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Metabolic risk factors and ovarian cancer in the Metabolic Syndrome and Cancer project

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Background No studies have so far evaluated the impact of the metabolic syndrome (MetS) as an entity on ovarian cancer risk. The authors aimed to examine the association between factors in the MetS, individually and combined, and risk of ovarian cancer incidence and mortality.

Methods Altogether, 290 000 women from Austria, Norway and Sweden were enrolled during 1974–2005, with measurements taken of height, weight, blood pressure and levels of glucose, cholesterol and triglycerides. Relative risks (RRs) of ovarian cancer were estimated using Cox regression for each MetS factor in quintiles and for standardized levels (*z*-scores), and for a composite *z*-score for the MetS. RRs were corrected for random error in measurements.

Results During follow-up, 644 epithelial ovarian cancers and 388 deaths from ovarian cancer were identified. There was no overall association between MetS and ovarian cancer risk. Increasing levels of cholesterol [RR 1.52, 95% confidence interval (95% CI) 1.01–2.29, per 1-U increment of *z*-score] and blood pressure (RR 1.79, 95% CI 1.12–2.86) conferred, however, increased risks of mucinous and endometrioid tumours, respectively. In women below the age of 50 years, there was increased risk of ovarian cancer mortality for MetS (RR 1.52, 95% CI 1.00–2.30). Increasing levels of BMI (RR 1.17, 95% CI 1.01–1.37) conferred increased risk of ovarian cancer mortality in women above the age of 50 years.

Conclusion There was no overall association between MetS and ovarian cancer risk. However, increasing levels of cholesterol and blood pressure increased the risks of mucinous and endometrioid tumours,

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respectively. Increasing levels of BMI conferred an increased risk of ovarian cancer mortality in women above the age of 50 years.

Keywords Ovarian cancer, metabolic syndrome, cohort study, CONOR, incidence, mortality

Introduction

Ovarian cancer is a disease of affluent societies, and is currently the sixth most common cancer in women worldwide, and seventh most common cause of cancer death.[1]

To our knowledge, no studies have so far evaluated the impact of the metabolic syndrome (MetS) as an entity on ovarian cancer risk. Individual components of the MetS have previously been linked to the development of ovarian cancer, but the results have been inconclusive.[2–4] Since ovarian cancer is hormone related,[5] factors that modify risk may differ before and after menopause and could contribute to the inconsistencies of previous reports.

In 2006, we initiated the Metabolic Syndrome and Cancer (Me-Can) project, combining long-standing cohorts in Austria, Norway and Sweden, to investigate the effects of MetS factors and the MetS as an entity on cancer risk.[6] So far, we have shown that metabolic factors influence the risk of two major female cancers: those of the breast and the endometrium.[7,8] The aim of the present study was to examine the association between MetS factors (both individually and combined) and the risk of ovarian cancer incidence and mortality.

Materials and methods

Study population

A comprehensive description of the Me-Can project has been published previously.[6] Briefly, for studies on female cancers, six cohorts from Austria, Norway and Sweden were pooled in 2006, and all women in the cohorts had undergone one or more health examination(s). Data on 288 834 women, collected during 1974–2005, were used.[7,8] Measurements of height, weight and systolic and diastolic blood pressure had been performed, and blood/plasma/serum levels of glucose, total cholesterol and triglycerides were analysed. Anthropometric measurements were conducted with participants wearing light indoor clothes and no shoes. Blood pressure was measured under different conditions in the cohorts (resting time before measurements, body positions and equipment), and also with various fasting times before blood draw.[6]

Detailed and complete information on known confounders of ovarian cancer risk such as reproductive history and exogenous hormone use (oral contraceptives and use/type/duration of hormone replacement therapy) were not available in all the individual Me-Can cohorts, and neither were data on hysterectomy/oophorectomy status. In the Norwegian cohorts, however, information on parity, year of childbirth(s) and physical activity were available.

Incident cases of ovarian cancer [International Classification of Diseases, seventh revision (ICD-7): 175.0] were identified through linkages with national cancer registries. When analysing incident cancer, only histologically verified epithelial tumours were included,[9] and in some analyses major histological subtypes (serous, mucinous and endometrioid tumours). Some cases (29%) were not included in these major groups or the information in the registries was not specific enough for this categorization. Borderline tumours were not included. The study cohort was linked to the respective National Cause of Death Registers, and in Norway and Sweden, to the Register of the Total Population and Population Changes, for vital status. Causes of death were coded according to the Eurostat European shortlist for causes of death.[10]

To reduce the possibility of reverse causation, follow-up started 1 year after the baseline examination. While exploring the ovarian cancer incidence, the follow-up ended at the date of the first cancer diagnosis, emigration, death or 31 December 2003 (Austria), 2005 (Norway) and 2006 (Sweden). While exploring the ovarian cancer mortality, the follow-up ended at the date of death or emigration or 31 December 2003 (Austria) and 2004 (Norway and Sweden). At the time of the data linkage, we used the most updated data available from the different sources in each country.

Statistical analysis

Cox proportional hazards regression models with age as the time variable, were fitted to obtain hazard ratios, here denoted as relative risks (RRs), of ovarian cancer incidence and mortality with 95% confidence intervals (95% CIs).[11] Quintile cut-points for the exposure variables were determined within the six subcohorts and for glucose, cholesterol and triglycerides, also in categories of fasting time (fasting: >8 h and non-fasting: ⩽8 h). The models were stratified for cohort (six subcohorts), and adjusted for year of birth (⩽1929, 1930–39, 1940–49, 1950–59 and ⩾1960), age at measurement (as a continuous variable) and smoking status (never, former and current smokers). RRs for blood pressure, glucose, cholesterol and triglycerides were further adjusted for quintile

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levels of body mass index [BMI (weight in kg)/(height in metres)^2].

