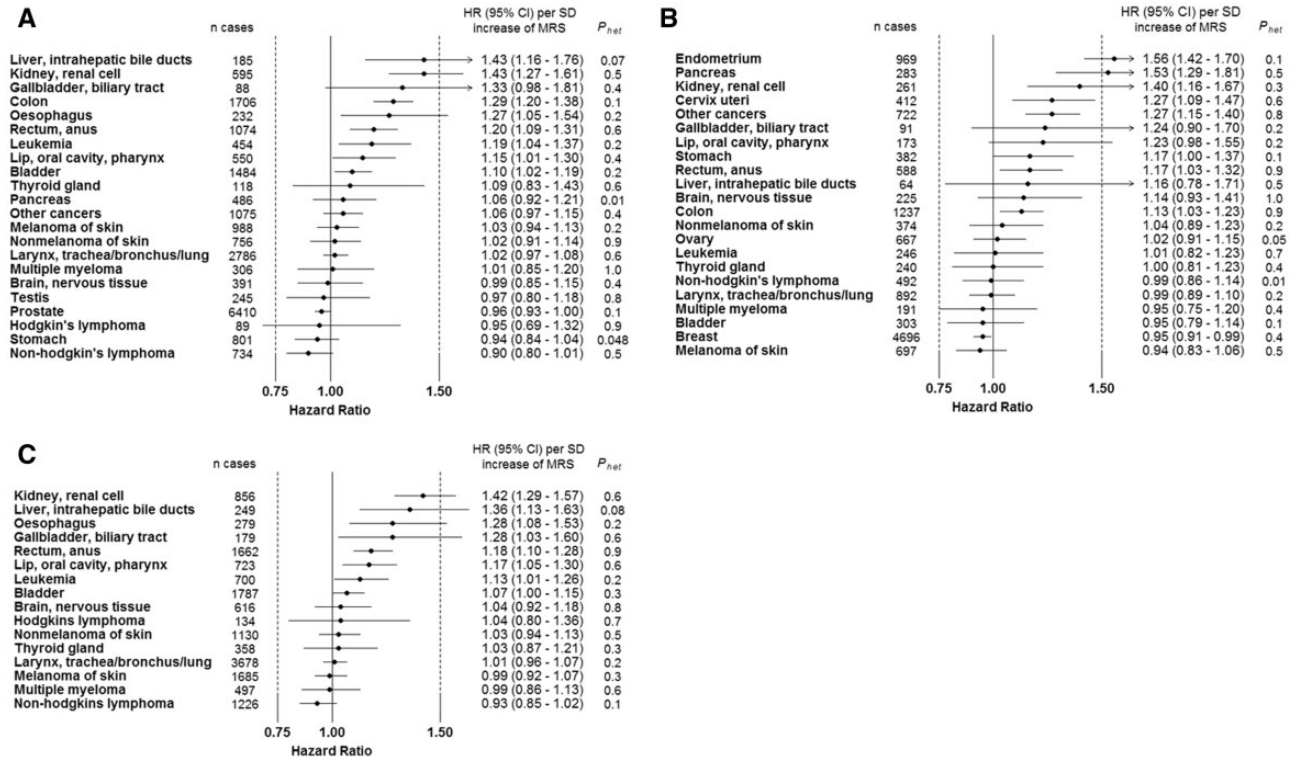

Figure 2. Hazard ratio (HR) and 95% confidence interval of incident cancer at separate sites in men (A), women (B) and men and women combined (C) by the metabolic risk score (MRS, mean = 0, SD = 1). HRs were derived from Cox regression models with attained age as timescale, strata for cohort, birth year and sex and adjustment for baseline age and smoking status. HRs were corrected for a regression dilution ratio of 0.69 for metabolic risk score by exp(log(HR)/0.69). ICD-7 180.0 and 180.9 denoting renal cell cancer, and ICD-7172 denoting endometrial cancer, include a fraction of tumours that morphologically differ from the clinical classification of these cancers. HRs for cancer of the stomach, colon and pancreas differed significantly between men and women, so these cancers are not included in (C). P_{het} refers to *P*-value for heterogeneity between cohorts which was tested by likelihood ratio tests in which a model with the continuous metabolic risk score was compared with a model additionally including a product term of metabolic risk score and cohort.

