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Metabolic predispositions and increased risk of colorectal adenocarcinoma by anatomical locations: a large population-based cohort study in Norway

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Abstract

Whether different definitions of metabolic syndrome (MtS) are differently associated with colorectal adenocarcinoma (CA) by anatomical location is unclear. A population-based cohort study in Norway (CONOR) was conducted from 1995 to 2010. Anthropometric measurements, blood samples and lifestyle data were collected at recruitment. CAs were identified through linkage to the Norwegian Cancer Register. A composite index of MtS defined by the International Diabetes Federation (IDF) or/and the National Cholesterol Education Program's Adult Treatment Panel III (ATP III) and single components of MtS, including anthropometrics, blood pressure, lipids, triglycerides, and glucose were analyzed. Cox proportional hazards regression was performed to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). Significant associations between single metabolic components and CA, except reduced high-density lipoprotein cholesterol and non-fasting glucose, were observed. MtS defined by two criteria separately showed a similar association with CA in general and MtS defined by both IDF and ATP III showed consistent results. Stronger associations were observed in the proximal colon in men (IDF HR=1.51, 95% CI: 1.24, 1.84; ATP III HR= 1.40, 95% CI: 1.15, 1.70), and the rectum in women (IDF HR=1.42, 95% CI: 1.07, 1.89; ATP III HR= 1.43, 95% CI: 1.08, 1.90).

Key words: Metabolic syndrome; Adenocarcinoma; Colon; Rectum; CONOR

Abbreviations:

IDF: the International Diabetes Federation definition

ATP III: the National Cholesterol Education Program's Adult Treatment Panel III (ATP III)

WHO: the World Health Organization

CONOR: The Cohort of Norway

HDL: High-density lipoprotein

SBP: systolic blood pressure

DBP: diastolic blood pressure

BMI: Body mass index

Introduction:

Metabolic syndrome, as assessed according to current international definitions by the key components central obesity, dyslipidemia, elevated blood pressure, and abnormal glucose metabolism, is associated with colorectal cancer in accumulating studies(1, 2). The definition of metabolic syndrome varies, however, which may indicate that the associations might be dissimilar. The three widely used definitions for metabolic syndrome are: a) the new International Diabetes Federation (IDF) definition; b) the National Cholesterol Education Program's Adult Treatment Panel III (ATP III) definition; c) the WHO (World Health Organization) clinical criteria for metabolic syndrome. Although several previous studies have demonstrated the positive association between metabolic syndrome and colorectal cancer risk (2-5), only one has investigated metabolic syndrome defined by different criteria in this context (4). Single components differ slightly in the different definitions of metabolic syndrome. It remains inconsistent, though, to what extent single components by different definitions account for such an association (4, 6-9). Furthermore, some studies found metabolic syndrome was only associated with colorectal cancer in men (6, 10), but others demonstrated the opposite (11). Due to the distinct sex-specific incidence pattern of colorectal adenocarcinoma in the proximal colon, distal colon and rectum, previous studies without examination by anatomical locations may have confounded the sex-specific association with metabolic syndrome and/or its single components. Most previous studies have analysed the colon and rectum separately, but omitted the distinction between the proximal and distal colon, which warrants further investigations.

In the current study, we examined the association of metabolic syndrome, based on different definitions, with a risk of colorectal cancer in the Cohort of Norway study (CONOR), a large, prospective population-based cohort in Norway. Since adenocarcinoma is the main

histological type of neoplasm in the colon and rectum (more than 90%), the study focuses on colorectal adenocarcinoma.

Materials and Methods

Study population

Study design and data collection in the CONOR study has been described in detail elsewhere(12). In summary, CONOR is a research collaboration between the Norwegian Institute of Public Health and the Universities of Bergen, Oslo, Tromsø, and Trondheim (Norwegian University of Science and Technology) from 1995 to 2010. Merging data from 10 epidemiological studies, CONOR was established as a national database to study risk factors of a wide range of diseases. In a recent cohort profile, the locations of these 10 study sites in Norway and the websites of each participating cohort are described (12). Letters of invitation were mailed approximately two weeks before the time of appointment. In total, 309 832 individuals were invited and 180 553 participated. Participants underwent a physical examination and a non-fasting blood sample was drawn at the screening. After excluding participants who were included in two rounds of surveys (7310), prevalent cancer cases (6075), those missing anthropometric data (21 234), and those missing daily smoking status (1551), 143 477 remained for the final analysis.

Identification of colorectal cancer cases

Using the unique 11-digit Norwegian citizens' national identity number, the CONOR cohort was followed-up through linkage to the Norwegian Cancer Register and Statistics Norway. Colorectal cancer was identified from the Cancer Register according to the International Classification of Diseases, 7th edition. The colorectal cancer codes by anatomical location included: proximal colon (the cecum, ascending colon, transverse colon, hepatic flexure, the splenic flexure and appendix): 1530 and 1531, distal colon (the descending colon, the

sigmoid colon): 1532, 1533, and 1534, and rectum: 1540. Each cohort participant was considered at risk from enrollment in the cohort until a diagnosis of colorectal cancer, death, being censored (e.g. lost to follow-up, emigration, diagnosis of other malignancies), or end of follow-up on December 31, 2010, whichever came first.

