Title:

Metabolic Factors and the Risk of Pancreatic cancer: A Prospective analysis of almost 580,000 men and women in the Me-Can project

Authors:

Dorthe Johansen[1], Tanja Stocks[2,3], Håkan Jonsson[4], Björn Lindkvist[5], Tone Björge[6,13], Hans Concin[7], Martin Almquist[8], Christel Häggström[2], Anders Engeland[6,13], Hanno Ulmer[9], Göran Hallmans[10], Randi Selmer[6], Gabriele Nagel[11], Steinar Tretli[12] , Pär Stattin[2], and Jonas Manjer[1, 14]

1. Department of Surgery, Skåne University Hospital, Lund University, Malmö, Sweden.
2. Department of Surgical and Perioperative Sciences, Urology and Andrology, Umeå University, Umeå, Sweden
3. Institute of Health Sciences, VU University, Amsterdam, The Netherlands
4. Department of Radiation Science, Oncology, Umeå University, Umeå, Sweden.
5. Department of Internal Medicine, Division of Gastroenterology and Hepatology, Sahlgrenska University Hospital, Göteborg, Sweden.
6. Norwegian Institute of Public Health, Oslo/Bergen, Norway
7. Agency for Preventive- and Social Medicine, Bregenz, Austria
8. Department of Surgery, Skåne University Hospital, Lunds University, Lund, Sweden.
9. Department of Medical Statistics, Informatics and Health Economics, Innsbruck Medical University, Austria
10. Department of Public Health and Clinical Medicine, Nutritional Research, Umeå University, Sweden
11. Institute of Epidemiology, Ulm University, Ulm, Germany
12. Cancer Registry of Norway, Institute of Population-based Cancer Research, Montebello, N-0310 Oslo, Norway
13. Department of Public Health and Primary Health Care, University of Bergen, Bergen, Norway
14. The Malmö Diet and Cancer Study, Lund University, Malmö, Sweden.

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

Correspondence:
Dorthe Johansen
Department of Surgery
Skåne University Hospital, SUS, Malmö
SE-205 02 Malmö
Sweden
E-mail: dorthe.johansen@med.lu.se

Formatted: Swedish (Sweden)

Phone: +46-(0)40-336556
Fax: +46-(0)40-927877

Abstract

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

Methods: The Metabolic Syndrome and Cancer Project ~~(Me Can)~~ is a pooled cohort containing data on body mass index ~~(BMI)~~, 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 above-mentioned 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 the MetS was done. All risk estimates were calibrated ~~in order~~ 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 ~~BM,I,~~ mid BP and glucose in women. The z-score for the adjusted mid-BP (~~,~~RR 1.10~~(~~;1.01~~;~~ 1.20~~)~~ and calibrated z-score for glucose~~,~~ (RR 1.37~~(~~;1.14~~;~~ 1.34) were positively associated with pancreatic cancer in men. In women, a positive~~ly~~ association w~~as~~~~ere~~ found for calibrated z-score 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 the MetS~~,~~ (RR1.58 ~~(~~;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 on ~~metabolic syndrome~~MetS and pancreatic cancer using pre-diagnostic measurements of the examined factors.

Introduction

Pancreatic cancer is characterized by an extremely dismal clinical course, with an overall 5-year survival of ~~less than~~< 4%~~.~~ (1),[1,] Despite the relatively low incidence, pancreatic cancer is rank~~s~~ed eight~~h~~ in the world~~wide~~ for ~~ranking of~~ cancer mortality due to its high fatality rate. The poor outcome is a strong motivation for epidemiologic~~al~~ 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),[1,] ~~-~~A recent study from Malmö showed that the association between body mass index (BMI) and risk of pancreatic cancer might~~ay~~ be modified by smoking exposure, increasing the risk several-fold in obese smokers (2).[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).

