

Metabolic Factors and the Risk of Pancreatic Cancer: A Prospective Analysis of almost 580,000 Men and Women in the Metabolic Syndrome and Cancer Project

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Abstract

Background: The aim of this study was to investigate the association between factors in metabolic syndrome (MetS; single and combined) and the risk of pancreatic cancer.

Methods: The Metabolic Syndrome and Cancer Project is a pooled cohort containing data on body mass index, blood pressure, and blood levels of glucose, cholesterol, and triglycerides. During follow-up, 862 individuals were diagnosed with pancreatic cancer. Cox proportional hazards analysis was used to calculate relative risks (RR) with 95% confidence intervals using the abovementioned factors categorized into quintiles and transformed into z-scores. All z-scores were summarized and a second z-transformation creating a composite z-score for MetS was done. All risk estimates were calibrated to correct for a regression dilution bias.

Results: The trend over quintiles was positively associated with the risk of pancreatic cancer for mid-blood pressure (mid-BP) and glucose in men and for body mass index, mid-BP, and glucose in women. The z-score for the adjusted mid-BP (RR, 1.10; 1.01-1.20) and the calibrated z-score for glucose (RR, 1.37; 1.14-1.34) were positively associated with pancreatic cancer in men. In women, a positive association was found for calibrated z-scores for mid-BP (RR, 1.34; 1.08-1.66), for the calibrated z-score for glucose (RR, 1.98; 1.41-2.76), and for the composite z-score for MetS (RR, 1.58; 1.34-1.87).

Conclusion: Our study adds further evidence to a possible link between abnormal glucose metabolism and risk of pancreatic cancer.

Impact: To our knowledge, this is the first study on MetS and pancreatic cancer using prediagnostic measurements of the examined factors. *Cancer Epidemiol Biomarkers Prev*; 19(9); 2307–17. ©2010 AACR.

Introduction

Pancreatic cancer is characterized by an extremely dismal clinical course, with an overall 5-year survival of <4% (1). Despite the relatively low incidence, pancreatic cancer is ranked eighth in the world for cancer mortality due to its high fatality rate. The poor outcome is a strong motivation for epidemiologic research aimed at identifying and/or reducing risk factors for pancreatic cancer. Besides age and genetic risk factors, several lifestyle and environmental factors such as smoking, obesity, low physical activity, and alcohol consumption have

been reported to be associated with pancreatic cancer (1). A recent study from Malmö showed that the association between body mass index (BMI) and risk of pancreatic cancer might be modified by smoking exposure, increasing the risk several-fold in obese smokers (2). Still, most cases of pancreatic cancer cannot be attributable to established risk factors, and as a consequence, several other potential risk factors have been suggested, one of these is the metabolic syndrome (MetS).

MetS was first described by Reaven in 1988 (3). Insulin resistance was described as a fundamental feature of several risk factors predisposing to cardiovascular morbidity

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and mortality. One of the main ideas was that the total influence of MetS should exceed the sum of each component. Today, there is a general consensus regarding the main components of the syndrome (4), but no consensus regarding the definition has been reached (5), and the prevalence of MetS therefore varies widely with the definition used. Regardless of this, a series of prospective studies have shown that the presence of MetS using different definitions is associated with a significantly increased risk of total mortality and cardiovascular disease (6).

Epidemiologic evidence linking MetS to cancer has thus far been sparse, although most of the components have been associated with the risk of cancer (7). Only a few prospective studies have indicated that the clustering of the components of MetS is associated with an increased risk of cancer (8, 9). The aim of this study was to investigate the association between MetS and its individual components in relation to the risk of pancreatic cancer. An additional aim was to examine if a potential association could be modified by tobacco smoking.

Materials and Methods

The Metabolic Syndrome and Cancer Project

The Metabolic Syndrome and Cancer Project (Me-Can) was initiated in 2006 to create a large pooled cohort to investigate the components of MetS on the association with overall and site-specific cancer risk. A detailed description of the project has recently been published (10). In brief, Me-Can includes data from seven population-based cohorts in Austria, Norway, and Sweden. The Austrian cohort consists of the Vorarlberg Health Monitoring and Prevention Program (VHM&PP; ref. 11); the Norwegian cohort includes the Oslo study I cohort (Oslo; ref. 12), the Norwegian Counties Study (NCS; ref. 13), the Cohort of Norway (CONOR; ref. 14), and the Age 40-programme (40-y; ref. 15); and the Swedish cohort is composed of the Västerbotten Intervention Project (VIP; ref. 16) and the Malmö Preventive Project (MPP; ref. 17).

Ethical clearance for the present study was obtained from the three countries' ethics committees.

Baseline examinations

In all Me-Can cohorts, baseline measurements of height and weight were done in a similar way; without shoes and wearing light indoor clothes. BMI was calculated as weight in kilograms divided by the squared height in meters (kg/m^2). Systolic and diastolic blood pressure was assessed in the supine position in the VIP and MPP cohorts. In the remaining cohorts, blood pressure was measured in a sitting position. Blood, plasma, or serum levels of glucose, total cholesterol, and triglycerides were analyzed. In the Norwegian cohorts, fasting was not required before health examination and fasting time was recorded as <1, 1 to 2, 2 to 4, 4 to 8, or >8 hours. Fasting time in the VIP was recorded as <4, 4 to 8, or

>8 hours, but from 1992 onwards, participants were asked to fast for at least 8 hours before the examination. In the MPP, and after an initial 3 years in the VHM&PP, a minimum of 8 hours of fasting was used as a standard procedure. Glucose levels were measured in serum using a nonenzymatic method (in the Oslo and NCS cohorts), a serum/enzymatic method (in CONOR and the 40-y cohorts), a plasma/enzymatic method (in the VHM&PP and the VIP cohorts), and a whole blood/enzymatic method (in the MPP cohort). Cholesterol and triglyceride levels were measured in serum using a nonenzymatic method in the Oslo and NCS cohorts up until 1980, and thereafter, using an enzymatic method. In the other cohorts, all measurements were obtained using an enzymatic method. For these two variables, levels from the nonenzymatic method have been compared with the enzymatic method (10) and to correspond with the enzymatic method, the original values were transformed according to the formulas: ($\text{cholesterol}_{\text{enzymatic}} = 0.92 \times \text{cholesterol}_{\text{nonenzymatic}} + 0.03$) and ($\text{triglycerides}_{\text{enzymatic}} = 0.90 \times \text{triglyceride}_{\text{nonenzymatic}} - 0.11$).