The Regional Committee for Medical and Health Research Ethics, Central Norway (ID: 2012/853/REK midt) approved the current study. All the individual studies included in CONOR were approved by their respective ethics committees in different areas. All participants signed an informed consent form.

Assessment of the metabolic syndrome components

Whole blood (5-7 ml) was collected from the participants, and serum was separated by centrifuging at the screening site. All laboratory assessments in CONOR were performed at the Department of Clinical Chemistry, Oslo University Hospital, Ullevål, except for HUNT II (The second Nord-Trøndelag Health Study) where the analyses were performed at the Department of Clinical Chemistry, Levanger Hospital, Levanger. Non-fasting serum total and High-density lipoprotein (HDL) cholesterol, glucose, and triglycerides were measured directly by an enzymatic method (Boehringer 148393, Boehringer Mannheim, Federal Republic of Germany - from 2000 onwards Hitachi 917 auto analyzer, Roche Diagnostic, Switzerland). An acceptable stability of the laboratory analyses over time in the population surveys has been reported(13).

Blood pressure and heart rate were measured by all the CONOR studies at dedicated research clinics. Three measurements were recorded and the mean value was calculated based on the second and third measurements (14). The stability of the blood pressure measures has been

evaluated as acceptable(15). Waist circumference was measured at the umbilicus to the nearest centimeter and with the subject standing and breathing normally. Hip circumference was measured as the maximum circumference around the buttocks. Waist to hip ratio was calculated from measurements of waist versus hip circumference. Body weight (in kilograms, to one decimal place) and height (in centimeters, to one decimal place) was measured with the participants wearing light clothing without shoes. The measurements were manually recorded until the year 2000 and, after that, an electronic height and weight scale was used. Body mass index (BMI) was calculated as body weight (kilograms) divided by the square of height (meters square). The use of lipid-lowering or anti-hypertensive drugs was collected through self-reported data.

Definition of the metabolic syndrome

Based on the available data in CONOR, two definitions of the metabolic syndrome, the IDF and the ATP III, were analyzed and compared (Table 1) (16, 17). The WHO criteria included components of impaired glucose tolerance, impaired fasting glucose, or insulin resistance, which were not available or not computable in this study. Thus, analysis of the overall definition of metabolic syndrome based on the WHO criteria was omitted, but accessible single components were analyzed, including waist to hip ratio (men ≥0.90, women ≥0.85), reduced HDL (men <0.9 mmol/L, women <1.0 mmol/L), hypertension (systolic blood pressure (SBP) ≥140mmHg or diastolic blood pressure (DBP) ≥90 mmHg), and raised fasting glucose (≥6.1 mmol/L).

According to the IDF definition(17, 18), a person with metabolic syndrome has central obesity (waist circumference based on European standards (men ⩾94 cm, women ⩾80 cm or BMI ⩾30) plus any two of the following four factors: 1) raised triglyceride level (⩾1.7

mmol/L) or use of lipid-lowering drugs; 2) reduced HDL cholesterol (men <1.03mmol/L, women <1.29 mmol/L); 3) raised blood pressure (SBP ⩾130 mmHg, DBP ⩾85 mmHg or use of antihypertensive drugs), and 4) raised fasting plasma glucose (⩾5.6 mmol/L) (Table 1). Raised fasting glucose was defined by plasma glucose level and a diagnosis of diabetes. Since blood samples were collected based on non-fasting status (time from last meal changed from two to eight hours), these results might not reflect the real fasting glucose level. According to the ATP III criteria, a person with metabolic syndrome has three or more of the single components: 1) central obesity (men ⩾102 cm, women ⩾88 cm); 2) hypertension (SBP ⩾130 mmHg, DBP ⩾85 mmHg or use of antihypertensive drugs); 3) hypertriglyceridemia (⩾1.7 mmol/L), reduced HDL cholesterol (men <1.03, women <1.29), and elevated fasting glucose (≥5.6 mmol/L) (Table 1)(16).

Statistical analysis

Cox proportional hazard models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (95% CIs). Associations between single metabolic syndrome components, the overall metabolic syndrome definition, use of IDF and ATP III criteria, and colorectal cancer by anatomical location were computed. All of the variables were analyzed based on categorical status.

Each single component of the metabolic syndrome was analyzed based on a crude model adjusted for age and sex, and a multivariable model adjusted for potential confounders. Since the results based on the crude and the multivariable models were not materially different, only the multivariable analyses were reported. Confounders were chosen based on previous etiological studies on colorectal cancer together with stepwise selection approaches. The following co-variables were included in the final model: age (<50, 50-60, ≥60), education

(none/primary school/secondary school, high school, university), daily smoking status (never/seldom, current), alcohol consumption (never/seldom, about once a week, 2-3 times per month, about once a week, several times per week), physical activity (hours per week: none, <1, 1-2, ≥3. Further analyses of anthropometric measurements were stratified by sex.