~~The metabolic syndrome (~~MetS~~)~~ was first described by Reaven in 1988 (3).[3,] Insulin resistance was described as a fundamental feature of several risk factors predisposing to cardiovascular morbidity and mortality. One of the main ideas was that the total influence of the MetS should exceed the sum of each component. Today there is a general consensus regarding the main components of the syndrome (4),[4,] but no consensus regarding the definition has been reached (5)[5], and the prevalence of ~~the~~ 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 (CVD) (6).[6,]

Formatted: Superscript
Formatted: Superscript
Formatted: Superscript
Formatted: Superscript
Formatted: Superscript
Formatted: Superscript
Formatted: Superscript
Formatted: Superscript
Formatted: Superscript

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

Formatted: Superscript

Formatted: Superscript

Material and methods

The Metabolic Syndrome and Cancer project (Me-Can)

The Metabolic Syndrome and Cancer project (Me-Can) was initiated in 2006 ~~in order~~ to create a large pooled cohort to investigate components of ~~the~~ MetS on the association with overall~~-~~ and site~~-~~specific cancer risk. A detailed description of the project has recently been published (10)[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)[11]~~;~~ the Norwegian cohort includes the Oslo study I cohort (Oslo~~)~~; ref. ~~(~~ 12)[12], the Norwegian Counties Study (NCS~~;)~~ ref. ~~(~~13)[13], the Cohort of Norway (CONOR~~;)~~ ref. ~~(~~14)[14]~~,~~ and the Age 40-programme (40-y; ref.~~)~~ ~~(~~15)[15]~~;~~ The Swedish cohorts ~~are~~ is composed of the Västerbotten Intervention Project (VIP; ref. ~~)~~ ~~(~~116)[16] and the Malmö Preventive Project (MPP; ref.~~)~~ ~~(~~17)[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 performed done in a similar way; without shoes and wearing light indoor clothes. Body mass index (BMI) was calculated as weight in kilograms divided by the squared height in meter (kg/m²). 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 less than< 1 hour, 1– to 2, 2 -to 4, 4 -to 8 or more than> 8 hours. Fasting time in the VIP was recorded as less than< 4 hours, 4 -to 8 hours or more than> 8 hours, but from 1992 onwards, participants wereas asked to fast for at least eight8 hours before the examination. In the MPP and after the initial three 3 years in the VHM&PP, a minimum of eight 8 hours of fasting was used as a standard procedure. In the Oslo and the NCS cohorts gGlucose levels were measured in serum with using a non-enzymatic method (in the Oslo and NCS cohorts);, in CONOR and the 40-y cohort with a serum/enzymatic method (in CONOR and the 40-y cohorts),; in the VHM&PP and the VIP with a plasma/enzymatic method (in the VHM&PP and the VIP cohorts),; and in MPP with a whole blood/enzymatic method (in the MPP cohort). Cholesterol- and triglyceride levels were measured in serum, with a non-enzymatic method in the Oslo and NCS cohorts up until 1980 and thereafter with anusing an enzymatic method. In the other cohorts, all measurements wereas obtained by anusing an enzymatic method. **For these two variables, levels from the non-enzymatic method have been compared with the enzymatic method (10)[10] and in order to correspond to with the enzymatic method, the original values have beenwere transformed according to the formulas: [$cholesterol_{enzymatic} = 0.92 \times cholesterol_{non\text{-}enzymatic} + 0.03$] and [$triglycerides_{enzymatic} = 0.90 \times triglyceride_{non\text{-}enzymatic} - 0.11$].**

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 ~~these issues~~ 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 ~~lower than~~of < 1 mmol/~~l~~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 observations for each subject were selected. If data from a fasting state and data on smoking status were available, the first of these observations was 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 ~~approximately~~ 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)[~~10~~,~~18~~].

After matching the 578,700 subjects to the date of 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 ~~less than~~< ~~a~~ 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 ~~E~~ends of follow-up for each cohort were as follows: The Austrian d) cohort ~~(a)~~ 2003 (a) , ~~(b)~~ no information available (b), and ~~(c-d)~~ 2003 (c-d); the Norwegian cohorts ~~(a-c)~~ 2005 (a-c), ~~(d)~~ 2004 (d); and the Swedish cohorts ~~(a-c)~~ 2006 (a-c), ~~(d)~~ 2004 (d). Incident pancreatic cancer was identified through linkage to the National Cancer registries, using the International Classification of Diseases ~~, seventh edition (ICD-7),~~(7th edition; code 157), resulting in 862 cases of pancreatic cancer, 315 in women and 547 in men.