Tests for trend across quintiles were calculated using the mean levels of cohort specific quintiles, and for glucose, cholesterol and triglycerides, also in fasting time categories.

The variables BMI, blood pressure [(systolic blood pressure + diastolic blood pressure)/2],[12] glucose, cholesterol and triglycerides were standardized to z-score variables with mean = 0 and standard deviation (SD) = 1. The variables were standardized separately for the six subcohorts, and for glucose, cholesterol and triglycerides also for fasting time. As glucose and triglycerides were skewed and had outliers, they were log transformed before standardization. A score for the MetS, calculated by adding the individual z-scores for BMI, blood pressure, glucose, cholesterol and triglycerides, was also standardized to a z-score variable with mean = 0 and SD = 1. This variable was standardized separately for the six subcohorts and for fasting time.

We examined the possibility of effect modification by BMI status. Analyses were stratified on BMI at measurement (three lowest and two highest quintiles), and we tested for interactions.

As information on age at menopause was unavailable for most of the study subjects, we used age 50 years as a proxy for age at menopause, and stratified some analyses according to attained age <50 years and $\geqslant 50$ years. When analysing women with attained age <50 years, only those who were measured below the age of 50 years were included. During follow-up, these individuals were censored when they reached 50 years. When analysing women with attained age $\geqslant 50$ years, those who were measured below the age of 50 years were included at the age of 50 years. We also tested for interactions between attained age and the different metabolic risk factors.

In country-specific analyses for the Norwegian cohorts, potential confounders such as parity, maternal age at childbirth(s) and physical activity were also adjusted for. However, the inclusion of these variables in the regression models did not appreciably change the risk estimates and, consequently, were not included in the final overall models.

Risk estimates were adjusted for random error in exposure assessment, as described previously,[13] based on the observations from subjects in which two or more observations with the same fasting time before measurements were available. In brief, data from 71 789 women with 232 152 repeated observations (3.2 per woman on average) were used for analyses of random error. Mean time between the baseline measurement and repeated measurements was 6.9 years (SD = 3.9). RRs in quintiles were corrected directly by dividing the regression coefficient in the Cox model by the estimated regression dilution ratio (RDR) of exposure.[14] RRs of z-scores were corrected indirectly by replacing each original z-score in the Cox model with its conditional expected value, i.e. regression calibration (RC).[15] RRs of z-scores were adjusted for all metabolic factors, which all except BMI have substantial random error.[16–18] Therefore, the RC method that allows for correction for random error also for covariates in the model, was used in these analyses. Analyses of RDR and RC were based on linear mixed-effect models, similar to those described by Wood *et al*.[14,15]

The statistical package SPSS (version 14.0.2) was used for risk estimation, and R (version 2.7.2) for random error calculation.

Ethics

The Me-Can project has been approved by ethical committees in the respective countries.

Results

Incidence

The 287 320 women in this study were followed for an average of 11 years (range 0–32 years) after measurement, constituting 2.9 million person-years when excluding the first year after measurements (Table 1). The mean age at measurement was 44 years. During follow-up, 644 epithelial ovarian cancers were diagnosed. The mean age at diagnosis was 59 years, and the epithelial ovarian cancer cases had their measurements taken, on average, 10 years prior to diagnosis.

The risk of epithelial ovarian cancer was first examined in quintile levels of the individual MetS factors (Table 2). When the analyses were stratified on attained age, glucose was inversely associated with risk in women above the age of 50 years. There were indications of an increasing risk with increasing systolic blood pressure in women below the age of 50 years, and a decreasing risk in women aged $\geqslant 50$ years.

The individual factors and the combined MetS score were further examined as continuous z-scores in relation to incident epithelial ovarian cancer. Table 3 gives estimates of the risk connected to a 1-U increase in the individual z-scores. There were no associations between the scores and overall ovarian cancer risk, neither in women below nor above 50 years. When testing for interactions between attained age and the different metabolic risk factors, the effect of blood pressure on the ovarian cancer risk was smaller in women with aged $\geqslant 50$ than <50 years. Stratifying the analyses on baseline BMI (three lowest and two highest quintiles), did not add further information (data not shown). No interactions were observed between baseline BMI (three lowest and two highest quintiles) and the other individual MetS factors.

We also calculated the risk of epithelial ovarian cancer according to the number of MetS factors

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Table 1 Characteristics of the study population in the Me-Can project

	Epithelial ovarian cancer incidence		Ovarian cancer mortality	
	Number of cases	Person-years	Number of cases	Person-years
Cohort				
Norway				
NCS[a]	205	653 973	156	658 099
CONOR[b]	75	352 278	35	302 828
40 years[c]	85	502 531	19	441 452
Austria				
VHM&PP[d]	117	837 945	78	855 768
Sweden				
VIP[e]	87	345 418	49	278 578
MPP[f]	75	200 320	51	194 342
Year of birth				
−1919	14	52 349	20	54 486
1920–29	136	302 846	106	305 690
1930–39	235	715 936	170	704 342
1940–49	111	482 972	53	458 495
1950–59	138	934 835	35	835 668
1960–	10	403 528	4	372 386
Age at measurement (years)				
⩽29	16	357 594	8	349 101
30–39	86	613 892	50	586 549
40–49	314	1 254 546	175	1 162 839
50–59	129	406 757	75	382 415
60–69	68	180 352	48	171 941
⩾70	31	79 324	32	78 222
Attained age (years)				
<50	161	1 486 602	49	1 408 584
50–59	180	644 415	98	597 668
⩾60	303	761 448	241	724 817
Smoking status				
Never smoker	346	1 464 075	226	1 401 562
Ex-smoker	142	653 749	57	593 354
Smoker	154	766 426	104	728 899
Missing	2	8 215	1	7 253
BMI (kg/m^2)				
<18.5	9	74 083	6	72 245
18.5–24.9	362	1 697 802	197	1 606 994
25.0–29.9	184	800 883	122	751 817
⩾30	89	319 697	63	300 011
Fasting time (hours)				
⩽8	379	1 511 269	222	1 404 782
>8	265	1 381 196	166	1 326 286
Follow-up (years)				
0–9	404	2 188 364	214	2 053 309
10–19	158	505 895	111	493 763
⩾20	82	198 206	63	183 996
Total	644	2 892 465	388	2 731 068