In sensitivity analyses, we excluded the first two years of follow-up in order to decrease the potential bias of reverse causality. Age was categorized into more refined groups (<40, 40-44, 45-49, 50-54, etc.) and analyzed in the multivariate model for the additional analysis. Since the results were not materially changed, we only showed it in Web Table 1. For missing values, we treated the variables in two different ways: 1) deleted the missing values, or, 2) treated a missing value as one category. Since the final results did not change materially, we chose either approach depending on the percentage of missing values in the relevant variables. Therefore, in the final analysis, smoking status missing values were deleted (1551, 0.89%) and the missing values of other variables were kept as a category. The proportional hazards assumption for the Cox regression model was tested on the basis of Schoenfeld residuals. All of the variables did not violate the assumption except age groups that were treated as a strata factor in the final model. A two-sided test with a significance level (α) of 0.05 was chosen. All analyses were performed using SAS 9.3 for Windows (SAS Institute Inc., Cary, North Carolina, USA) and Stata 13.0 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP).

Results

Population

With an average 11.3 years of follow-up, 2044 colorectal adenocarcinomas were identified from the total cohort (Table 2). In metabolic syndrome defined by IDF (43775), ATP III

(40234), or both (31500), 927, 823 and 695 colorectal adenocarcinomas were identified, respectively. Men had a higher incidence of adenocarcinoma in the distal colon (54.8%) and rectum (61.8 %), while women had a higher incidence in the proximal colon (51.9 %). The mean age in proximal colon cases (65.8 years) was slightly higher than in cases in the distal colon and rectum (63.4 and 63.5 years, respectively). Smoking and alcohol consumption (several times per week) seemed to be more frequent in rectal adenocarcinoma cases. Comorbidity (diabetes, cardiovascular diseases and asthma) was more prevalent in proximal adenocarcinoma cases (Table 2).

Single components of the metabolic syndrome

The risk of colorectal adenocarcinoma was increased by about 20% with both the European (men ≥94cm, women ≥80cm) and US (the United States) (men ≥102cm, women ≥88cm) definitions of central obesity using waist circumference (Table 3). The risk was mainly increased in the colon and not in the rectum. When central obesity was indirectly defined by BMI ≥30, the risk attenuated (16%). Increased waist to hip ratio showed similar results as waist circumference.

There was a marginally increased risk of colorectal adenocarcinoma (12%) with a higher triglycerides level (≥1.7 mmol/L compared with <1.7 mmol/L) (Table 3). However, lipid-lowering drugs seemed to potentially protect against colorectal adenocarcinoma, especially in the distal colon (HR=0.63, 95% CI: 0.42, 0.95) (Table 3). Reduced HDL cholesterol did not show a significant association with colorectal adenocarcinoma based on two categorizations (Table 3).

Raised blood pressure combined with the use of antihypertensive drugs was associated with an 18% and 13% increased risk of colorectal adenocarcinoma, using the IDF/ATP III definitions or the WHO definition of hypertension, respectively (Table 3).

Raised glucose levels were not associated with colorectal adenocarcinoma, however, self-reported diabetes increased the risk of colorectal adenocarcinoma by 36%, mainly in the proximal colon with 49% (Table 3).

Comparison of the IDF and ATP III definitions for metabolic syndrome

Both the IDF and ATP III definitions for metabolic syndrome showed positive associations with overall colorectal adenocarcinoma, regardless of sex (Tables 4). The IDF definition displayed slightly higher HRs than the ATP III definition regarding colorectal adenocarcinoma in general (IDF HR=1.24, 95% CI: 1.13, 1.36; ATP III HR=1.17, 95% CI: 1.07, 1.28). Both were consistently associated with proximal colon adenocarcinoma, especially in men (IDF: HR=1.51, 95% CI: 1.24, 1.84; ATP III: HR=1.40, 95% CI: 1.15, 1.70), and rectal adenocarcinoma in women (IDF: HR=1.42, 95% CI: 1.07, 1.89; ATP III: HR= 1.43, 95% CI: 1.08, 1.90), which was not indicated by the single components.

When assessing individuals classified with metabolic syndrome by both definitions (metabolic syndrome defined by IDF and ATP III), we also found an increased risk of colorectal adenocarcinoma overall (HR=1.26, 95% CI: 1.14, 1.40) (Table 5). Metabolic syndrome defined by both definitions was associated with an increased risk of adenocarcinoma in the proximal colon, especially in men (HR= 1.63, 95% CI: 1.30, 2.03 in men; HR=1.24, 95%CI: 1.00, 1.54 in women). Similar to results of the separate metabolic

syndrome definitions (Table 4), the increased risk of adenocarcinoma in the rectum in women was still apparent (HR=1.52, 95% CI: 1.13, 2.06).