Formatted: Superscript

Statistical analysis

To reduce the probability of reverse causation, all statistical analysis was calculated with follow-up starting ~~one~~ 1 year after baseline examination. Quintile cut-offs for five ~~parameters~~ varibles were calculated separately within each cohort and sex, and for glucose, cholesterol and triglycerides, ~~also~~ as well in categories of fasting time (i.e., ~~, as less than~~< ~~four~~4 hours, ~~from four to eight hours~~4-8, and ~~more than eight~~> 8 hours). The risk of pancreatic cancer was compared ~~to~~ with quintile levels of ~~body mass index (~~BMI~~)~~, mid- blood pressure [mid--BP = ($BP_{systolic}$ + $BP_{diastolic}$)/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 ~~(CI)~~. 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 was 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.

~~In order t~~To make the variables comparable on a continuous scale and to create a combined MetS variable, ~~the~~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 ~~standard deviation (~~SD~~)~~ of 1. The entire cohort was used as 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~~- blood pressure~~BP were standardized separately in groups defined by subcohort 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 the exposures with a~~the~~ 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 ~~the~~ MetS, all estimates were adjusted for age at baseline and smoking status. In the analyses of ~~the~~ separate exposures; BMI, mid~~- blood pressure-~~BP, glucose, cholesterol, and triglycerides, the adjusted model refers to adjustment for all other single metabolic factors on the same time.

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

Correction of a random error

The combined effect of measurement errors of the different exposures (BMI, mid~~- blood pressure~~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 ~~(RC)~~ (19-21)[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)[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~~to~~ 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 baseline measurement was done in the Oslo study a repeated measurement ~~performed~~ 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.

~~In order t~~To correct for potential regression dilution bias in the analysis based on quintiles, a regression coefficient was calculated~~,~~ (the ~~regression dilution ratio (~~RDR~~)~~ as described by Wood et al. (21))[21]. RDRs were estimated for the mean follow-up time in the full Me-Can database divided by two, i.e., ~~six~~ 6 years and modelled among men and women separately. This was performed as a linear mixed model, which included the actual exposure (repeated measurement as dependent and baseline measurement as independent variable), 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 ~~parameter~~ variable with

RDR [exp (log (RR)/RDR)], using a gender specific RDR. The estimated RDR correction values for men/women were for BMI 0.90/0.90, mid-BP 0.53/0.56, glucose 0.28/0.27, cholesterol 0.64/0.66, triglycerides 0.51/0.50 and the MetS 0.68/0.69. This indicates that all the metabolic factors except BMI have a substantial random error.

The correction by regression dilution ratioRDR was not suitable in models using more than one variable measured with error. In such situations, a regression calibration model (RC) was used (19)[19] for the analysis of the z score. With Using this methodthis 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 44.1 (SD = 12.3) (Table1). 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 rest of the cohort in either group. The prevalence of overweight, i.e., BMI greater than> 25 kg/m², was 55 % among men and 41% among women, but there were no great differences in the distribution over among weight categories between cases and rest of cohort in men or women. The means/medians for

mid-~~-~~BP, glucose and cholesterol were somewhat higher in the female case group as compared to the rest of the cohort.

Quintile levels of exposures and risk of pancreatic cancer

The risk of pancreatic cancer was examined in quintile levels of BMI, mid-~~- blood pressure~~BP, glucose, cholesterol and triglycerides, using the first quintile as the reference category (T~~t~~able 2). Absolute risks were calculated and revealed a 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 ~~positively~~ statistically significant positive association among men was for the fifth quintile of the mid-~~- blood pressure~~BP and pancreatic cancer, as well as ~~and~~ for the trend over the quintiles for the crude and adjusted glucose level. Among women, statistically significant associations was found in the fifth quintile of BMI, in the fifth quintile of mid-~~- blood pressure~~BP, and in the fourth and fifth quintile of glucose levels (Table 3). A statistically significant positive association were ~~furthermore~~ 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 similar as compared to uncorrected RRs among men, except for a somewhat stronger association between mid-~~- blood pressure~~BP and pancreatic cancer. Among women, the corrected RR was markedly higher for the ~~5~~th fifth glucose quintile.