[a]Norwegian Counties Study.
[b]Cohort of Norway.
[c]Age 40 Programme.
[d]Vorarlberg Health Monitoring and Prevention Programme.
[e]Västerbotten Intervention Project.
[f]Malmö Preventive Project.

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Table 2 RRs of incident epithelial ovarian cancer with 95% CIs obtained in Cox regression analyses

		Total			Attained age (years)	
Exposure	Cohort specific quintiles	Mean (SD)	Number of cases	RR (95% CI)[a]	<50 RR (95% CI)[a]	⩾50 RR (95% CI)[a]
BMI (kg/m^2)	1	20.0 (1.2)	105	1 (referent)	1 (referent)	1 (referent)
	2	22.3 (0.8)	134	1.13 (0.85–1.50)	0.76 (0.45–1.30)	1.27 (0.89–1.79)
	3	24.1 (0.8)	135	1.01 (0.76–1.35)	0.92 (0.55–1.55)	1.01 (0.71–1.44)
	4	26.4 (1.0)	108	0.72 (0.53–0.98)	0.85 (0.49–1.46)	0.67 (0.46–0.97)
	5	31.7 (3.6)	162	1.11 (0.84–1.48)	0.96 (0.56–1.65)	1.12 (0.80–1.57)
	P_{trend}			0.80	0.92	0.96
Systolic blood pressure (mmHg)	1	104.5 (5.9)	101	1 (referent)	1 (referent)	1 (referent)
	2	114.4 (3.3)	98	1.05 (0.62–1.77)	1.30 (0.52–3.23)	0.91 (0.48–1.72)
	3	122.7 (3.0)	132	1.04 (0.64–1.70)	1.05 (0.41–2.70)	0.95 (0.54–1.69)
	4	133.6 (4.8)	146	0.93 (0.57–1.53)	1.77 (0.70–4.49)	0.69 (0.38–1.24)
	5	156.3 (16.1)	165	0.83 (0.50–1.38)	2.05 (0.74–5.66)	0.63 (0.35–1.13)
	P_{trend}			0.21	0.19	0.07
Diastolic blood pressure (mmHg)	1	63.5 (5.5)	106	1 (referent)	1 (referent)	1 (referent)
	2	70.3 (3.5)	89	0.80 (0.46–1.39)	0.61 (0.21–1.73)	0.83 (0.43–1.59)
	3	76.9 (3.6)	155	1.01 (0.62–1.64)	1.68 (0.70–4.02)	0.77 (0.43–1.39)
	4	81.0 (3.5)	121	0.90 (0.53–1.53)	0.88 (0.31–2.44)	0.82 (0.44–1.53)
	5	92.6 (7.6)	171	1.00 (0.60–1.65)	1.81 (0.69–4.80)	0.78 (0.44–1.41)
	P_{trend}			1.00	0.21	0.44
Glucose (mmol/l)	1	4.1 (0.5)	124	1 (referent)	1 (referent)	1 (referent)
	2	4.6 (0.3)	126	0.94 (0.38–2.37)	3.03 (0.55–16.1)	0.58 (0.20–1.74)
	3	5.0 (0.3)	136	0.71 (0.29–1.75)	0.83 (0.13–5.22)	0.66 (0.23–1.86)
	4	5.4 (0.3)	130	0.77 (0.31–1.92)	0.49 (0.07–3.47)	0.83 (0.30–2.36)
	5	6.6 (1.7)	128	0.59 (0.23–1.48)	2.48 (0.40–15.2)	0.38 (0.13–1.11)
	P_{trend}			0.08	0.65	0.02
Cholesterol (mmol/l)	1	4.2 (0.4)	80	1 (referent)	1 (referent)	1 (referent)
	2	4.9 (0.2)	113	1.43 (0.93–2.21)	1.36 (0.67–2.74)	1.40 (0.80–2.46)
	3	5.5 (0.3)	128	1.42 (0.93–2.19)	1.07 (0.51–2.25)	1.51 (0.88–2.59)
	4	6.1 (0.3)	152	1.61 (1.06–2.46)	1.31 (0.62–2.78)	1.65 (0.98–2.81)
	5	7.3 (0.9)	169	1.51 (0.98–2.32)	1.29 (0.57–2.91)	1.55 (0.91–2.63)
	P_{trend}			0.12	0.70	0.16
Triglycerides (mmol/l)	1	0.6 (0.1)	104	1 (referent)	1 (referent)	1 (referent)
	2	0.9 (0.1)	111	1.10 (0.65–1.88)	0.57 (0.22–1.47)	1.55 (0.80–2.99)
	3	1.1 (0.1)	134	1.34 (0.80–2.24)	0.87 (0.35–2.15)	1.75 (0.93–3.33)
	4	1.5 (0.2)	136	1.20 (0.71–2.03)	0.65 (0.24–1.71)	1.70 (0.90–3.23)
	5	2.5 (1.1)	142	1.12 (0.65–1.91)	0.58 (0.20–1.64)	1.61 (0.84–3.08)
	P_{trend}			0.81	0.20	0.30

[a]Stratified for cohort, and adjusted for year of birth, age at measurement, smoking and quintile levels of BMI (except BMI). RRs are corrected for RDR; conversion into uncorrected RR = exp[log(RR)*RDR]. RDR: BMI, 0.90; systolic blood pressure, 0.54; diastolic blood pressure, 0.51; glucose, 0.27; cholesterol, 0.66; triglycerides, 0.50.