We also investigated how central obesity played a role in the definitions of metabolic syndrome on the risk of colorectal adenocarcinoma, compared with non-central obesity (Figures 1 and 2, see also Web Tables 2 and 3). The results in both figures showed that central obesity alone was not associated with an increased risk of colorectal adenocarcinoma, while metabolic syndrome with central obesity was. The association was quite consistent with the aforementioned results in Tables 4 and 5. However, we also observed two exceptional results in men: First, central obesity was negatively associated with rectal adenocarcinoma based on the IDF criteria (Figure 1). Second, central obesity alone seemed to be associated with a 60% increased risk of adenocarcinoma in the distal colon (Figure 2) when using the ATP III definition. Since the definition of central obesity is different in the IDF and ATP III criteria, these results may need to be further interpreted based on the specific definitions.

Discussion

The current study found that the metabolic syndrome as a composite index defined by IDF, ATP III, or both, and single components of metabolic syndrome, e.g., central obesity, raised triglycerides and raised blood pressure, were associated with an increased risk of colorectal adenocarcinoma in general. Metabolic syndrome with central obesity contributes to the development of colorectal adenocarcinoma. The association of metabolic syndrome as a composite index was more prominent with adenocarcinoma of the proximal colon in men and rectal adenocarcinoma in women.

The strength of this study includes the large prospective cohort with a high number of colorectal adenocarcinoma cases. Moreover, the anthropometric data were measured objectively by standardized protocols at baseline. Furthermore, blood samples were collected and lipid levels were measured by standard procedures. A weakness is that the blood samples were not collected in fasting status, so fasting glucose was not available. However, data of prevalent diabetes were collected. In addition, the use of lipid-lowering drugs or anti-hypertensive drugs was collected through self-reported data, which might not cover the complete medications information. Another weakness is the lack of detailed information on food/nutrients intake, which may result in residual confounding.

In the current study, single components of the metabolic syndrome, including central obesity, raised triglycerides and raised blood pressure, showed positive associations with colorectal adenocarcinoma especially in the proximal colon, although some components displayed a stronger relation. In the Women's Health Initiative, a positive association of the metabolic syndrome with colorectal cancer was largely accounted for by serum glucose levels and SBP(5). In the Physicians' Health Study (male participants with 494 colorectal cancer cases), being overweight and diabetes were associated with an increased risk of colorectal cancer, but not elevated blood pressure and hypercholesterolemia(3). In the European Prospective Investigation into Cancer and Nutrition, abnormal glucose metabolism and/or central obesity were regarded as the main contributors of metabolic syndrome which were associated with an increased risk of colorectal cancer(4). Recent studies have demonstrated that central obesity may primarily account for this association (5, 8, 19). This is consistent with our results. More interestingly, our results showed that central obesity alone was associated with an increased risk of adenocarcinoma in the distal colon in men based on the ATP III criteria, but a decreased risk of rectal adenocarcinoma based on the IDF definition. As the definition of central obesity is more stringent in the ATP III criteria, it indicates that central obesity might

be an independent risk factor for distal colon adenocarcinoma. Furthermore, people who have central obesity but no metabolic syndrome in the IDF definition are most likely obese, but metabolically healthy individuals. This indicates that obesity but a metabolically heathy status might be associated with a reduced risk of rectal adenocarcinoma in men. The underlying mechanism is, however, unclear.

The other single components of the metabolic syndrome are more or less related with, or a consequence of, central obesity (20, 21). Waist circumference, a surrogate measure of visceral adipose tissue, is the commonly used index for central obesity. Visceral adipose tissue is physiologically more active than subcutaneous adipose tissue and generates hormones and cytokines with inflammatory, metabolic, and direct carcinogenic potential, which may directly or indirectly increase colorectal cancer risk(22). Current evidence suggests that obesity acts as a risk factor for colorectal cancer by several mechanisms, including chronic low-grade inflammation, hyperinsulinemia, as well as alterations in insulin-like growth factor and adipokine concentrations(22, 23). Specific molecules derived from the visceral adipose tissue, including adiponectin, leptin and resistin, are able to establish a positive feedback loop, thus increasing the pro-inflammatory and insulin-resistant state and promoting tumorigenesis (22, 24). The metabolic syndrome may be a marker of a physiologic milieu of growth that encourages tumor initiation, promotion, and progression.

Previous studies have found that the metabolic syndrome is associated with colorectal cancer in men but not in women, but the results are largely inconsistent (4-6, 10, 25, 26). The present study found significant associations for both sexes, but also sex-specific associations, e.g., a stronger association for rectal adenocarcinoma in women, which is consistent with a recent meta-analysis(19, 27). Another study found that only high levels of metabolic factors confer an increased risk (7). However, in the present study, a lower level of waist circumference

(based on the European definition) conferred a more evident association. A negative association between the use of lipid-lowering drugs and distal colon adenocarcinoma was observed. This was actually consistent with previous studies regarding the potential negative association of lipid-lowering drugs with cancer, e.g., statins(28).