In the Me-Can cohort, except for VHM&PP, participants were asked to fill in a questionnaire concerning smoking habits. In VHM&PP, questions regarding smoking were asked by the examining physician, and the answers were recorded. Smoking status was classified as never, former, and current smokers.

Study population

The Me-Can study population includes 940,060 subjects with data from 1,600,296 health examinations. Exclusions were made for observations with a cancer diagnosis before the date of baseline examination, for a glucose level of <1 mmol/L, and for missing data on height and weight. Furthermore, exclusions were made for observations with data missing on glucose or fasting time and for observations in the 40-y cohort from 1993, for which glucose levels had been considered unrealistically low. Of the remaining 611,459 subjects with 1,025,940 observations eligible for the study, the first of the observations for each subject were selected. If data from a fasting state and data on smoking status were available, the first of these observations were selected.

A policy imposed by the Norwegian Institute of Public Health states that the proportion of Norwegian subjects in Me-Can studies must not exceed ~50% (56% after above selection), a further 1,868 subjects in Norway without data on smoking status were excluded, leaving a total of 288,834 women and 289,866 men (578,700 subjects) eligible for the present study. For a more detailed description of inclusions and exclusions, please see Stocks et al. (10, 18).

After matching the 578,700 subjects to the date of the event, i.e., diagnosis of pancreatic cancer, or until the date of death, migration or end of follow-up, whichever occurred first, a further 1,385 subjects with a follow-up of <1 year were excluded, leaving a total of 577,315 individuals in the present study population.

Follow-up of cancer diagnosis and cause of death

The seven cohorts were linked to the respective National registers for (a) cancer diagnosis, (b) migration, (c) vital status, and (d) cause of death. The ends of follow-up for each cohort were as follows: the Austrian cohort, 2003 (a), no information available (b), and 2003 (c-d); the Norwegian cohorts, 2005 (a-c) and 2004 (d); and the Swedish cohorts, 2006 (a-c) and 2004 (d). Incident pancreatic cancer was identified through linkage to the National Cancer registries, using the International Classification of Diseases (7th edition; code 157), resulting in 862 cases of pancreatic cancer; 315 in women and 547 in men.

Statistical analysis

To reduce the probability of reverse causation, all statistical analyses were calculated with follow-up starting 1 year after baseline examination. Quintile cutoffs for five variables were calculated separately within each cohort and sex, and for glucose, cholesterol, and triglycerides, as well as in categories of fasting time (i.e., <4, 4-8, and >8 h). The risk of pancreatic cancer was compared with quintile levels of BMI, mid-blood pressure [mid-BP = $(BP_{\text{systolic}} + BP_{\text{diastolic}})/2$] and quintile levels of glucose, cholesterol, and triglycerides. A Cox proportional hazards analysis was used to calculate relative risks (RR) with a 95% confidence interval. Attained age was used as the time scale and the models were stratified by cohort and by categories of birth year: before 1923, 1923 to 1930, 1931 to 1938, 1939 to 1946, 1947 to 1954, 1955 and later. The RRs were adjusted for age at baseline as a continuous variable, and for smoking status and quintile levels of BMI (except BMI) as categorical variables. The *P* value for trend over quintiles refers to the Wald test of a linear risk estimate.

To make the variables comparable on a continuous scale and to create a combined MetS variable, a z-score standardization was used [(exposure level – mean)/SD], resulting in a z-score of the exposures with a mean of 0 and a SD of 1. The entire cohort was used as a reference when the z-score was calculated. Glucose and triglycerides were log-transformed before standardization, as they were skewed and had outliers. BMI and mid-BP were standardized separately in groups defined by sub-cohort and sex. In addition, log(glucose), cholesterol, and log(triglycerides) were standardized based on subcohort, sex, and fasting time. The MetS score was calculated by summarizing the five individual z-scores before standardization. Cox proportional hazard regression was used to calculate RRs for the continuous z-score of exposures with a risk of pancreatic cancer. Again, attained age was used as the time scale and the model was stratified by cohort and birth year categories. In the analysis of MetS, all estimates were adjusted for age at baseline and smoking status. In the analysis of separate exposures, BMI, mid-BP, glucose, cholesterol, and triglycerides, the adjusted model refers to adjustment for all other single metabolic factors at the same time.

To detect modifying effects, all analyses were made separately for men and women, and the z-score analyses were also stratified for smoking status. Interactions between gender and the examined factors, and between smoking status and the examined factors, were analyzed by entering one covariate multiplied by the other as an interaction term. *P* < 0.05 was considered to be indicative of a statistically significant interaction. All statistical analysis were done using the software SPSS 17.0.