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Table 3 RRs of epithelial ovarian cancer incidence by a 1-U increase in continuous *z*-scores with 95% CIs obtained in Cox regression analyses, stratified by attained age

	Attained age <50 years		Attained age ⩾50 years	
Exposure	RR (95% CI)[a]	RR (95% CI)[b]	RR (95% CI)[a]	RR (95% CI)[b]
BMI	0.98 (0.82–1.18)	0.95 (0.74–1.21)	1.02 (0.92–1.12)	1.08 (0.95–1.23)
Blood pressure	1.30 (0.95–1.78)	1.29 (0.90–1.86)	0.97 (0.82–1.15)	0.98 (0.82–1.17)
Glucose	1.16 (0.64–2.10)	1.26 (0.66–2.39)	0.76 (0.54–1.06)	0.76 (0.53–1.08)
Cholesterol	1.12 (0.87–1.45)	1.25 (0.93–1.69)	1.08 (0.94–1.24)	1.04 (0.89–1.22)
Triglycerides	0.83 (0.58–1.16)	0.72 (0.48–1.08)	1.05 (0.86–1.27)	1.08 (0.86–1.35)
MetS[c]	1.09 (0.86–1.40)		0.99 (0.86–1.15)	

[a]Stratified for cohort and adjusted for year of birth, age at measurement and smoking. RRs are corrected for RDR; conversion into uncorrected RR = exp[log(RR)*RDR]. RDR: BMI, 0.90; blood pressure, 0.56; glucose, 0.27; cholesterol, 0.66; triglycerides, 0.50.
[b]Stratified for cohort and adjusted for year of birth, smoking and the other individual *z*-scores. *Z*-scores, derived from original values, were calibrated.
[c]Standardized sum of the *z*-scores for BMI, blood pressure, glucose, cholesterol and triglycerides.

Table 4 RRs of epithelial ovarian cancer incidence with 95% CIs obtained in Cox regression analyses, according to number of high level (>1 SD) exposure variables present

Number of metabolic risk factors[a] with high levels (>1 SD)	Number of cases	RR (95% CI)[b]
0	317	1 (referent)
1	166	0.87 (0.72–1.06)
2	80	0.84 (0.65–1.08)
3	47	1.11 (0.81–1.53)
4	13	0.98 (0.56–1.72)
5	2	0.88 (0.22–3.56)

[a]BMI, blood pressure, glucose, cholesterol and triglycerides.
[b]Stratified for cohort and adjusted for year of birth and smoking.

present at high levels (>1 SD). The risk did not change by increasing the number of single components present (Table 4). Further, when comparing the presence of three or more MetS factors vs less than three, no association was found (RR 1.17, 95% CI 0.89–1.53).

When analysing the different histological subtypes, increasing levels of cholesterol and blood pressure conferred increased risks of mucinous and endometrioid tumours, respectively (Table 5). The RRs (calibrated values) for cholesterol and blood pressure were 1.52 (95% CI 1.01–2.29) and 1.79 (95% CI 1.12–2.86), per 1-U increment of *z*-score.

Mortality

During follow-up, 388 deaths from ovarian cancer were identified. Of these cases, 83% had a diagnosis of incident ovarian cancer after the date of measurements.

In analyses of quintile levels for the individual MetS factors (Table 6), there was an indication of a decreased risk of ovarian cancer mortality with increasing systolic and diastolic blood pressure.

Of the continuous *z*-score factors, increasing levels of the MetS conferred an increased risk in women <50 years [RR 1.52 (95% CI 1.00–2.30), per 1-U increment of *z*-score] (Table 7). Increasing levels of BMI conferred an increased risk in women above the age of 50 years after adjustment for the other individual *z*-scores [RR 1.17 (95% CI 1.01–1.37), per 1-U increment of *z*-score]. There was, however, a decreasing risk with increasing blood pressure [RR 0.82 (95% CI 0.65–1.02), per 1-U increment of *z*-score].

Stratifying the analyses on baseline BMI (three lowest and two highest quintiles), there was an increased risk for the MetS and also for glucose (calibrated values) among the heaviest women with attained age <50 years, with RRs 1.88 (95% CI 1.02–3.49) and 3.52 (95% CI 1.15–10.8), respectively, per 1-U increment of *z*-score.

The risk of ovarian cancer mortality did not change by increasing the number of single components present at high levels (>1 SD) (Table 8). Also, when comparing the presence of three or more MetS factors vs less than three, no association was found (RR 1.21, 95% CI 0.68–1.88).

Discussion

In this large, prospective cohort study, there was no overall association between the MetS and epithelial ovarian cancer risk. However, increasing levels of cholesterol and blood pressure increased the risk of mucinous and endometrioid tumours. Increasing levels of BMI conferred an increased risk of ovarian cancer mortality in women aged ⩾50 years.