Few studies have compared the risk of colorectal adenocarcinoma by anatomical locations using the single components, or composite index of the metabolic syndrome defined by IDF or ATP III, or the metabolic syndrome defined by both. Our findings regarding a significant association of metabolic syndrome with proximal colon cancer were consistent with previous studies (29, 30). Furthermore, the current study observed a significant association between the metabolic syndrome as a composite index with rectal adenocarcinoma in women, which was actually not obvious for single components. The distinct incidence pattern of colorectal adenocarcinoma by anatomical locations, e.g., female predominance in the proximal colon, male predominance in the distal colon and rectum, and older age-specific incidence in the proximal colon may indicate etiological differences. The proximal colon might be more influenced by internal disorders of metabolic factors, especially sex hormones, which are different in obese women and men. A hypothesis raised by McMichael and Potter in the 1980s considered that sex hormones may alter bile acid synthesis, which possibly acts in a more concentrated manner on the proximal colon where fecal bile acids are reabsorbed(31). Experimental studies have also demonstrated a remarkable difference in the expression pattern of genes according to the anatomical location of colorectal cancer, which may interpret the stronger association of metabolic syndrome with adenocarcinoma in the proximal colon in the current study(32). By contrast, adenocarcinoma in the distal colon and rectum seemed to be affected more evidently by factors involved in energy balance, such as obesity, physical activities, diet and gut microbiota. A recent meta-analysis found that

physical activity was differently associated with cancer in the colon and the rectum, although no difference between the colonic subsites was observed (33).

In summary, the metabolic syndrome and its components were associated with an increased risk of colorectal adenocarcinoma, especially in the proximal colon in men and the rectum in women. Central obesity may play a pivotal role connected with other components. Understanding the links of metabolic syndrome and its components to carcinogenesis has a major clinical significance and may have profound health benefits on colorectal cancer, which represents an important cause of mortality and morbidity in our societies.

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Conflict of interest statement

All the authors have no conflicts of interest to declare.

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Table 1: Components of the metabolic syndrome and definitions by IDF[*] and ATP III[#]

Category	IDF[a]	ATP III[b]
Central obesity		
Waist circumference	≥94 cm for Europid men; ≥80 cm for Europid women; ethnicity-specific values for other groups	Men >102 cm (>40 in); women >88cm (>35in)
Body mass index[c]	If BMI >30 central obesity can be assumed and waist circumference does not need to be measured	
Raised triglycerides	≥150 mg/dL (≥1.7 mmol/L); or specific treatment for this lipid abnormality	≥150 mg/dL (≥1.7 mmol/L)
Reduced HDL[d] cholesterol	<40 mg/dL (<1.03 mmol/L) in men; < 50 mg/dL (<1.29 mmol/L) in women; or specific treatment for this lipid abnormality	<40 mg/dL (<1.03 mmol/L) in men; <50 mg/dL (<1.29 mmol/L) in women
Raised blood pressure	Systolic blood pressure ≥ 130 mmHg; or diastolic blood pressure ≥ 85 mm Hg; or treatment of previously diagnosed hypertension	Systolic blood pressure ≥ 130 mmHg; or diastolic blood pressure ≥ 85 mmHg; or use of blood pressure lowering agents
Raised fasting plasma glucose	Fasting glucose ≥100 mg/dL (≥5.6 mmol/L); or previously diagnosed type 2 diabetes; If ≥100 mg/dL (≥5.6 mmol/L), OGTT[e] is strongly recommended but is not necessary to define presence of the syndrome	Fasting glucose ≥ 100 mg/dL; or use of glucose lowering agents.

Definition of metabolic syndrome	Central obesity (defined as waist circumference with ethnicity specific values) plus any two of the other above four factors	Complying three or more above abnormalities

[a] IDF: International Diabetes Federation; [b]ATP III: the National Cholesterol Education Program's Adult Treatment Panel III. [c] Body mass index (BMI) presented as kg/m^2; [d] HDL: High-density lipoprotein; [e]OGTT: oral glucose challenge test.

Table 2. Characteristics of colorectal adenocarcinoma cases and cohort participants in CONOR, Norway, 1995-2010

Variables	Cohort participants (n=143 477)		Colorectal adenocarcinoma (n=2044)		Colon				Rectum (n=555)	
					Proximal colon (n=853)		Distal colon (n=606)			
	No.	%	No.	%	No.	%	No.	%	No.	%
Sex										
Men	70033	48.81	1101	53.86	410	48.07	332	54.79	343	61.80
Women	73444	51.19	943	46.14	443	51.93	274	45.21	212	38.20
Age at examination										
Mean (Standard deviation)	50.9 (15.5)[a]		64.5(11.8) [a]		65.8(11.4) [a]		63.4(11.8) [a]		63.5(12.2) [a]	
Age by groups										
<50	81232	56.62	341	16.68	119	13.95	117	19.31	103	18.56
50-59	17559	12.24	269	13.16	96	11.25	91	15.02	80	14.41
≥60	44686	31.15	1434	70.16	638	74.79	398	65.68	372	67.03
Education, n(%)										
None/primary school/Secondary school	32423	22.60	724	35.42	320	37.51	198	32.67	198	35.68
High school	44964	31.34	468	22.90	193	22.63	136	22.44	134	24.14
University	29227	20.37	237	11.59	88	10.32	94	15.51	51	9.19
Missing	36863	25.69	615	30.09	252	29.54	178	29.37	172	30.99
Smoking status										
Not daily smoker	101,341	70.63	1542	75.44	653	76.55	461	76.07	402	72.43
Daily smoker	42,136	29.37	502	24.56	200	23.45	145	23.93	153	27.57