Z-score of exposures and risk of pancreatic cancer

In the analysis of the continuous z-scores for the five exposures and the exposures combined (MetS),~~,~~ there was a statistically significant association between mid-BP ~~blood pressure~~ and pancreatic cancer as well as ~~, and~~ between glucose and pancreatic cancer~~,~~ in

both men and women (, tTable 4). Moreover, in women, there was a positively statistically significant positive association between the MetS and the risk of pancreatic cancer. Following regression calibration, n (RC) most point estimates were slightly stronger and CIs 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, (tTable 5). In male never-smokers, a positive risk associations were found for the adjusted and calibrated z-score for glucose. In current smokers, there was a statistically significant association between pancreatic cancer and the crude, adjusted and calibrated mid blood pressure BP. In female never-smokers, the risk of pancreatic cancer wasere positively associated with the crude, adjusted and calibrated mid-BP, glucose and for the MetS. In female former smoking femalesers, an associations were found for the crude BMI, glucose, triglycerides and as well as for the crude, adjusted and calibrated MetS. In female current smoking femalesers, a positively significantly positive associations were found for the crude, adjusted and calibrated glucose z-score, as well as for the MetS z-score adjusted and calibrated MetS Z-score. 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, Likewise for triglycerides, but for cholesterol the risk was found to be statistically significantly higher in never-smokers as compared to former smokers. In women, the risk associated with glucose was statistically significant higher in former and current smokers, as compared to never-smokers. The risk associated with

cholesterol in current smokers was statistically significantly higher than the risk in never-smokers. For ~~the~~ 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-~~blood pressure~~ BP, glucose and ~~the~~ MetS ~~respectively~~ and pancreatic cancer~~,~~ w~~ere~~as found among women, with the strongest association for glucose. In men, there was an indication of a positive association between mid-~~blood pressure~~ 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 ~~the~~ MetS should be a more important risk factor in women than in men is not clear. The calculation of absolute risks in this ~~paper~~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 were confirmed in this ~~paper~~report. Later in life, incidence rates become nearly equivalent (22)[22]. There is, at present, no support in the literature that women with ~~the~~ MetS or its individual components are more susceptible to developing pancreatic cancer. Estrogens and/or androgens have tumour promoting effects in relation 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 are unclear.

There is only one study on the putative association between ~~the~~ MetS and pancreatic cancer. Russo et al used subjects who were simultaneously ~~were~~ prescribed with antihypertensive, lipid-~~-~~lowering and anti-~~-~~diabetic drugs in a small study of 43 individuals and found a positive association between ~~the~~ MetS and the risk of pancreatic cancer, but only in men (23)[23]. This was not confirmed by the present study, which indicated an association between mid-~~blood pressure~~ BP and glucose levels and risk of pancreatic cancer, whereas the analysis of the MetS z-score did not reveal any significant association. Epidemiologic~~al~~ data supports a relationship between obesity and pancreatic cancer (24, 25)[24, 25] and between high glucose levels and pancreatic cancer (26-28)[26-28], but most studies have reported null associations between cholesterol / hypertension and the risk of pancreatic cancer (29, 30)[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~~s.~~ the lowest. It is, however, possible, as suggested by Li et al (24)[24], that obesity at a younger age has a more profound effect on risk of pancreatic cancer~~, than has~~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 ~~demonstrate~~ show a statistically significant association when BMI was taken into account. However, in a recently published paper on colorectal cancer and ~~metabolic syndrome~~MetS in the Me-Can cohort (31)[31], a positive association were found among men, but not among women. Furthermore, a meta-analysis performed by Grossman et al. (32)[32] revealed that

systolic hypertension, in particular, was associated with a general increase in cancer mortality. Whether or not the finding in this ~~paper~~ 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 ~~two~~2-fold risk increase (33)[33]. In the present study, the risk of pancreatic cancer was~~ere~~ analysed in strata of smoking habits, but no consistent pattern was~~ere~~ found. It is possible that this was ~~it is~~ due to chance, but in studies on breast and endometrial cancer it has been shown that the risk of cancer ~~are~~ is increased in former smokers (34)[34]. ~~To what~~ The extent to which smoking modifies~~y~~ metabolic 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~~to~~ 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)[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 intra~~-~~individual variation of the analysed 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 ~~it is~~we know,~~n~~ there is no ~~known~~ rekognized 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)[2, 38]. Alcohol is thought to exert its carcinogenic effect via reactive oxygen production (39)[39], i.e., it acts on the same pathway as the components of ~~the~~ 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)[38] have shown that physical activity is inversely related to pancreatic cancer in obese, but not in subjects with a BMI < 25, and it has been shown that physical activity can lower plasma glucose levels (40)[40].

