**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](http://en.wikipedia.org/wiki/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](#_ENREF_1), [2](#_ENREF_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](#_ENREF_2)), only one has investigated metabolic syndrome defined by different criteria in this context ([4](#_ENREF_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](#_ENREF_4), [6-9](#_ENREF_6)). Furthermore, some studies found metabolic syndrome was only associated with colorectal cancer in men ([6](#_ENREF_6), [10](#_ENREF_10)), but others demonstrated the opposite ([11](#_ENREF_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](#_ENREF_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](http://www.ntnu.edu/)) 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](#_ENREF_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](http://en.wikipedia.org/wiki/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](#_ENREF_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](#_ENREF_14)). The stability of the blood pressure measures has been evaluated as acceptable([15](#_ENREF_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](#_ENREF_16), [17](#_ENREF_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](#_ENREF_17), [18](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_4)). Recent studies have demonstrated that central obesity may primarily account for this association ([5](#_ENREF_5), [8](#_ENREF_8), [19](#_ENREF_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](#_ENREF_20), [21](#_ENREF_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](#_ENREF_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](#_ENREF_22), [23](#_ENREF_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](#_ENREF_22), [24](#_ENREF_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](#_ENREF_4), [10](#_ENREF_10), [25](#_ENREF_25), [26](#_ENREF_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](#_ENREF_19), [27](#_ENREF_27)). Another study found that only high levels of metabolic factors confer an increased risk ([7](#_ENREF_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](#_ENREF_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](#_ENREF_29), [30](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_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.

**References**

1. Pais, R., H. Silaghi, A.C. Silaghi, et al. Metabolic syndrome and risk of subsequent colorectal cancer*.* *World J Gastroenterol*. 2009; **15**(41):5141-5148.

2. Stocks, T., A. Lukanova, T. Bjorge, et al. Metabolic factors and the risk of colorectal cancer in 580,000 men and women in the metabolic syndrome and cancer project (Me-Can)*.* *Cancer*. 2011; **117**(11):2398-2407.

3. Sturmer, T., J.E. Buring, I.M. Lee, et al. Metabolic abnormalities and risk for colorectal cancer in the physicians' health study*.* *Cancer Epidemiol Biomarkers Prev*. 2006; **15**(12):2391-2397.

4. Aleksandrova, K., H. Boeing, M. Jenab, et al. Metabolic syndrome and risks of colon and rectal cancer: the European prospective investigation into cancer and nutrition study*.* *Cancer Prev Res (Phila)*. 2011; **4**(11):1873-1883.

5. Kabat, G.C., M.Y. Kim, U. Peters, et al. A longitudinal study of the metabolic syndrome and risk of colorectal cancer in postmenopausal women*.* *Eur J Cancer Prev*. 2012; **21**(4):326-332.

6. Ahmed, R.L., K.H. Schmitz, K.E. Anderson, et al. The metabolic syndrome and risk of incident colorectal cancer*.* *Cancer*. 2006; **107**(1):28-36.

7. Stocks, T., A. Lukanova, M. Johansson, et al. Components of the metabolic syndrome and colorectal cancer risk; a prospective study*.* *Int J Obes (Lond)*. 2008; **32**(2):304-314.

8. Bowers, K., D. Albanes, P. Limburg, et al. A prospective study of anthropometric and clinical measurements associated with insulin resistance syndrome and colorectal cancer in male smokers*.* *Am J Epidemiol*. 2006; **164**(7):652-664.

9. Kontou, N., T. Psaltopoulou, N. Soupos, et al. Metabolic syndrome and colorectal cancer: the protective role of Mediterranean diet--a case-control study*.* *Angiology*. 2012; **63**(5):390-396.

10. Pelucchi, C., E. Negri, R. Talamini, et al. Metabolic syndrome is associated with colorectal cancer in men*.* *Eur J Cancer*. 2010; **46**(10):1866-1872.

11. Russo, A., M. Autelitano, and L. Bisanti Metabolic syndrome and cancer risk*.* *Eur J Cancer*. 2008; **44**(2):293-297.

12. Naess, O., A.J. Sogaard, E. Arnesen, et al. Cohort profile: cohort of Norway (CONOR)*.* *Int J Epidemiol*. 2008; **37**(3):481-485.

13. Foss, O.P. and P. Urdal Cholesterol for more than 25 years: could the results be compared throughout all this time? *.* *Nor J Epidemiol.* 2003; **13**(1):85–88.

14. Martin, R.M., L. Vatten, D. Gunnell, et al. Blood pressure and risk of prostate cancer: Cohort Norway (CONOR)*.* *Cancer Causes Control*. 2010; **21**(3):463-472.

15. Lund-Larsen, P.G. Blood pressure measured with sphygmomanometer and with Dinamap under field conditions - a comparison. *.* *Nor J Epidemiol*. 1997; **7**(2):235–241.

16. Grundy, S.M., H.B. Brewer, Jr., J.I. Cleeman, et al. Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition*.* *Circulation*. 2004; **109**(3):433-438.

17. International Diabetes Federation: The IDF consensus worldwide definition of the metabolic syndrome*.* *IDF Communications, Brussels, Belgium*. 2006.