Alcohol consumption last year										
Never/seldom	41,694	29.06	690	33.76	316	37.05	182	30.03	185	33.33
About 1-3 times per month	45,233	31.53	465	22.75	174	20.40	149	24.59	135	24.32
About once a week	26,106	18.20	331	16.19	123	14.42	116	19.14	89	16.04
Several times per week	17,187	11.98	265	12.96	104	12.19	77	12.71	80	14.41
Missing	13,257	9.24	293	14.33	136	15.94	82	13.53	66	11.89
Physical activity										
None	43,492	30.31	720	35.23	318	37.28	225	37.13	167	30.09
Less than once a week	30,222	21.06	342	16.73	117	13.72	108	17.82	113	20.36
1-2 hours per week	28,226	19.67	284	13.89	113	13.25	86	14.19	84	15.14
3 or more hours per week	15,581	10.86	129	6.31	49	5.74	41	6.77	36	6.49
Missing	25,956	18.09	569	27.84	256	30.01	146	24.09	155	27.93
[b] Family history of cancer	36,309	25.31	672	32.88	385	45.13	211	34.82	169	30.45
Diabetes	4463	3.11	122	5.97	57	6.68	31	5.12	33	5.95
[c] Cardiovascular diseases	11,373	7.93	301	14.73	137	16.06	78	12.87	81	14.59
Asthma	12,087	8.42	210	10.27	99	11.61	62	10.23	46	8.29

[a] Given as mean (standard deviation); [b] Family history of cancer: self-reported cancer among parents, siblings and children; [c] Cardiovascular diseases: including angina pectoris, myocardial infarction and stroke.

Table 3: Single components of the metabolic syndrome and risk of colorectal adenocarcinoma by anatomical locations, the CONOR study, 1995-2010[a]

Components of metabolic syndrome	Colorectal adenocarcinoma by anatomical locations															
	Colorectum				Proximal Colon				Distal Colon				Rectum			
	No.	%	HR	95%CI	No.	%	HR	95%CI	No.	%	HR	95%CI	No.	%	HR	95%CI
Central obesity																
Waist circumference (cm)																
[b]Men<94, women <80	816	39.9	Referent		310	36	Referent		243	40.1	Referent		248	44.7	Referent	
Men≥94, women ≥80	1228	60.1	1.20	1.07,1.35	543	64	1.40	1.17,1.69	363	59.9	1.21	0.98,1.50	307	55.3	0.98	0.79,1.23
[c]Men<102, women<88	1409	31.1	Referent		566	66	Referent		422	69.6	Referent		401	72.3	Referent	
Men≥102, women≥88	635	68.9	1.22	1.07,1.39	287	34	1.25	1.03,1.53	184	30.4	1.20	0.95,1.53	154	27.7	1.14	0.88,1.47
[b]Body mass index (BMI)																
BMI<30	1611	21.2	Referent		667	78	Referent		480	79.2	Referent		438	78.9	Referent	
BMI≥30	433	78.8	1.16	1.04,1.29	186	22	1.15	0.97,1.35	126	20.8	1.16	0.95,1.41	117	21.1	1.20	0.98,1.48
[d]Waist to hip ratio (WHR)																
Men<0.90, women<0.85	996	48.6	Referent		412	48	Referent		298	49.3	Referent		270	48.7	Referent	
Men≥0.90, women≥0.85	1047	51.3	1.23	1.12,1.35	441	52	1.34	1.16,1.55	307	50.7	1.23	1.03,1.47	285	51.3	1.11	0.93,1.33
Raised triglycerides																
[b, c]Triglycerides (mmol/L)																
<1.7	1078	52.8	Referent		438	51	Referent		333	55.1	Referent		288	51.9	Referent	
≥1.7	962	47.2	1.12	1.02,1.22	414	49	1.18	1.03,1.36	271	44.9	1.04	0.88,1.22	267	48.1	1.13	0.95,1.34
Use of lipids lowering drugs																
No	616	83.6	Referent		233	81	Referent		189	87.5	Referent		184	84.8	Referent	
Yes	121	16.4	0.86	0.70,1.04	56	19	1.01	0.76,1.36	27	12.5	0.63	0.42,0.95	33	15.2	0.80	0.55,1.16