Correction of a random error

The combined effect of measurement errors of the different exposures (BMI, mid-BP, glucose, cholesterol, and triglycerides) and long-term fluctuations within the individuals may lead to a regression dilution bias. Corrections were made by calculating the regression dilution ratio (RDR) and by using regression calibration (19-21). These calculations were based on repeated health examinations in 133,820 subjects, including 406,364 observations in the full Me-Can database (10). The database was cleared from measurements preceded by a cancer diagnosis, from repeated measurements from a different cohort, and from measurements with a different fasting time as compared with baseline measurements. An exception from this was made pairwise for the Oslo and the NCS cohorts and for the CONOR and 40-y cohorts. That is, if a baseline measurement was done in the Oslo study, a repeated measurement done in the NCS was accepted, but not from CONOR or the 40-y cohort and visa versa. Finally, exclusions were made if there was missing data on any of the exposures included in the MetS and fasting time.

To correct for potential regression dilution bias in the analysis based on quintiles, a regression coefficient was calculated [the RDR as described by Wood et al. (21)]. RDRs were estimated for the mean follow-up time in the full Me-Can database divided by two, i.e., 6 years and modeled among men and women separately. This was done as a linear mixed model, which included the actual exposure (repeated measurement as dependent and baseline measurement as independent variables), age at baseline, birth year, fasting time, smoking status, and time from baseline as fixed effects and cohort as random effect. Correction of the RRs for RDRs were obtained in a direct way by dividing the estimated variable with RDR ($\exp[\log(\text{RR})/\text{RDR}]$), using a gender-specific RDR. The estimated RDR correction values for men/women were 0.90/0.90 for BMI, 0.53/0.56 for mid-BP, 0.28/0.27 for glucose, 0.64/0.66 for cholesterol, 0.51/0.50 for triglycerides, and 0.68/0.69 for MetS. This indicates that all the metabolic factors, except BMI, have a substantial random error.

The correction by RDR was not suitable in models using more than one variable measured with error. In such situations, a regression calibration model was used (19) for the analysis of the z-score. Using this method, the exposure measured with error (the observed measurement) was replaced with a predicted value calculated from a regression

model, similar as described above, but also including the other metabolic factors as adjustment. The corrected measurement was then used in risk model estimation.

Results

Baseline characteristics

Age at baseline among male participants in Me-Can was 43.9 (SD = 11.1) and age among female participants was 44.1 (SD = 12.3; Table 1). The majority of participants were aged between 30 and 59 years. The mean follow-up time was 12.8 years (SD = 8.5) among men and 11.3 years (SD = 6.9) among women. There were no great differences between follow-up time of cases and the rest of the cohort in either group. The

prevalence of overweight, i.e., BMI of >25 kg/m², was 55% among men and 41% among women, but there were no great differences in the distribution among weight categories between cases and the rest of the cohort in men or women. The means/medians for mid-BP, glucose, and cholesterol were somewhat higher in the female case group as compared with the rest of the cohort.

Quintile levels of exposure and risk of pancreatic cancer

The risk of pancreatic cancer was examined in quintile levels of BMI, mid-BP, glucose, cholesterol, and triglycerides, using the first quintile as the reference category (Table 2). Absolute risks were calculated and revealed a

Table 1. Baseline characteristics

	Men		Women	
	Cases	Rest of cohort	Cases	Rest of cohort
Subjects (n)	547	288,429	315	288,024
Age at baseline, mean (SD)	49.3 (9.6)	43.9 (11.1)	52.8 (10.6)	44.1 (12.3)
Cohort (%)				
Oslo	119 (21.8)	16,596 (5.8)	0 (0)	0 (0)
NCS	98 (17.9)	25,781 (8.9)	80 (25.4)	24,971 (8.7)
CONOR	35 (6.4)	51,890 (18.0)	22 (7.0)	57,492 (20.0)
40-y	19 (3.5)	60,585 (21.0)	15 (4.8)	68,135 (23.7)
VHM&PP	94 (17.2)	72,843 (25.3)	83 (26.3)	86,420 (30.0)
VIP	49 (9.0)	38,697 (13.4)	52 (16.5)	40,562 (14.1)
MPP	133 (24.3)	22,034 (7.6)	63 (20.0)	10,444 (3.6)
Fasting time (%)				
<4 h	223 (40.8)	119,951 (41.6)	103 (32.7)	122,016 (42.4)
4-8 h	42 (7.7)	30,627 (10.6)	23 (7.3)	26,727 (9.3)
>8 h	282 (51.6)	137,851 (47.8)	189 (60.0)	139,281 (48.4)
BMI (kg/m ²)				
Mean (SD)	25.3 (3.5)	25.7 (3.5)	25.8 (4.3)	24.9 (4.4)
Mid-BP (mm Hg)				
Mean (SD)	110.7 (13.7)	108.2 (35.9)	116.4 (72.3)	101.8 (14.2)
Missing (%)	0 (0)	411 (0.1)	2 (0.6)	485 (0.2)
Glucose (mmol/L)				
Median (IQR)	5.3 (1.4)	5.2 (1.3)	5.3 (2.2)	5.0 (1.2)
Missing (%)	2 (0.4)	414 (0.1)	2 (0.6)	355 (0.1)
Cholesterol (mmol/L)				
Mean (SD)	5.9 (1.1)	5.7 (1.2)	6.2 (1.2)	5.5 (1.2)
Missing (%)	2 (0.4)	590 (0.2)	1 (0.3)	775 (0.3)
Triglycerides (mmol/L)				
Median (IQR)	1.5 (1.1)	1.5 (1.3)	1.3 (1.0)	1.1 (0.8)
Missing (%)	16 (2.9)	7,738 (2.7)	9 (2.9)	4,514 (1.6)
Smoking status, n (%)				
Never	141 (25.8)	113,046 (39.2)	155 (49.2)	144,384 (50.1)
Former	127 (23.2)	85,747 (29.7)	42 (13.5)	72,464 (25.2)
Current	277 (50.6)	88,777 (30.8)	115 (36.9)	70,484 (24.5)
missing	2 (0.4)	859 (0.3)	3 (1.0)	692 (0.2)

NOTE: All percentages are column percent.
Abbreviation: IQR, interquartile range.