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Table 5 RRs of epithelial ovarian cancer incidence by a 1-U increase in continuous *z*-scores with 95% CIs obtained in Cox regression analyses, by major histological subgroups

	Serous tumours (327 cases)		Mucinous tumours (62 cases)		Endometrioid tumours (66 cases)	
Exposure	RR (95% CI)[a]	RR (95% CI)[b]	RR (95% CI)[a]	RR (95% CI)[b]	RR (95% CI)[a]	RR (95% CI)[b]
BMI	1.03 (0.9–1.16)	1.06 (0.90–1.25)	0.95 (0.70–1.28)	1.07 (0.73–1.57)	1.05 (0.74–1.50)	0.99 (0.69–1.42)
Blood pressure	0.92 (0.74–1.14)	0.93 (0.74–1.17)	0.80 (0.47–1.36)	0.72 (0.41–1.26)	1.63 (1.16–2.28)	1.79 (1.12–2.86)
Glucose	0.77 (0.51–1.16)	0.80 (0.51–1.23)	1.16 (0.46–2.92)	1.24 (0.46–3.34)	0.91 (0.63–1.31)	0.82 (0.30–2.21)
Cholesterol	1.17 (0.99–1.38)	1.11 (0.92–1.34)	1.32 (0.91–1.92)	1.52 (1.01–2.29)	1.06 (0.73–1.54)	1.03 (0.66–1.61)
Triglycerides	1.15 (0.91–1.46)	1.16 (0.88–1.54)	0.93 (0.54–1.62)	0.82 (0.43–1.56)	0.95 (0.64–1.40)	0.78 (0.42–1.45)
MetS[c]	1.07 (0.90–1.27)		1.02 (0.67–1.54)		1.12 (0.77–1.65)	

[a]Stratified for cohort and adjusted for year of birth, age at measurement and smoking. RRs are corrected for RDR; conversion into uncorrected RR = exp[log(RR)*RDR]. RDR: BMI, 0.90; blood pressure, 0.56; glucose, 0.27; cholesterol, 0.66; triglycerides, 0.50.
[b]Stratified for cohort and adjusted for year of birth, smoking and the other individual *z*-scores. *Z*-scores, derived from original values, were calibrated.
[c]Standardized sum of the *z*-scores for BMI, blood pressure, glucose, cholesterol and triglycerides.

Strengths and limitations

The main strengths of our study have been described previously.[7] In brief, they include its large size, prospective design, almost complete coverage of data for measured exposure factors in the included cohorts, and high-quality national registries for follow-up of subjects.[19–21] In addition, the large number of repeated measurements within the cohorts allowed us to adjust for random error in the individual MetS factors.[13]

Similarly, the limitations of our study have been described previously.[7] We lack complete information on hysterectomy/oophorectomy status, reproductive history and exogenous hormone use. Although hysterectomy rates have been increasing in Norway and Sweden (the Nordic cohorts contribute with ~70% of the person-years in this study), its frequency is substantially lower than in the USA.[8] Thus, we do not believe this limitation will affect the results substantially. Data on parity, year of childbirth(s) and physical activity were, however, available in the Norwegian cohorts, but adjusting for these variables did not appreciably change the risk estimates. Further, cohort-specific characteristics were accounted for in stratified analyses, and we used standardized *z*-scores to account for different distributions and measurement methods of the risk factors in the different subcohorts.

Although the use of *z*-scores might be difficult to interpret form a public health perspective, we believe it is useful to have a combined risk score for the MetS as well as scores for the individual components of the MetS. This approach allows us to detect an overall association with relatively small increments in the individual factors, even if none of them would be strongly associated with risk.[22,23] By transforming all exposures into a *z*-distribution, we increased the comparability of the strength of the association for individual metabolic factors. Further, the use of a continuous variable has increased our ability to detect associations with risk.

There is no single universally accepted definition of the MetS, and also some controversy regarding the existence of this syndrome.[24] Nevertheless, all existing definitions[25–28] include indicators of insulin resistance, lipid abnormalities, blood pressure and obesity. As lipid subfractions, such as high-density lipoprotein cholesterol, were not available in all Me-Can cohorts, we included total cholesterol in our analyses instead.

Comparisons with the literature

Incidence

To our knowledge, no studies have previously assessed the MetS as an entity to ovarian cancer risk, although the individual factors have been evaluated to some extent.

Obesity is the most explored individual factor of the MetS. Nevertheless, the evidence for an association with ovarian cancer remains unclear. Most studies have reported positive associations for premenopausal women and no association for postmenopausal women.[29,30] However, in a recent study from EPIC (European Prospective Investigation into Cancer and Nutrition), it was found that BMI was an important risk factor for epithelial ovarian cancer, especially among post-menopausal women, and waist–hip ratio was related to increased risk of mucinous tumours.[3] In our study, no association of BMI and ovarian cancer risk was seen, neither by menopausal status nor for the major histological subtypes.