[b, c]Raised triglycerides																
No	1010	49.5	Referent		408	48	Referent		316	52.2	Referent		270	48.7	Referent	
Yes	1032	50.5	1.11	1.02,1.21	445	52	1.19	1.04,1.36	289	47.8	1.02	0.87,1.20	285	51.3	1.12	0.94.1.32
Reduced HDL HDL-cholesterol (mmol/L)																
[b, c]Men≥1.03, women≥1.29	1475	72.3	Referent		613	72	Referent		440	72.9	Referent		399	71.9	Referent	
Men<1.03, women<1.29	565	27.7	1.07	0.97,1.18	239	28	1.08	0.92,1.25	164	27.1	1.04	0.87,1.25	156	28.1	1.09	0.90.1.31
[d]Men≥0.9, women≥1.0	1878	92.1	Referent		781	92	Referent		559	92.6	Referent		510	91.9	Referent	
Men<0.9, women<1.0	162	7.9	1.08	0.92,1.27	71	8.3	1.17	0.91,1.49	45	7.4	1.01	0.74,1.37	45	8.1	1.06	0.78,1.44
Raised blood pressure SBP (mmHg)																
[b, c] <130	530	25.9	Referent		214	25	Referent		168	27.7	Referent		144	26	Referent	
≥ 130	1514	74.1	1.17	1.06,1.30	639	75	1.14	0.97,1.35	438	72.3	1.15	0.95,1.39	411	74	1.20	0.99,1.47
[d]<140	917	44.9	Referent		387	45	Referent		282	46.5	Referent		239	43.1	Referent	
≥ 140	1127	55.1	1.11	1.01,1.22	466	55	1.00	0.86,1.15	324	53.5	1.12	0.94,1.33	316	56.9	1.27	1.06,1.52
DBP (mmHg)																
[b, c]<85 mmHg	1280	62.6	Referent		558	65	Referent		375	61.9	Referent		336	60.5	Referent	
≥85 mmHg	764	37.4	1.06	0.96,1.16	295	35	0.92	0.79,1.06	231	38.1	1.13	0.96,1.34	219	39.5	1.14	0.96,1.36
[d]<90 mm Hg	1568	76.7	Referent		673	79	Referent		453	74.8	Referent		427	76.9	Referent	
≥ 90 mm Hg	476	23.3	1.04	0.93,1.15	180	21	0.89	0.76,1.06	153	25.3	1.21	1.00,1.46	128	23.1	1.01	0.83,1.24
Use of antihypertensive drugs																
[b, c]No	1471	72.6	Referent		598	71	Referent		428	71.2	Referent		421	76.4	Referent	
Yes	556	27.4	1.17	1.06,1.30	247	29	1.21	1.04,1.41	173	28.8	1.34	1.11,1.61	130	23.6	0.99	0.81,1.22

[b, c]Hypertension definition 1																
No	447	21.9	Referent		175	21	Referent		146	24.1	Referent		123	22.2	Referent	
Yes	1597	78.1	1.18	1.05,1.32	678	80	1.20	1.00,1.43	460	75.9	1.12	0.92,1.37	432	77.8	1.19	0.96,1.47
[d]Hypertension definition 2																
No	752	36.8	Referent		308	36	Referent		232	38.3	Referent		207	37.3	Referent	
Yes	1292	63.2	1.13	1.02,1.24	545	64	1.07	0.92,1.24	374	61.7	1.15	0.96,1.38	348	62.7	1.15	0.96,1.39
Raised fasting glucose																
Glucose																
[b, c]<5.6 mmol/L	1261	61.8	Referent		522	61	Referent		392	64.9	Referent		334	60.2	Referent	
≥5.6 mmol/L	779	38.2	1.04	0.95,1.14	330	39	1.05	0.91,1.21	212	35.1	0.94	0.79,1.11	221	39.8	1.11	0.93,1.32
[d]<6.1 mmol/L	1582	77.6	Referent		658	77	Referent		473	78.3	Referent		431	77.7	Referent	
≥6.1 mmol/L	458	22.4	1.03	0.93,1.14	194	23	1.04	0.88,1.22	131	21.7	1.02	0.84,1.24	124	22.3	1.01	0.83,1.24
Prevalent type 2 diabetes																
No	1901	94	Referent		796	93	Referent		575	94.9	Referent		522	94.1	Referent	
Yes	122	6	1.36	1.13,1.64	57	6.7	1.49	1.14,1.95	31	5.1	1.21	0.84,1.74	33	5.9	1.39	0.97,1.98
[b, c]Raised glucose																
No	1245	60.9	Referent		513	60	Referent		388	64	Referent		330	59.5	Referent	
Yes	799	39.1	1.05	0.96,1.15	340	40	1.07	0.93,1.23	218	36	0.95	0.80,1.12	225	40.5	1.12	0.94,1.33

[a] adjusted for age, sex, smoking, alcohol consumption, physical activity, education, history of family cancer, and body mass index (BMI) when appropriate. BMI was presented as kg/m^2 ;
[b]single component defined by IDF (International Diabetes Federation); [c] single component defined by ATP III (the National Cholesterol Education Program's Adult Treatment Panel III); [d] single component defined by the World Health Organization standard.