Table 2. Risk of pancreatic cancer in the Me-Can cohort in relation to metabolic factors

Exposures	Quintile level*	Mean (SD)	n, cases	Incidence/100,000 person years	RR crude [†]	RR adjusted [‡]	RR RDR corrected [§]
BMI (kg/m ²)	1	21.0 (1.3)	101	13.5	1.00	1.00	1.00
	2	23.3 (0.7)	105	13.9	0.92 (0.70-1.20)	0.96 (0.73-1.26)	0.96 (0.70-1.29)
	3	24.8 (0.7)	115	15.4	0.93 (0.71-1.22)	0.99 (0.76-1.29)	0.99 (0.74-1.33)
	4	26.5 (1.0)	101	13.6	0.77 (0.59-1.02)	0.83 (0.63-1.10)	0.81 (0.60-1.11)
	5	30.1 (2.9)	123	17.3	0.72 (0.73-1.24)	1.04 (0.79-1.35)	1.04 (0.77-1.40)
	All		545	14.7	<i>P</i> trend; 0.42	<i>P</i> trend; 0.54	
Mid-BP (mm Hg)	1	92.2 (5.5)	79	10.1	1.00	1.00	1.00
	2	101.0 (3.0)	96	12.3	1.08 (0.81-1.46)	1.12 (0.83-1.51)	1.24 (0.70-2.18)
	3	106.9 (2.8)	112	15.8	1.25 (0.93-1.66)	1.32 (0.99-1.76)	1.69 (0.98-2.92)
	4	112.7 (3.2)	101	13.7	0.96 (0.72-1.30)	1.04 (0.77-1.41)	1.08 (0.61-1.92)
	5	127.2 (10.3)	157	21.1	1.26 (0.95-1.66)	1.39 (1.04-1.85)	1.87 (1.08-3.21)
	All		545	14.7	<i>P</i> trend; 0.16	<i>P</i> trend; 0.06	
Glucose (mmol/L)	1	4.2 (0.5)	102	13.2	1.00	1.00	1.00
	2	4.8 (0.3)	81	10.9	0.80 (0.60-1.07)	0.81 (0.60-1.08)	0.49 (0.18-1.29)
	3	5.1 (0.3)	121	16.1	1.12 (0.86-1.46)	1.14 (0.88-1.49)	1.55 (0.65-3.81)
	4	5.6 (0.3)	101	14.2	0.99 (0.75-1.30)	1.01 (0.76-1.34)	1.03 (0.40-2.67)
	5	6.9 (2.0)	138	19.2	1.20 (0.92-1.55)	1.24 (0.95-1.61)	2.05 (0.84-4.94)
	All		543	14.6	<i>P</i> trend; 0.05	<i>P</i> trend; 0.03	
Cholesterol (mmol/L)	1	4.5 (0.5)	100	13.6	1.00	1.00	1.00
	2	5.3 (0.3)	98	13.1	0.79 (0.60-1.04)	0.78 (0.59-1.03)	0.68 (0.44-1.04)
	3	5.8 (0.4)	120	16.2	0.90 (0.69-1.17)	0.88 (0.68-1.15)	0.82 (0.55-1.24)
	4	6.4 (0.4)	117	15.9	0.81 (0.62-1.06)	0.79 (0.61-1.04)	0.69 (0.46-1.06)
	5	7.6 (0.7)	108	14.6	0.73 (0.56-0.97)	0.70 (0.53-0.93)	0.57 (0.37-0.89)
	All		543	14.6	<i>P</i> trend; 0.20	<i>P</i> trend; 0.12	
Triglycerides (mmol/L)	1	0.8 (0.2)	87	12.0	1.00	1.00	1.00
	2	1.2 (0.2)	108	14.7	1.13 (0.85-1.49)	1.10 (0.83-1.47)	1.20 (0.69-2.12)
	3	1.5 (0.3)	109	15.1	1.12 (0.84-1.48)	1.09 (0.82-1.44)	1.18 (0.68-2.03)
	4	2.0 (0.3)	111	15.4	1.21 (0.85-1.49)	1.08 (0.81-1.44)	1.16 (0.66-2.04)
	5	3.4 (1.4)	114	16.0	1.19 (0.90-1.56)	1.13 (0.84-1.52)	1.30 (0.71-2.27)
	All		529	14.3	<i>P</i> trend; 0.82	<i>P</i> trend; 0.94	

NOTE: Quintile analysis in men.

*Quintile levels grouped by cohort and sex and for glucose, cholesterol, and triglycerides even for fasting time.

[†]RR estimated from Cox regression models with attained age as time scale, stratified by cohort and categories of birth years.

[‡]Adjusted for quintiles levels of BMI (except BMI) and smoking status as categorical variables and age at baseline as a continuous variable.