The relationship between hypertension and the risk of hormone-related cancers in women has previously been evaluated in a network of Italian case–control studies.[4] No association was observed for ovarian cancer. For endometrial and breast cancer,

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Table 6 RRs of ovarian cancer mortality with 95% CIs obtained in Cox regression analyses

Exposure	Cohort specific quintiles	Total			Attained age (years)	
		Mean (SD)	Number of cases	RR (95% CI)[a]	<50 RR (95% CI)[a]	⩾50 RR (95% CI)[a]
BMI (kg/m^2)	1	20.0 (1.2)	65	1 (referent)	1 (referent)	1 (referent)
	2	22.2 (0.8)	69	0.87 (0.60–1.27)	0.22 (0.06–0.75)	1.03 (0.68–1.56)
	3	24.1 (0.8)	70	0.77 (0.53–1.13)	0.46 (0.17–1.24)	0.83 (0.54–1.26)
	4	26.4 (1.0)	59	0.55 (0.37–0.83)	0.68 (0.27–1.70)	0.54 (0.35–0.85)
	5	31.7 (3.6)	125	1.23 (0.87–1.74)	1.15 (0.50–2.64)	1.26 (0.85–1.85)
	P_{trend}			0.04	0.21	0.10
Systolic blood pressure (mmHg)	1	105.4 (5.8)	63	1 (referent)	1 (referent)	1 (referent)
	2	115.4 (2.9)	49	0.99 (0.49–2.00)	0.76 (0.15–3.82)	1.04 (0.48–2.27)
	3	122.7 (3.0)	76	0.93 (0.49–1.74)	0.95 (0.22–4.18)	0.90 (0.45–1.81)
	4	133.6 (4.8)	93	0.88 (0.47–1.64)	0.33 (0.05–2.08)	0.95 (0.48–1.88)
	5	156.3 (16.1)	107	0.61 (0.32–1.17)	1.27 (0.23–7.04)	0.60 (0.30–1.20)
	P_{trend}			0.05	0.93	0.06
Diastolic blood pressure (mmHg)	1	63.5 (5.5)	60	1 (referent)	1 (referent)	1 (referent)
	2	70.4 (3.4)	53	0.82 (0.40–1.70)	0.98 (0.14–6.85)	0.76 (0.35–1.66)
	3	77.0 (3.6)	102	1.05 (0.56–1.97)	5.18 (1.10–24.3)	0.74 (0.37–1.47)
	4	81.0 (3.5)	83	1.04 (0.53–2.05)	0.78 (0.10–6.07)	0.99 (0.48–2.02)
	5	92.6 (7.7)	90	0.53 (0.27–1.04)	0.79 (0.10–6.44)	0.46 (0.23–0.95)
	P_{trend}			0.06	0.87	0.05
Glucose (mmol/l)	1	4.1 (0.5)	76	1 (referent)	1 (referent)	1 (referent)
	2	4.7 (0.3)	64	0.37 (0.11–1.28)	1.67 (0.05–56.5)	0.30 (0.08–1.11)
	3	5.0 (0.3)	81	0.61 (0.19–1.96)	2.68 (0.09–83.9)	0.49 (0.14–1.70)
	4	5.4 (0.3)	69	0.39 (0.12–1.30)	1.49 (0.04–56.3)	0.32 (0.09–1.15)
	5	6.6 (1.7)	98	0.94 (0.30–2.90)	18.9 (0.74–486)	0.62 (0.19–2.06)
	P_{trend}			0.52	0.05	0.91
Cholesterol (mmol/l)	1	4.2 (0.4)	48	1 (referent)	1 (referent)	1 (referent)
	2	4.9 (0.2)	60	1.07 (0.60–1.92)	1.48 (0.39–5.66)	0.94 (0.49–1.79)
	3	5.5 (0.3)	79	1.29 (0.74–2.24)	1.88 (0.50–7.06)	1.12 (0.61–2.05)
	4	6.1 (0.3)	100	1.43 (0.83–2.45)	1.23 (0.28–5.33)	1.32 (0.74–2.38)
	5	7.3 (0.9)	101	1.03 (0.59–1.79)	2.08 (0.49–8.92)	0.89 (0.49–1.62)
	P_{trend}			0.98	0.47	0.75
Triglycerides (mmol/l)	1	0.6 (0.1)	56	1 (referent)	1 (referent)	1 (referent)
	2	0.9 (0.1)	70	1.24 (0.61–2.50)	1.64 (0.24–11.0)	1.16 (0.55–2.47)
	3	1.1 (0.1)	68	0.93 (0.46–1.90)	2.24 (0.35–14.5)	0.81 (0.38–1.75)
	4	1.5 (0.2)	81	1.03 (0.51–2.07)	1.90 (0.27–13.3)	0.95 (0.45–2.00)
	5	2.5 (1.1)	102	1.22 (0.61–2.44)	3.76 (0.56–25.3)	1.07 (0.51–2.24)
	P_{trend}			0.45	0.16	0.64

[a]Stratified for cohort, and adjusted for year of birth, age at measurement, smoking and quintile levels of BMI (except BMI). RRs are corrected for RDR; conversion into uncorrected RR = exp[log(RR)*RDR]. RDR: BMI, 0.90; systolic blood pressure, 0.54; diastolic blood pressure, 0.51; glucose, 0.27; cholesterol, 0.66; triglycerides, 0.50.

however, there was an increased risk. In our study, there was an increased risk of endometrioid ovarian tumours with increasing levels of blood pressure. Also in our previous studies on MetS and female cancers within the Me-Can project, there was an increased risk of endometrial carcinoma connected to increasing levels of blood pressure, in particular, among the heaviest women, and an increased risk of breast cancer mortality among post-menopausal women.[7,8]

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Table 7 RRs of ovarian cancer mortality by a 1-U increase in continuous *z*-scores with 95% CIs obtained in Cox regression analyses, stratified by attained age