The attendance rate in the various cohorts ranged from 56 to ~~–~~90% (10)[10], it might~~ay~~ therefore be difficult to apply the results in this study to the general population. However, we consider that the internal comparisons and calculations of ~~relative risks~~RRs are less sensitive to a potential selection bias. Another concern is the geographical differences between the cohorts and the pooling of data from already existing data sets, which entailed limited data on covariates and some difference in measurement methods. To overcome these problems, quintile classification and the z-score were stratified for the individual cohorts. Furthermore, ~~C~~calculations were ~~furthermore~~ 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 tumour and most patients who are diagnosed with pancreatic cancer die within 1~~a~~ year; ~~and~~ the 5-year survival rate is ~~less than~~< 4% (1)[1]. In this study, the majority of cases (83%) had a follow-up after baseline measurement of ~~more than~~> 5 years and exclusion were made for cases diagnosed within ~~one~~ 1 year of health check-up. Poor survival indicative of a rapidly progressive disease, compatible with a short sub-clinical phase, makes the findings in this ~~paper~~ report less likely to be due to reverse causality. ~~In order t~~To examine if subclinical pancreatic cancer

begins to manifest as problems with glucose homeostasis, risk estimates were ~~furthermore~~ also calculated excluding the first two and the first three years of mortality. Overall, no significant changes in RR for the z-scores were revealed, except for glucose in men, were the estimates went from RR, 1.09 (1.00-1.18) to RR, 1.08 (0.99-1.17) excluding the first ~~two~~ 2 years and RR, 1.06 (0.97-1.15) excluding the first ~~three~~ 3 years.

Several comparisons were made and the risk of a t~~T~~ype 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 à 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 ~~less than~~< 1 year. Confidence intervals were generally narrow, which indicates that statistical power was good.

The question is how ~~the~~ MetS might promote the development of cancer. One theory is that insulin resistance holds the potential to explain most of the factors associated with ~~the~~ MetS (7)[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~~an~~ trigger mitotic activity (28, 41)[28, 41] and in vitro studies have shown~~ed~~ that hyperinsulinemia can stimulate cell proliferation in the pancreas (42)[42]. ~~Besides~~Moreover, adipocytes act~~s,~~ not only as storage sites for triglycerides, they also synthesiz~~s~~e and secrete hormones and cytokines, the latter with the propensity for inflammation, which has been suggested to affect the risk of pancreatic cancer (43)[43]. Hyperglycaemia induces elevation of insulin and insulin-like growth factor-I ~~(IGF-1)~~ (44)[44], and glucose may itself have a direct tumour promoting effect. Glucose is used as an energy substrate in tumour cells,

particularly in fast-growing, highly proliferative tumour cells (45)[45]. Excess glucose promotes the formation of reactive oxygen species, which ~~can~~ could damage DNA in genes that are important in cell proliferation or cell survival, which in turn, can trigger cancer progression (46)[46]. Reactive oxygen stress may also explain the effect of elevated triglycerides, and increased oxidative stress in fat has been demonstrated to be an important pathogenic mechanism in ~~the~~ MetS (47)[47]. How cholesterol and hypertension might~~ay~~ 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)[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 ~~positively~~ significant positive association between single metabolic factors and pancreatic cancer among women.. In men, there was a positive association between mid ~~blood pressure~~ BP and pancreatic cancer, and an indication of an association between high glucose levels and the risk of pancreatic cancer. The findings in this ~~paper~~ report add further evidence to the association between ~~metabolic syndrome~~MetS and pancreatic cancer, ~~in~~ particularly regarding glucose and blood pressure. Considering some of the limitations in this study ~~(of~~ pooling data of 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.

Acknowledgements

Financial support was received by the World Cancer Research Fund (Grant 2007/09), The Swedish Research Council, The Ernhold Lundström Foundation, The Einar and Inga Nilsson Foundation, The Malmö University Hospital Cancer Research Fund, The Malmö University Hospital Funds and Donations, The Crafoord Foundation and The Mossfelt Foundation.