[§]Corrected RR was obtained by (exp [log (adj.RR)/RDR]).

lower risk in women, as compared with men in the lower quintiles; for high quintiles, the risk became nearly equal, although still generally lower in women. The only statistically significant positive association among men was for the fifth quintile of the mid-BP and pancreatic cancer, as well as for the trend over the quintiles for the crude and adjusted glucose levels. Among women, statistically significant associations were found in the fifth quintile of BMI, in the fifth quintile of mid-BP, and in the fourth and fifth quintiles of glucose levels (Table 3). A statistically significant positive association was also found for the crude and adjusted trend for mid-BP and glucose and for the crude RR for triglycerides in relation to risk of pancreatic cancer. The RRs corrected for RDR were sim-

ilar as compared with uncorrected RRs among men, except for a somewhat stronger association between mid-BP and pancreatic cancer. Among women, the corrected RR was markedly higher for the fifth glucose quintile.

z-score of exposures and risk of pancreatic cancer

In the analysis of continuous z-scores for the five exposures and the exposures combined (MetS), there was a statistically significant association between mid-BP and pancreatic cancer as well as between glucose and pancreatic cancer in both men and women (Table 4). Moreover, in women, there was a statistically significant positive association between MetS and the risk of pancreatic cancer. Following regression calibration, most point

Table 3. Risk of pancreatic cancer in the Me-Can cohort in relation to metabolic factors

Exposures	Quintile level*	Mean (SD)	n, cases	Incidence/100,000 person years	RR crude [†]	RR adjusted [‡]	RR RDR corrected [§]
BMI (kg/m ²)	1	20.0 (1.2)	37	5.7	1.00	1.00	1.00
	2	22.3 (0.8)	55	8.4	1.18 (0.78-1.79)	1.26 (0.83-1.91)	1.29 (0.81-2.06)
	3	24.1 (0.8)	59	9.0	1.05 (0.69-1.59)	1.16 (0.77-1.76)	1.18 (0.75-1.88)
	4	26.4 (1.0)	74	11.3	1.13 (0.76-1.68)	1.29 (0.86-1.93)	1.33 (0.85-2.08)
	5	31.7 (3.7)	90	14.1	1.31 (0.89-1.93)	1.54 (1.04-2.29)	1.62 (1.04-2.52)
	All		315	9.7	<i>P</i> trend; 0.61	<i>P</i> trend; 0.23	
Mid-BP (mm Hg)	1	88.7 (4.7)	29	4.6	1.00	1.00	1.00
	2	95.8 (2.2)	37	5.9	1.11 (0.68-1.81)	1.18 (0.72-1.92)	1.35 (0.55-3.24)
	3	101.2 (2.5)	58	8.2	1.31 (0.83-2.05)	1.42 (0.90-2.24)	1.88 (0.83-4.28)
	4	109.2 (3.3)	70	10.7	1.17 (0.76-1.83)	1.33 (0.85-2.08)	1.67 (0.75-3.74)
	5	126.4 (10.7)	119	18.7	1.68 (1.09-2.56)	1.94 (1.24-3.00)	3.30 (1.47-7.24)
	All		313	9.6	<i>P</i> trend; 0.04	<i>P</i> trend; 0.01	
Glucose (mmol/L)	1	4.1 (0.6)	34	5.1	1.00	1.00	1.00
	2	4.8 (0.4)	51	7.5	1.36 (0.88-2.10)	1.36 (0.88-2.09)	2.96 (0.64-13.53)
	3	5.0 (0.4)	49	7.8	1.31 (0.85-2.04)	1.32 (0.85-2.05)	2.67 (0.56-12.64)
	4	5.4 (0.4)	73	10.9	1.77 (1.18-2.67)	1.79 (1.19-2.70)	7.82 (1.85-33.44)
	5	7.1 (3.3)	106	17.3	2.31 (1.57-3.41)	2.39 (1.61-3.54)	21.7 (5.38-87.08)
	All		313	9.6	<i>P</i> trend; <0.01	<i>P</i> trend; <0.01	
Cholesterol (mmol/L)	1	4.4 (0.5)	38	5.9	1.00	1.00	1.00
	2	5.1 (0.3)	43	6.6	0.86 (0.56-1.34)	0.87 (0.56-1.34)	0.81 (0.42-1.56)
	3	5.7 (0.3)	50	7.8	0.80 (0.52-1.22)	0.81 (0.53-1.25)	0.73 (0.38-1.40)
	4	6.3 (0.3)	73	11.2	0.95 (0.64-1.42)	0.96 (0.64-1.44)	0.94 (0.51-1.74)
	5	7.6 (0.8)	110	16.7	1.12 (0.76-1.65)	1.11 (0.75-1.64)	1.17 (0.64-2.12)
	All		314	9.6	<i>P</i> trend; 0.35	<i>P</i> trend; 0.42	
Triglycerides (mmol/L)	1	0.6 (0.1)	46	7.0	1.00	1.00	1.00
	2	0.9 (0.1)	36	5.9	0.72 (0.46-1.11)	0.67 (0.44-1.05)	0.45 (0.20-1.10)
	3	1.1 (0.1)	60	9.4	1.01 (0.68-1.48)	0.91 (0.62-1.34)	0.83 (0.39-1.79)
	4	1.4 (0.2)	65	10.1	0.99 (0.68-1.46)	0.86 (0.58-1.27)	0.74 (0.34-1.61)
	5	2.5 (1.2)	99	15.4	1.33 (0.93-1.01)	1.09 (0.75-1.59)	1.19 (0.57-2.51)
	All		306	9.4	<i>P</i> trend; 0.03	<i>P</i> trend; 0.16	

NOTE: Quintile analysis in women.

*Quintile levels grouped by cohort and sex and for glucose, cholesterol and triglycerides even fasting time.

[†]RR estimated from Cox regression model with attained age as time scale, stratified by cohort and categories of birth years.

[‡]Adjusted for quintiles levels of BMI (except BMI) and smoking status as categorical variables and age at baseline as a continuous variable.

[§]Corrected RR was obtained by (exp [log (adj.RR)/RDR]).

estimates were slightly stronger and confidence intervals were wider. Significant effect modification was found towards a larger effect among women ($P = 0.02$).