	Attained age < 50 years		Attained age ⩾ 50 years	
Exposure	RR (95% CI)[a]	RR (95% CI)[b]	RR (95% CI)[a]	RR (95% CI)[b]
BMI	1.20 (0.90–1.61)	1.02 (0.67–1.55)	1.10 (0.98–1.23)	1.17 (1.01–1.37)
Blood pressure	0.88 (0.47–1.62)	0.72 (0.36–1.43)	0.80 (0.65–0.99)	0.82 (0.65–1.02)
Glucose	2.20 (0.89–5.45)	2.06 (0.76–5.60)	0.89 (0.61–1.31)	0.87 (0.57–1.32)
Cholesterol	1.34 (0.87–2.08)	1.30 (0.78–2.17)	0.98 (0.83–1.16)	0.95 (0.78–1.14)
Triglycerides	1.42 (0.78–2.59)	1.16 (0.57–2.36)	1.03 (0.82–1.30)	1.12 (0.85–1.47)
MetS[c]	1.52 (1.00–2.30)		0.99 (0.84–1.18)	

[a]Stratified for cohort, and adjusted for year of birth, age at measurement and smoking. RRs are corrected for RDR; conversion into uncorrected RR = exp[log(RR)*RDR]. RDR: BMI, 0.90; blood pressure, 0.56; glucose, 0.27; cholesterol, 0.66; triglycerides, 0.50.
[b]Stratified for cohort, and adjusted for year of birth, smoking and the other individual *z*-scores. *Z*-scores, derived from original values, were calibrated.
[c]Standardized sum of the *z*-scores for BMI, blood pressure, glucose, cholesterol and triglycerides.

Table 8 RRs of ovarian cancer mortality with 95% CIs obtained in Cox regression analyses, according to number of high level (>1 SD) exposure variables present

Number of metabolic risk factors[a] with high levels (>1 SD)	Number of cases	RR (95% CI)[b]
0	165	1 (referent)
1	113	1.04 (0,81–1.33)
2	55	0.95 (0.69–1.31)
3	33	1.25 (0.85–1.85)
4	9	1.06 (0.54–2.10)
5	2	1.38 (0.34–5.62)

[a]BMI, blood pressure, glucose, cholesterol and triglycerides.
[b]Stratified for cohort and adjusted for year of birth and smoking.

In our study, we found an increased risk of mucinous tumours with increasing levels of cholesterol. Several epidemiological studies have reported on a negative association between cholesterol and cancer, and the association has largely been attributed to reverse causation, i.e. to an effect of pre-clinical cancer.[31] However, other studies have found higher cancer risk in individuals with high cholesterol or no associations.[32,33]

Recent epidemiological studies have suggested a role for dysregulated glucose metabolism in the pathogenesis of a number of cancers,[13,34] and it has also been hypothesized that hyperglycemia provides a nutrient- and growth signal-rich environment for epithelial ovarian cancer.[35] In our study, there was no strong indication of such an association.

Relatively little is known about the association between triglyceride levels and cancer risk, and studies show contradictory results.[36,37] In our data, triglyceride levels were not associated with ovarian cancer incidence and mortality.

Mortality

In a recent literature review on associations between weight, physical activity, diet and prognosis in breast and gynaecological cancers,[38] it was concluded that the limited data available on the association of weight with prognosis of ovarian cancer were inconclusive. Some studies indicated that obesity was a negative prognostic factor, whereas other studies did not demonstrate differences in outcome. In our study, increasing levels of BMI conferred an increased risk of ovarian cancer mortality in women aged ⩾50 years, whereas no effect was seen in women aged <50 years. A possible mechanism could involve elevations in circulating oestrogens, as BMI is related to greater exposure to oestrogens only after the transition to menopause and low overall oestrogenic environment.[39]

Conclusion

There was no overall association between MetS and ovarian cancer risk. However, increasing levels of cholesterol and blood pressure increased the risks of mucinous and endometrioid tumours, respectively. Increasing levels of BMI conferred an increased risk of ovarian cancer mortality in women aged ⩾50 years.

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Conflict of interest: None declared.

KEY MESSAGES

- This is the first prospective study to evaluate the association of the MetS as an entity with risk of ovarian cancer.
- In this large prospective study, there was no overall association between the MetS and epithelial ovarian cancer risk.
- Metabolic factors, however, increased the risk of major subtypes of epithelial ovarian cancer and ovarian cancer mortality.