linear associations of single metabolic risk factors with risk of incident overall cancer,[11,12,25,26] and the present analysis showed the same for MRS, which further supports the use of linear models in analysis of incident cancer. The linear model approach also maximizes statistical power, resulting in robust results for a comparison of effect sizes for the impact of a composite MRS on different cancer forms. The drawback of our method is that the results are cohort-specific and cannot be applied to absolute levels and are therefore not attractive to use in clinical work.

Our results are in accordance with other, mostly smaller studies, which have shown an increased risk for cancer of the colorectum, liver, pancreas or endometrium in individuals with the metabolic syndrome.[8,27] Strong positive associations, as previously reported in Me-Can[3,28–30] but in few other studies, were also shown for MRS and cancer of the renal cells and gallbladder in both men and women, oesophageal cancer in men and cervical cancer in women. We also report novel findings for a strong positive association between MRS and risk for cancer of the oral cavity in both men and women. For total cancer in both men and women, our results indicated that the MRS, blood pressure, blood glucose and triglycerides, were more strongly associated with cancer mortality than with cancer incidence. A possible explanation could be that metabolic factors are involved both in tumour progression and its initiation,[31] causing higher HRs for cancer mortality.

Obesity is often regarded as an underlying factor for metabolic syndrome[32] but it was not the primary factor driving the association between MRS and cancer risk in our study. Obesity assessed by BMI was only moderately related to cancer risk in women and not related to risk in men, which is in agreement with other studies.[2,33] The strongest individual risk factors for total incident cancer were in men high levels of blood pressure and triglycerides, and in women high blood glucose levels. Individual cancers that have been strongly related to BMI, such as cancer of the renal cells, oesophagus, endometrium and colorectum,[1,2] were among the cancers that were most strongly related to MRS in this study. Our previous analyses of these cancers suggested that high BMI together with various other factors in the MRS were the strongest individual risk factors.[3,5,6,30] Liver cancer was in our previous study most strongly related to blood glucose,[14] and consequently liver cancer in men

relative to other cancers was more strongly related to MRS (1st rank) than it has been related to BMI. Although some chance findings might have occurred given the many tests in this study, overall our observations show that a combination of high levels of metabolic risk factors increases the risk for cancer, and the factor(s) driving the association varies between different cancer forms.

Our study has several strengths. It is very large and we were able to follow participants for a long period of time. Further, we were able to correct for measurement error and long-term variations in metabolic factors by use of repeated measurement data. Moreover, the capture rate of cancer cases in Norway and Sweden was nearly 100% using of national cancer registers,[34,35] and the cancer register in Austria also indicates good coverage with approximately 95% of cancer deaths covered by the cancer register.[36]

There are also some weaknesses in our study. We lacked data on body composition and detailed blood lipid data, for which BMI and total cholesterol served as surrogates. Waist circumference is related to all-cause mortality independently of BMI and is more strongly associated with cancer risk than BMI.[33] Although BMI is commonly used in large epidemiological studies, it will not fully capture an association when abdominal obesity rather than general obesity and body size is the causal link to cancer. Also, whereas serum high-density lipoproteins are commonly included as lipid risk factors for cardiovascular disease,[7] we had to use total cholesterol instead which is less specific. We also lacked data on socioeconomic factors, diet, physical activity, hormonal and reproductive factors in women and detailed data on tobacco smoking, which might have confounded some of our observed associations.

In conclusion, this study showed that an MRS of five metabolic factors was positively associated with risk of overall cancer incidence and mortality as well as incidence from several separate cancers. The strongest associations were found for renal cell and liver cancer in men and endometrial and pancreatic cancer in women. Strong associations were found for cancers typically related to high BMI and obesity, but factors other than BMI were in this study, and in some previous Me-Can studies of single cancers, stronger drivers of the MRS-cancer association.

Supplementary Data

Supplementary data are available at *IJE* online.

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Conflict of interest

None declared.

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