References

1. Welsch T, Kleeff J, Seitz HK., Bûchler P, Friess H, Bûchler MW. Update on pancreatic cancer and alcohol-associated risk. Journal of Gastroenterology and Hepatology 2006;21:S69-S75.
2. Johansen D, Borgström A, Lindkvist B, Manjer J. Different markers of Alcohol consumption, smoking and body mass index in relation to risk of pancreatic cancer. Pancreatology 2009;9:677-86.
3. Reaven GM. Banting Lecture 1988. Role of insulin resistance in human disease. 1988. Nutrition 1997;13:65; discussion 4, 6.
4. Daskalopoulou SS, Athyros VG, Kolovou GD, Anagnostopoulou KK, Mikhailidis DP. Definitions of metabolic syndrome: Where are we now? Curr Vasc Pharmacol 2006;4:185-97.
5. Day C. Metabolic syndrome, or What you will: definitions and epidemiology. Diab Vasc Dis Res 2007;4:32-8.
6. Hu G, Qiao Q, Tuomilehto J. The metabolic syndrome and cardiovascular risk. Curr Diabetes Rev 2005;1:137-43.
7. Cowey S, Hardy RW. The metabolic syndrome: A high-risk state for cancer? Am J Pathol 2006;169:1505-22.
8. Colangelo LA, Gapstur SM, Gann PH, Dyer AR, Liu K. Colorectal cancer mortality and factors related to the insulin resistance syndrome. Cancer Epidemiol Biomarkers Prev 2002;11:385-91.
9. Trevisan M, Liu J, Muti P, Misciagna G, Menotti A, Fucci F. Markers of insulin resistance and colorectal cancer mortality. Cancer Epidemiol Biomarkers Prev 2001;10:937-41.
10. Stocks T, Borena W, Strohmaier S et al. Cohort Profile: The Metabolic syndrome and Cancer project (Me-Can). Int. J. Epidemiology 2009:1-8.
11. 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.
12. Leren P, Askevold EM, Foss OP et al. The Oslo study. Cardiovascular disease in middle-aged and young Oslo men. Acta Med Scand Suppl 1975;588:1-38.
13. Bjartveit K, Foss OP, Gjervig T. The cardiovascular disease study in Norwegian counties. Results from first screening. Acta Med Scand Suppl 1983;675:1-184.
14. Naess O, Sogaard AJ, Arnesen E et al. Cohort profile: cohort of Norway (CONOR). Int J Epidemiol 2008;37:481-5.

15. Aires N, Selmer R, Thelle D. The validity of self-reported leisure time physical activity, and its relationship to serum cholesterol, blood pressure and body mass index. A population based study of 332,182 men and women aged 40-42 years. Eur J Epidemiol 2003;18:479-85.
16. Lindahl B, Weinehall L, Asplund K, Hallmans G. Screening for impaired glucose tolerance. Results from a population-based study in 21,057 individuals. Diabetes Care 1999;22:1988-92.
17. Berglund G, Eriksson KF, Israelsson B et al. Cardiovascular risk groups and mortality in an urban swedish male population: the Malmo Preventive Project. J Intern Med 1996;239:489-97.
18. Stocks T, Rapp K, Bjorge 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.
19. Di Angelantonio E, Kaptoge S, Liwington S et al. Fibrinogen Studies Collaboration. Correcting for multivariate measurement error by regression calibration in meta-analyses of epidemiological studies. Stat Med 2009;28:1067-92.
20. 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.
21. 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.
22. WHO. World Cancer Report vol. 2008: International Agency for Research on Cancer, 2008.
23. Russo A, Autelitano M, Bisanti L. Metabolic syndrome and cancer risk. Eur J Cancer 2008;44:293-7.
24. LLi D, Morris JS, Liu J et al. Body mass index and risk, age of onset, and survival in patients with pancreatic cancer. Jama 2009;301:2553-62.
25. Berrington de Gonzalez A, Sweetland S, Spencer E. A meta-analysis of obesity and the risk of pancreatic cancer. Br J Cancer 2003;89:519-23.
26. Yun JE, Jo I, Park J et al. Cigarette smoking, elevated fasting serum glucose, and risk of pancreatic cancer in Korean men. Int J Cancer 2006;119:208-12.
27. Fisher WE. Diabetes: risk factor for the development of pancreatic cancer or manifestation of the disease? World J Surg 2001;25:503-8.
28. Gapstur SM, Gann PH, Lowe W, Liu K, Colangelo L, Dyer A. Abnormal glucose metabolism and pancreatic cancer mortality. Jama 2000;283:2552-8.
29. Batty GD, Kivimaki M, Morrison D et al. Risk factors for pancreatic cancer mortality: extended follow-up of the original Whitehall Study. Cancer Epidemiol Biomarkers Prev 2009;18:673-5.
30. Berrington de Gonzalez A, Yun JE, Lee SY, Klein AP, Jee SH. Pancreatic cancer and factors associated with the insulin resistance syndrome in the Korean cancer prevention study. Cancer Epidemiol Biomarkers Prev 2008;17:359-64.
31. Stocks T, Lukanova A, Johansson M et al. Components of the metabolic syndrome and colorectal cancer risk; a prospective study. Int J Obes (Lond) 2008;32:304-14.
32. Grossman E, Messerli FH, Boyko V, Goldbourt U. Is there an association between hypertension and cancer mortality? Am J Med 2002;112:479-86.
33. Lowenfels AB, Maisonneuve P. Epidemiology and Prevention of Pancreatic Cancer. Japanese Journal of Clinical Oncology 2004;34:238-44.