Metabolic factors and risk of pancreatic cancer in relation to smoking

To explore the possible interaction with smoking status, the continuous z-score was analyzed in different strata of never-smokers, former smokers, and current smokers for men and women separately (Table 5). In male never-smokers, positive risk associations were found for the adjusted and calibrated z-scores for glucose. In current smokers, there was a statistically significant association between pancreatic cancer and

the crude, adjusted, and calibrated mid-BP. In female never-smokers, the risk of pancreatic cancer was positively associated with the crude, adjusted, and calibrated mid-BP, glucose, and MetS. In female former smokers, associations were found for the crude BMI, glucose, and triglycerides as well as for the crude, adjusted, and calibrated MetS. In female current smokers, significantly positive associations were found for the crude, adjusted, and calibrated glucose z-scores as well as for adjusted and calibrated MetS z-scores. In men, the risk of pancreatic cancer associated with mid-BP (and triglycerides) in current smokers was statistically significantly higher than the risk associated with mid-BP in never-smokers. However, for cholesterol the risk was found to be statistically

significantly higher in never-smokers as compared with former smokers. In women, the risk associated with glucose was statistically significantly higher in former and current smokers as compared with never-smokers. The risk associated with cholesterol in current smokers was statistically significantly higher than the risk in never-smokers. For MetS, the risk was higher in former smokers, but the relationship was inverted between current smokers and never-smokers, i.e., with a larger effect in never-smokers.

Discussion

In this large prospective cohort study of almost 600,000 individuals, with 862 incident cases of pancreatic cancer, a statistically significant association between mid-BP, glucose, and MetS and pancreatic cancer was found among women, with the strongest association for glucose. In men, there was an indication of a positive association between mid-BP and glucose and risk of pancreatic cancer. Risk estimates obtained after correction for measurement error made the associations somewhat stronger, indicating an underestimation of the true associations.

Why should MetS be a more important risk factor in women than in men is not clear. The calculation of absolute risks in this report indicated a protective effect in women in lower quintiles, but this difference disappeared at higher exposure levels. Incidence rates of pancreatic cancer are higher in men than in women, which was confirmed in this report. Later in life, incidence rates become nearly equivalent (22). There is, at present, no support in the literature that women with MetS or its individual components are more susceptible to developing pancreatic cancer. Estrogens and/or androgens have

tumor-promoting effects in relation to other cancer forms. Whether or not sex hormones affect the development of pancreatic cancer or if these hormones could modify other risk factors and thereby explain different risk factor profiles in men and women is unclear.

There is only one study on the putative association between MetS and pancreatic cancer. Russo et al. used subjects who were simultaneously prescribed with anti-hypertensive, lipid-lowering, and antidiabetic drugs in a small study of 43 individuals and found a positive association between MetS and the risk of pancreatic cancer, but only in men (23). This was not confirmed by the present study, which indicated an association between mid-BP and glucose levels and risk of pancreatic cancer, whereas the analysis of MetS z-score did not reveal any significant association. Epidemiologic data supports a relationship between obesity and pancreatic cancer (24, 25), and between high glucose levels and pancreatic cancer (26-28), but most studies have reported null associations between cholesterol/hypertension and the risk of pancreatic cancer (29, 30). The results in the present study are in accordance with these findings, except that there was no positive association between BMI and pancreatic cancer in men. In women, a positive association was only seen in the highest quintile versus the lowest. It is, however, possible, as suggested by Li et al. (24), that obesity at a younger age has a more profound effect on risk of pancreatic cancer compared with obesity at an older age.

High blood pressure was related to an increased risk for pancreatic cancer in both men and women. Most studies on hypertension and cancer have failed to show a statistically significant association when BMI was taken into account. However, in a recently published article on

Table 4. Risk of pancreatic cancer in the Me-Can cohort in relation to metabolic factors

Exposure	Men (n = 545)			Women (n = 315)			Interaction [§] P value
	z-score, crude*	z-score, adjusted [†]	z-score, calibrated [‡]	z-score, crude*	z-score, adjusted [†]	z-score, calibrated [‡]	
BMI	0.98 (0.90-1.07)	0.97 (0.88-1.07)	0.90 (0.80-1.02)	1.07 (0.96-1.20)	1.04 (0.92-1.17)	0.92 (0.79-1.07)	0.45
Mid-BP	1.07 (0.98-1.16)	1.10 (1.01-1.20)	1.15 (0.97-1.35)	1.19 (1.07-1.32)	1.22 (1.09-1.36)	1.34 (1.08-1.66)	0.06
Glucose	1.08 (1.00-1.17)	1.09 (1.00-1.18)	1.37 (1.01-1.85)	1.23 (1.14-1.34)	1.20 (1.10-1.32)	1.98 (1.41-2.76)	0.02
Cholesterol	0.92 (0.84-1.00)	0.87 (0.79-0.96)	0.81 (0.69-0.95)	1.10 (0.99-1.23)	1.09 (0.96-1.22)	1.16 (0.96-1.41)	0.08
Triglycerides	1.05 (0.96-1.14)	1.04 (0.94-1.15)	1.04 (0.84-1.29)	1.16 (1.04-1.29)	1.00 (0.88-1.22)	0.91 (0.69-1.96)	0.22
MetS	1.04 (0.95-1.14)	1.13 (0.90-1.41)	1.07 (0.94-1.22)	1.32 (1.18-1.47)	1.36 (1.22-1.53)	1.58 (1.34-1.87)	0.18

NOTE: z-score analysis of single factors and the combined MetS score.

*Relative risk calculated from Cox regression models, with attained age as time scale, stratified by cohort and categories of birth year.

[†]Adjusted for age at baseline, smoking status and for the z-score of analyzed factors, i.e., BMI, mid-BP, glucose, cholesterol, and triglycerides. The MetS adjusted for age at baseline and smoking status.

[‡]Regression calibration adjusted as for z-score.

[§]P value for interaction between sex and exposure. Adjusted as in z-score.

^{||}z-score for MetS is adjusted for age at baseline and smoking status.