References

[1] Boyle P, Levin B. *World Cancer Report* 2008. International Agency for Research on Cancer, Lyon, France, 2008.
[2] Kotsopoulos J, Baer HJ, Tworoger SS. Anthropometric measures and risk of epithelial ovarian cancer: results from the nurses' health study. *Obesity* 2010;**18:**1625–31.
[3] Lahmann PH, Cust AE, Friedenreich CM *et al*. Anthropometric measures and epithelial ovarian cancer risk in the European Prospective Investigation into Cancer and Nutrition. *Int J Cancer* 2010;**126:**2404–15.
[4] Soler M, Chatenoud L, Negri E, Parazzini F, Franceschi S, la Vecchia C. Hypertension and hormone-related neoplasms in women. *Hypertension* 1999;**34:**320–25.
[5] Lukanova A, Kaaks R. Endogenous hormones and ovarian cancer: epidemiology and current hypotheses. *Cancer Epidemiology, Biomarkers and Prevention* 2005;**14:**98–107.
[6] Stocks T, Borena W, Strohmaier S *et al*. Cohort profile: the Metabolic Syndrome and Cancer project (Me-Can). *Int J Epidemiol* 2009;**39:**660–67.
[7] Bjørge T, Lukanova A, Jonsson H *et al*. Metabolic syndrome and breast cancer in the Me-Can (Metabolic Syndrome and Cancer) project. *Cancer Epidemiol Biomarkers Prev* 2010;**19:**1737–45.
[8] Bjørge T, Stocks T, Lukanova A *et al*. Metabolic syndrome and endometrial carcinoma. *Am J Epidemiol* 2010;**171:** 892–902.
[9] Lee KR, Tavassoli FA, Prat J *et al*. Tumours of the ovary and peritoneum. Surface epithelial-stromal tumours. In: Tavassoli FA, Devilee P (eds). *Pathology and Genetics. Tumours of the Breast and Female Genital Organs*. Lyon: IARC Press, 2003, pp. 117–45.
[10] Eurostat, European shortlist for causes of death, 1998. http://ec.europa.eu/eurostat/ramon/nomenclatures/index.cfm?TargetUrl=LST_NOM_DTL&StrNom=COD_1998. 2009. 10 August 2011, date last accessed.
[11] Cox DR, Oakes D. *Analysis of Survival Data*. London: Chapman and Hall Ltd, 1984, pp. 1–201.
[12] Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;**360:** 1903–13.
[13] Stocks T, Rapp K, Bjørge T *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.
[14] 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.
[15] Fibrinogen Studies Collaboration. Correcting for multivariate measurement error by regression calibration in meta-analyses of epidemiological studies. *Stat Med* 2009; **28:**1067–92.
[16] Clarke R, Shipley M, Lewington S *et al*. Underestimation of risk associations due to regression dilution in long-term follow-up of prospective studies. *Am J Epidemiol* 1999;**150:**341–53.
[17] 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.
[18] Whitlock G, Clark T, Vander HS *et al*. Random errors in the measurement of 10 cardiovascular risk factors. *Eur J Epidemiol* 2001;**17:**907–9.
[19] Barlow L, Westergren K, Holmberg L, Talback M. The completeness of the Swedish Cancer Register: a sample survey for year 1998. *Acta Oncol* 2009;**48:**27–33.
[20] Larsen IK, Småstuen M, Johannesen TB *et al*. Data quality at the Cancer Registry of Norway: an overview of comparability, completeness, validity and timeliness. *Eur J Cancer* 2009;**45:**1218–31.
[21] Rapp K, Schroeder J, Klenk J *et al*. Fasting blood glucose and cancer risk in a cohort of more than 140,000 adults in Austria. *Diabetologia* 2006;**49:**945–52.
[22] Eisenmann JC. On the use of a continuous metabolic syndrome score in pediatric research. *Cardiovasc Diabetol* 2008;**7:**17.
[23] Franks PW, Ekelund U, Brage S, Wong MY, Wareham NJ. Does the association of habitual physical activity with the metabolic syndrome differ by level of cardiorespiratory fitness? *Diabetes Care* 2004;**27:** 1187–93.

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[24] Kahn R, Buse J, Ferrannini E, Stern M. The metabolic syndrome: time for a critical appraisal: joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2005;**28:**2289–304.
[25] Alberti KG, Eckel RH, Grundy SM *et al*. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* 2009;**120:**1640–5.
[26] Kahn R. Metabolic syndrome—What is the clinical usefulness? *Lancet* 2008;**371:**1892–3.
[27] Stocks T, Lukanova A, Johansson M *et al*. Components of the metabolic syndrome and colorectal cancer risk; a prospective study. *Int J Obesity* 2008;**32:**304–14.
[28] Unwin N. The metabolic syndrome. *J R Soc Med* 2006;**99:** 457–62.
[29] Engeland A, Tretli S, Bjørge T. Height, body mass index, and ovarian cancer: a follow-up of 1.1 million Norwegian women. *J Natl Cancer Inst* 2003;**95:**1244–48.
[30] Schouten LJ, Rivera C, Hunter DJ *et al*. Height, body mass index, and ovarian cancer: a pooled analysis of 12 cohort studies. *Cancer Epidemiol, Biomarkers Prev* 2008;**17:** 902–12.
[31] Strasak AM, Pfeiffer RM, Brant LJ *et al*. Time-dependent association of total serum cholesterol and cancer incidence in a cohort of 172 210 men and women: a prospective 19-year follow-up study. *Ann Oncol* 2009;**20:** 1113–20.
[32] Stolzenberg-Solomon RZ, Pietinen P, Taylor PR, Virtamo J, Albanes D. A prospective study of medical conditions, anthropometry, physical activity, and pancreatic cancer in male smokers (Finland). *Cancer Causes Control* 2002;**13:**417–26.
[33] Törnberg SA, Holm LE, Carstensen JM, Eklund GA. Risks of cancer of the colon and rectum in relation to serum cholesterol and beta-lipoprotein. *N Engl J Med* 1986;**315:** 1629–33.
[34] Hemminki K, Li X, Sundquist J, Sundquist K. Risk of cancer following hospitalization for type 2 diabetes. *Oncologist* 2010;**15:**548–55.
[35] Kellenberger LD, Bruin JE, Greenaway J *et al*. The role of dysregulated glucose metabolism in epithelial ovarian cancer. *J Oncol* 2010;**2010:** doi:10.1155/2010/514310 [Epub 17 February 2010].
[36] Lund HL, Wisloff TF, Holme I, Nafstad P. Metabolic syndrome predicts prostate cancer in a cohort of middle-aged Norwegian men followed for 27 years. *Am J Epidemiol* 2006;**164:**769–74.
[37] McKeown-Eyssen G. Epidemiology of colorectal cancer revisited: are serum triglycerides and/or plasma glucose associated with risk? *Cancer Epidemiol Biomarkers Prev* 1994;**3:**687–95.
[38] McTiernan A, Irwin M, Vongruenigen V. Weight, physical activity, diet, and prognosis in breast and gynecologic cancers. *J Clin Oncol* 2010;**28:**4074–80.
[39] Key TJ, Allen NE, Verkasalo PK, Banks E. Energy balance and cancer: the role of sex hormones. *Proc Nutr Soc* 2001; **60:**81–89.

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