34. Manjer J, Berglund G, Bondesson L, Garne JP, Janzon L, Malina J. Breast cancer incidence in relation to smoking cessation. Breast Cancer Res Treat 2000;61:121-9.
35. 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.
36. Larsen IK, Smastuen 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.
37. Rapp K, Schroeder J, Klenk J et al. Obesity and incidence of cancer: a large cohort study of over 145,000 adults in Austria. Br J Cancer 2005;93:1062-7.
38. Michaud DS, Giovannucci E, Willett WC, Colditz GA, Stampfer MJ, Fuchs CS. Physical activity, obesity, height, and the risk of pancreatic cancer. Jama 2001;286:921-9.
39. Go VL, Gukovskaya A, Pandol SJ. Alcohol and pancreatic cancer. Alcohol 2005;35:205-11.
40. Henriksen EJ. Invited review: Effects of acute exercise and exercise training on insulin resistance. J Appl Physiol 2002;93:788-96.
41. Fisher WE, Boros LG, Schirmer WJ. Insulin promotes pancreatic cancer: evidence for endocrine influence on exocrine pancreatic tumors. J Surg Res 1996;63:310-3.
42. Luo J, Iwasaki M, Inoue M et al. Body mass index, physical activity and the risk of pancreatic cancer in relation to smoking status and history of diabetes: a large-scale population-based cohort study in Japan--the JPHC study. Cancer Causes Control 2007;18:603-12.
43. Farrow B, Evers BM. Inflammation and the development of pancreatic cancer. Surg Oncol 2002;10:153-69.
44. Dossus L, Kaaks R. Nutrition, metabolic factors and cancer risk. Best Pract Res Clin Endocrinol Metab 2008;22:551-71.
45. Moreno-Sanchez R, Rodriguez-Enriquez S, Marin-Hernandez A, Saavedra E. Energy metabolism in tumor cells. FEBS J 2007;274:1393-418.
46. Valko M, Rhodes CJ, Moncol J, Izakovic M, Mazur M. Free radicals, metals and antioxidants in oxidative stress-induced cancer. Chem Biol Interact 2006;160:1-40.
47. Furukawa S, Fujita T, Shimabukuro M et al. Increased oxidative stress in obesity and its impact on metabolic syndrome. J Clin Invest 2004;114:1752-61.
48. Mason RP. Calcium channel blockers, apoptosis and cancer: is there a biologic relationship? J Am Coll Cardiol 1999;34:1857-66.

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 hrs	223 (40.8)	119,951 (41.6)	103 (32.7)	122,016 (42.4)
4-8 hrs	42 (7.7)	30,627 (10.6)	23 (7.3)	26,727 (9.3)
> 8 hrs	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, mmHg				
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)

SD, standard deviation; IQR, interquartile range; BMI, body mass index; Mid BP, mid blood pressure; all percentages are column percent.

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

Exposures	Quintile level [1]	Mean (SD)	*n*, cases	Incidence/ 100,000 pers.yrs	RR crude [2]	RR adjusted [3]	RR RDR corrected [4]
BMI	**1**	21.0 (1.3)	101	13.5	1.00	1.00	1.00
(kg/m^2)	**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	P trend; 0.42	P trend; 0.54	
Mid BP	**1**	92.2 (5.5)	79	10.1	1.00	1.00	1.00
(mmHg)	**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	P trend; 0.16	P trend; 0.06	
Glucose	**1**	4.2 (0.5)	102	13.2	1.00	1.00	1.00
(mmol/l)	**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	P trend; 0.05	P trend; 0.03	
Cholesterol	**1**	4.5 (0.5)	100	13.6	1.00	1.00	1.00
(mmol/l)	**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	P trend; 0.20	P trend; 0.12	
Triglycerides	**1**	0.8 (0.2)	87	12.0	1.00	1.00	1.00
(mmol/l)	**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	P trend; 0.82	P trend; 0.94	