Table 5. Risk of pancreatic cancer in the Me-Can cohort in relation to metabolic factors

Smoking status	Exposure	Men				Women			
		z-score, crude*	z-score, adjusted†	z-score, calibrated‡	Interaction§ P value	z-score, crude*	z-score, adjusted†	z-score, calibrated‡	Interaction§ P value
Never-smoker	BMI	1.03 (0.87-1.22)	1.04 (0.86-1.27)	1.05 (0.85-1.30)		1.12 (0.95-1.30)	1.01 (0.85-1.20)	1.01 (0.83-1.23)	
	Mid-BP	1.03 (0.87-1.21)	1.02 (0.85-1.22)	1.04 (0.74-1.46)		1.35 (1.17-1.56)	1.35 (1.15-1.57)	1.72 (1.29-2.25)	
	Glucose	1.12 (0.97-1.29)	1.18 (1.02-1.36)	1.79 (1.07-2.96)		1.21 (1.07-1.35)	1.15 (1.00-1.31)	1.67 (1.00-2.71)	
	Cholesterol	0.90 (0.75-1.08)	0.91 (0.75-1.11)	0.86 (0.64-1.18)		1.06 (0.90-1.24)	1.04 (0.88-1.24)	1.06 (0.82-1.39)	
	Triglycerides	0.94 (0.78-1.13)	0.92 (0.75-1.13)	0.85 (0.57-1.27)		1.13 (0.96-1.33)	1.04 (0.86-1.24)	1.08 (0.74-1.53)	
	Mets	1.02 (0.85-1.23)	1.04 (0.87-1.25)	1.06 (0.81-1.39)		1.34 (1.41-1.57)	1.39 (1.18-1.63)	1.61 (1.27-2.03)	
Former smoker	BMI	0.99 (0.82-1.19)	0.97 (0.79-1.19)	0.99 (0.77-1.21)	0.37	1.42 (1.11-1.81)	1.30 (0.99-1.72)	1.34 (0.99-1.83)	0.13
	Mid-BP	1.02 (0.86-1.21)	1.05 (0.88-1.27)	1.10 (0.78-1.57)	0.91	1.22 (0.91-1.63)	1.06 (0.77-1.46)	1.11 (0.62-1.98)	0.43
	Glucose	1.12 (0.96-1.31)	1.14 (0.97-1.34)	1.59 (0.90-2.81)	0.21	1.31 (1.07-1.60)	1.22 (0.99-1.52)	2.08 (0.96-4.69)	0.03
	Cholesterol	0.89 (0.74-1.08)	0.84 (0.68-1.03)	0.76 (0.55-1.05)	0.05	1.12 (0.83-1.51)	1.03 (0.75-1.43)	1.05 (0.65-1.72)	0.67
	Triglycerides	1.02 (0.85-1.22)	1.04 (0.85-1.28)	1.08 (0.73-1.62)	0.84	1.42 (1.06-1.90)	1.18 (0.84-1.65)	1.39 (0.71-2.70)	0.17
Current smoker	MetS	1.02 (0.84-1.24)	1.03 (0.85-1.25)	1.04 (0.79-1.39)	0.83	1.59 (1.21-2.10)	1.64 (1.25-2.15)	2.04 (1.38-3.02)	<0.01
	BMI	1.01 (0.89-1.13)	0.95 (0.83-1.09)	0.94 (0.81-1.10)	0.64	0.93 (0.76-1.14)	0.91 (0.73-1.34)	0.90 (0.70-1.39)	0.15
	Mid-BP	1.14 (1.02-1.28)	1.16 (1.03-1.31)	1.32 (1.06-1.67)	0.01	1.06 (0.88-1.28)	1.11 (0.91-1.35)	1.21 (0.84-1.72)	0.37
	Glucose	1.05 (0.94-1.81)	1.02 (0.91-1.16)	1.07 (0.72-1.23)	0.45	1.26 (1.10-1.46)	1.29 (1.12-1.49)	2.55 (1.52-4.36)	<0.01
	Cholesterol	0.91 (0.80-1.03)	0.87 (0.76-0.99)	0.81 (0.65-0.98)	0.22	1.11 (0.93-1.33)	1.18 (0.98-1.43)	1.29 (0.97-1.72)	0.01
	Triglycerides	1.08 (0.95-1.21)	1.10 (0.96-1.27)	0.66 (0.92-1.59)	0.05	1.00 (0.83-1.21)	0.89 (0.72-1.10)	0.79 (0.52-1.21)	0.70
	MetS	1.06 (0.94-1.21)	1.07 (0.94-1.21)	1.11 (0.91-1.33)	0.16	1.20 (0.99-1.45)	1.23 (1.01-1.49)	1.35 (1.01-1.78)	<0.01

NOTE: z-score analysis (single and combined MetS score), stratified for smoking status and sex.

*Relative risk estimate with attained age as time scale and stratified within the model for cohort, sex, and categories of birth year.

†Adjusted for age at baseline and all exposures BMI, mid-BP, glucose, cholesterol, and triglycerides. Except MetS which are adjusted for age at baseline.

‡Regression calibrated z-score adjusted as for z-score.

§P value for interaction between smoking status and exposure.

colorectal cancer and MetS in the Me-Can cohort (31), a positive association was found among men, but not among women. Furthermore, a meta-analysis done by Grossman et al. (32) revealed that systolic hypertension, in particular, was associated with a general increase in cancer mortality. Whether or not the finding in this report is due to chance will have to be confirmed in future studies.

Smoking is a well-known risk factor for pancreatic cancer, and most studies have found a 2-fold risk increase (33). In the present study, the risk of pancreatic cancer was analyzed in strata of smoking habits, but no consistent pattern was found. It is possible that this was due to chance, but in studies on breast and endometrial cancer, it has been shown that the risk of cancer is increased in former smokers (34). The extent to which smoking modifies the association between metabolic effects and the risk of pancreatic cancer remains to be elucidated.