Table 4: Association of metabolic syndrome (IDF[a] or ATP III [b] definition, respectively) with risk of colorectal adenocarcinoma by anatomical locations in CONOR, Norway, 1995-2010

Metabolic syndrome definition	Colorectum			Proximal Colon			Distal Colon			Rectum		
	No.	HR[c]	95%CI[c]	No.	HR[c]	95%CI[c]	No.	HR[c]	95%CI[c]	No.	HR[c]	95%CI[c]
IDF definition												
Total												
No	1117	Referent		436	Referent		349	Referent		313	Referent	
Yes	927	1.24	1.13,1.36	417	1.36	1.19,1.56	257	1.14	0.97,1.35	242	1.20	1.01,1.42
Men												
No	608	Referent		208	Referent		187	Referent		202	Referent	
Yes	493	1.28	1.13,1.44	202	1.51	1.24,1.84	145	1.24	0.99,1.55	140	1.09	0.88,1.36
Women												
No	509	Referent		228	Referent		162	Referent		111	Referent	
Yes	434	1.22	1.06,1.39	215	1.24	1.02,1.51	112	1.07	0.83,1.38	102	1.42	1.07,1.89
ATP III definition												
Total												
No	1221	Referent		486	Referent		378	Referent		340	Referent	
Yes	823	1.17	1.07,1.28	367	1.27	1.10,1.46	228	1.09	0.94,1.29	215	1.12	0.94,1.33
Men												
No	650	Referent		225	Referent		200	Referent		218	Referent	
Yes	451	1.18	1.05,1.34	185	1.40	1.15,1.70	132	1.15	0.92,1.43	125	0.98	0.79,1.23
Women												
No	571	Referent		261	Referent		178	Referent		122	Referent	
Yes	372	1.18	1.03,1.36	182	1.17	0.96,1.43	96	1.07	0.82,1.38	90	1.43	1.08,1.90

[a]IDF: the International Diabetes Federation; [b]ATP III: the National Cholesterol Education Program's Adult Treatment Panel III; [c]adjusted for age, sex, smoking, alcohol consumption, physical activity, education and history of family cancer. HR: hazard ratio; CI: confidence interval.

Table 5: Association of metabolic syndrome (IDF[a] or/and ATP III[b] definitions) with risk of colorectal adenocarcinoma by anatomical locations

Metabolic syndrome definition	Colorectum			Proximal Colon			Distal Colon			Rectum		
	No.	HR[c]	95%CI[c]	No.	HR[c]	95%CI[c]	No.	HR[c]	95%CI[c]	No.	HR[c]	95%CI[c]
Total												
None	989	Referent		383	Referent		316	Referent		276	Referent	
Either IDF or ATP III[d]	360	1.10	0.97, 1.24	156	1.22	1.01,1.47	95	0.93	0.74,1.17	101	1.08	0.86,1.36
IDF and ATP III[e]	695	1.26	1.14,1.40	314	1.40	1.20,1.63	195	1.16	0.97,1.40	178	1.20	0.99,1.46
Men												
None	512	Referent		175	Referent		161	Referent		170	Referent	
Either IDF or ATP III[d]	234	1.12	0.96,1.31	83	1.16	0.89,1.51	65	1.01	0.75,1.34	81	1.17	0.90,1.53
IDF and ATP III[e]	355	1.31	1.14,1.51	152	1.63	1.30,2.03	106	1.27	0.99,1.63	92	1.03	0.79,1.33
Women												
None	477	Referent		208	Referent		155	Referent		106	Referent	
Either IDF or ATP III[d]	126	1.09	0.89,1.33	73	1.34	1.02,1.76	30	0.86	0.58,1.28	20	0.82	0.51,1.33
IDF and ATP III[e]	340	1.24	1.07,1.44	162	1.24	1.00,1.54	89	1.09	0.83,1.44	86	1.52	1.13,2.06

[a] IDF: the International Diabetes Federation; [b] ATP III: the National Cholesterol Education Program's Adult Treatment Panel III; [c] adjusted for age, sex, smoking, alcohol consumption, physical activity, education, history of family cancer, and body mass index when appropriate. HR(95%CI): hazard ratio and 95% confidence interval; [d] Metabolic syndrome was defined by any of IDF or ATP III definition; [e] Metabolic syndrome was defined by both of IDF and ATPIII definition.

Figure 1. Categories of metabolic syndrome with central obesity by definition of IDF (the International Diabetes Federation definition) and risk of colorectal adenocarcinoma in CONOR, Norway,1995-2010.

Remarks: A) total participants, B) Men, C) Women; HR: Hazard ratio; CI: confidence interval; Ref: reference.

Figure 2. Categories of metabolic syndrome with central obesity by definition of ATP III (the National Cholesterol Education Program's Adult Treatment Panel III) and risk of colorectal adenocarcinoma in CONOR, Norway,1995-2010.

Remarks: A) total participants, B) Men, C) Women; HR: Hazard ratio; CI: confidence interval; Ref: reference.