RR, relative risk; SD, standard deviation; Pers.yrs, person years; BMI, body mass index; Mid BP, mid blood pressure; RDR, regression dilution ratio
[1] Quintile levels grouped by cohort and sex and for glucose, cholesterol and triglycerides even for fasting time.
[2] RR estimated from Cox regression model with attained age as time scale, stratified by cohort and categories of birth years
[3] Adjusted for quintiles levels of BMI (except BMI) and smoking status as categorical variables and age at baseline as a continuous variable
[4] Corrected RR was obtained by [exp (log (adj.RR)/RDR)].

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

Exposures	Quintile level [1]	Mean (SD)	*n*, cases	Incidence/ 100,000 pers.yrs	RR crude [2]	RR adjusted [3]	RR RDR corrected [4]
BMI	**1**	20.0 (1.2)	37	5.7	1.00	1.00	1.00
(kg/m^2)	**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	P trend; 0.61	P trend; 0.23	
Mid BP	**1**	88.7 (4.7)	29	4.6	1.00	1.00	1.00
(mmHg)	**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	P trend; 0.04	P trend; 0.01	
Glucose	**1**	4.1 (0.6)	34	5.1	1.00	1.00	1.00
(mmol/l)	**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	P trend; < 0.01	P trend;.< 0.01	
Cholesterol	**1**	4.4 (0.5)	38	5.9	1.00	1.00	1.00
(mmol/l)	**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	P trend; 0.35	P trend; 0.42	
Triglycerides	**1**	0.6 (0.1)	46	7.0	1.00	1.00	1.00
(mmol/l)	**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	P trend; 0.03	P trend; 0.16	

RR, relative risk; SD, standard deviation; Pers.yrs, person years, BMI, body mass index; Mid BP, mid blood pressure; RDR, regression dilution ratio
[1] Quintile levels grouped by cohort and sex and for glucose, cholesterol and triglycerides even fasting time.

[2] RR estimated from Cox regression model with attained age as time scale, stratified by cohort and categories of birth years
[3] Adjusted for quintiles levels of BMI (except BMI) and smoking status as categorical variables and age at baseline as a continuous variable
[4] Corrected RR was obtained by [exp (log (adj.RR)/RDR)].

Table 4. Risk of pancreatic cancer in the Me-Can cohort in relation to metabolic factors. Z-score analysis of single factors and the combined MetS score

	Men (n= 545)			*Women (n= 315)*			**Interaction[5] p-value**
Exposure	***z-score, crude[1]***	***z-score, adjusted[2]***	***z-score, calibrated[3]***	***Z score, Crude[1]***	***Z score, adjusted[2]***	***z score. calibrated[3]***	
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 blood pressure	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[4]	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

MetS, metabolic syndrome; BMI, body mass index;
[1] Relative risk calculated from Cox regression models, with attained age as time scale, stratified by cohort and categories of birth year.
[2] 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
[3] Regression calibration adjusted as for z-score adjusted
[4] Z score for MetS is adj. for age at baseline and smoking status.
[5] P-value for interaction between sex and exposure. Adjusted as in z score adjusted[4].

Table 5. . Risk of pancreatic cancer in the Me-Can cohort in relation to metabolic factors. Z-score analysis single and combined MetS score, stratified for smoking status and sex.

		Men				*Women*			
Smoking status	**Exposure**	**z-score, crude[1]**	**z-score, adjusted[2]**	**z-score, calibrated[3]**	**Interaction[4] p-value**	**z-score, crude[1]**	**z-score, adjusted[2]**	**z-score, calibrated[3]**	**Interaction[4] 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 (083-1.23)	
	MidBP	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
	MidBP	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
	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
Current smoker	*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
	MidBP	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

RR, relative risk; MetS, metabolic syndrome; BMI, body mass index; Mid BP, mid blood pressure

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

[2] Adjusted for age at baseline and all exposures BMI, mid BP, glucose, cholesterol and triglycerides. Except MetS which are adjusted for age at baseline
[3] Regression calibrated z-score adjusted as for z-score adjusted.
[4] P-value for interaction between smoking status and exposure. Adjusted as for z score adjusted[3].