The main strengths of this study are the large sample size from seven population-based cohorts in Europe and the possibility of performing record linkage with national cancer registries. The validity of these registries has been evaluated previously, and it can be expected that the correctness of the pancreatic cancer diagnosis is almost perfect, although completeness may be somewhat lower (35-37). However, it is unlikely that misclassification of some pancreatic cancer cases as healthy subjects would have affected the estimates to any great extent. Other major strengths were the repeated health examinations, which allowed us to adjust risk estimates for intraindividual variation of the analyzed exposures and thereby decrease the risk of a misclassification bias related to the measured exposure, a potential regression dilution bias.

All cohorts had data available on BMI and smoking status, which allowed for adjustment for these potential risk factors. A limitation is that there were no data on covariates such as genetic risk factors, alcohol consumption, and physical activity. As far as we know, there is no recognized association between genetic factors associated with pancreatic cancer and metabolic factors. Hence, confounding by such factors ought to have been a minor problem. Alcohol consumption and physical activity have both been related to pancreatic cancer (2, 38). Alcohol is thought to exert its carcinogenic effect via reactive oxygen production (39), i.e., it acts on the same pathway as the components of MetS. If this is true, it would have been problematic to include alcohol in the multivariate analysis. The same might be applicable to physical activity. Indeed, Michaud et al. (38) have shown that physical activity is inversely related to pancreatic cancer in obese subjects, but not in subjects with a BMI of <25, and it has been shown that physical activity can lower plasma glucose levels (40).

The attendance rate in the various cohorts ranged from 56% to 90% (10), it might therefore be difficult to apply the results in this study to the general population. However, we consider that the internal comparisons and calculations of RRs are less sensitive to a potential selection bias. Another concern is the geographic differences

between the cohorts and the pooling of data from already existing data sets, which entailed limited data on covariates and some differences in measurement methods. To overcome these problems, quintile classification and the z-score were stratified for the individual cohorts. Furthermore, calculations were repeated without cohort stratification in the model and did not reveal any material changes in the risk estimates and there is nothing to suggest that baseline risks differed considerably between cohorts.

Pancreatic cancer is a highly aggressive tumor and most patients who are diagnosed with pancreatic cancer die within 1 year; the 5-year survival rate is <4% (1). In this study, the majority of cases (83%) had a follow-up after baseline measurement of >5 years and exclusions were made for cases diagnosed within 1 year of health check-up. Poor survival indicative of a rapidly progressive disease, compatible with a short subclinical phase, makes the findings in this report less likely to be due to reverse causality. To examine if subclinical pancreatic cancer begins to manifest as problems with glucose homeostasis, risk estimates were also calculated excluding the first 2 and the first 3 years of mortality. Overall, no significant changes in RR for the z-scores were revealed, except for glucose in men, in which the estimates went from RR, 1.09 (1.00-1.18) to RR, 1.08 (0.99-1.17) excluding the first 2 years and RR, 1.06 (0.97-1.15) excluding the first 3 years.

Several comparisons were made and the risk of a type I error has to be considered. The results show a clear pattern when different statistical models are used. This, together with the fact that significant findings are in line with the a priori hypothesis, supports the view that the results were not simply due to chance. The exception was cholesterol among men, which was negatively associated with the risk of pancreatic cancer. This finding will have to be interpreted with caution, considering the exclusion of cases with a follow-up of <1 year. Confidence intervals were generally narrow, which indicates that statistical power was good.

The question is how MetS might promote the development of cancer. One theory is that insulin resistance holds the potential to explain most of the factors associated with MetS (7), and this is thought to be the main mechanism between obesity and pancreatic cancer, i.e., obesity promotes insulin resistance, which in turn, promotes the development of hyperinsulinemia. A hyperinsulinemic state could trigger mitotic activity (28, 41) and *in vitro* studies have shown that hyperinsulinemia can stimulate cell proliferation in the pancreas (42). Moreover, adipocytes act not only as storage sites for triglycerides, they also synthesize and secrete hormones and cytokines, the latter with the propensity for inflammation, which has been suggested to affect the risk of pancreatic cancer (43). Hyperglycemia induces the elevation of insulin and insulin-like growth factor-I (44), and glucose may itself have a direct tumor-promoting effect. Glucose is used as an energy substrate in tumor cells, particularly in fast-growing, highly proliferative tumor cells (45). Excess glucose promotes the formation of reactive oxygen

species, which could damage DNA in genes that are important in cell proliferation or cell survival, which in turn, could trigger cancer progression (46). Reactive oxygen stress may also explain the effect of elevated triglycerides, and increased oxidative stress in fat has been shown to be an important pathogenic mechanism in MetS (47). How cholesterol and hypertension might be linked to cancer development remains unclear, although hypertension has been suggested to increase cancer risk by blocking and subsequently modifying apoptosis and thereby affecting cell turnover (48).

Conclusion

A MetS score based on BMI, blood pressure, glucose, cholesterol, and triglycerides was positively associated with the risk of pancreatic cancer in women, but not in men. In the overall analysis, there was a statistically significant positive association between single metabolic factors and pancreatic cancer among women. In men, there was a positive association between mid-BP and pancreatic cancer, and an indication of an association between high glucose levels and the risk of pancreatic cancer. The findings in this report add further evidence

to the association between MetS and pancreatic cancer, particularly, regarding glucose and blood pressure. Considering some of the limitations in this study (pooling data from already existing data sets, limited data on covariates, and differences in measurement methods), it would be of great value to further investigate this relationship in future studies.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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