18. Alberti, K.G., P. Zimmet, and J. Shaw Metabolic syndrome--a new world-wide definition. A Consensus Statement from the International Diabetes Federation*.* *Diabet Med*. 2006; **23**(5):469-480.

19. Esposito, K., P. Chiodini, A. Capuano, et al. Colorectal cancer association with metabolic syndrome and its components: a systematic review with meta-analysis*.* *Endocrine*. 2013; **44**(3):634-647.

20. Chute, C.G., W.C. Willett, G.A. Colditz, et al. A prospective study of body mass, height, and smoking on the risk of colorectal cancer in women*.* *Cancer causes & control : CCC*. 1991; **2**(2):117-124.

21. Giovannucci, E., A. Ascherio, E.B. Rimm, et al. Physical activity, obesity, and risk for colon cancer and adenoma in men*.* *Annals of internal medicine*. 1995; **122**(5):327-334.

22. Vazzana, N., S. Riondino, V. Toto, et al. Obesity-driven inflammation and colorectal cancer*.* *Curr Med Chem*. 2012; **19**(34):5837-5853.

23. Kaaks, R., P. Toniolo, A. Akhmedkhanov, et al. Serum C-peptide, insulin-like growth factor (IGF)-I, IGF-binding proteins, and colorectal cancer risk in women*.* *J Natl Cancer Inst*. 2000; **92**(19):1592-1600.

24. Lysaght, J., E.P. van der Stok, E.H. Allott, et al. Pro-inflammatory and tumour proliferative properties of excess visceral adipose tissue*.* *Cancer Lett*. 2011; **312**(1):62-72.

25. Healy, L.A., J.M. Howard, A.M. Ryan, et al. Metabolic syndrome and leptin are associated with adverse pathological features in male colorectal cancer patients*.* *Colorectal Dis*. 2012; **14**(2):157-165.

26. Harima, S., S. Hashimoto, H. Shibata, et al. Correlations between obesity/metabolic syndrome-related factors and risk of developing colorectal tumors*.* *Hepatogastroenterology*. 2013; **60**(124):733-737.

27. Esposito, K., P. Chiodini, A. Colao, et al. Metabolic syndrome and risk of cancer: a systematic review and meta-analysis*.* *Diabetes Care*. 2012; **35**(11):2402-2411.

28. Simon, M.S., C.A. Rosenberg, R.J. Rodabough, et al. Prospective analysis of association between use of statins or other lipid-lowering agents and colorectal cancer risk*.* *Ann Epidemiol*. 2012; **22**(1):17-27.

29. Chiu, H.M., J.T. Lin, C.T. Shun, et al. Association of metabolic syndrome with proximal and synchronous colorectal neoplasm*.* *Clin Gastroenterol Hepatol*. 2007; **5**(2):221-229; quiz 141.

30. Morita, T., S. Tabata, M. Mineshita, et al. The metabolic syndrome is associated with increased risk of colorectal adenoma development: the Self-Defense Forces health study*.* *Asian Pac J Cancer Prev*. 2005; **6**(4):485-489.

31. McMichael, A.J. and J.D. Potter Reproduction, endogenous and exogenous sex hormones, and colon cancer: a review and hypothesis*.* *J Natl Cancer Inst*. 1980; **65**(6):1201-1207.

32. Komuro, K., M. Tada, E. Tamoto, et al. Right- and left-sided colorectal cancers display distinct expression profiles and the anatomical stratification allows a high accuracy prediction of lymph node metastasis*.* *J Surg Res*. 2005; **124**(2):216-224.

33. Robsahm, T.E., B. Aagnes, A. Hjartaker, et al. Body mass index, physical activity, and colorectal cancer by anatomical subsites: a systematic review and meta-analysis of cohort studies*.* *Eur J Cancer Prev*. 2013; **22**(6):492-505.

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| Table 1: Components of the metabolic syndrome and definitions by IDF\* and ATP III# |  |  |
|  Category | IDFa |   | ATP IIIb |
| 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 indexc | 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 HDLd 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), OGTTe 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; bATP III: the National Cholesterol Education Program’s Adult Treatment Panel III. c Body mass index (BMI) presented as kg/m2; d [HDL: High-density lipoprotein;](http://en.wikipedia.org/wiki/High-density_lipoprotein) eOGTT: oral glucose challenge test. |
|  |  |  |  |

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| --- |
| 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. |

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| Table 3: Single components of the metabolic syndrome and risk of colorectal adenocarcinoma by anatomical locations, the CONOR study, 1995-2010a |
| 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) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| bMen<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 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| cMen<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 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| bBody 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 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| dWaist 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,cTriglycerides (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,cRaised 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,cMen≥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 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| dMen≥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,cNo | 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,cHypertension 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 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| dHypertension 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,cRaised 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/m2 ; bsingle 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.

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| Table 4: Association of metabolic syndrome (IDFa  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. | HRc | 95%CIc | No. | HRc | 95%CIc | No. | HRc | 95%CIc | No. | HRc | 95%CIc |
| 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 |

aIDF: the International Diabetes Federation; bATP III: the National Cholesterol Education Program’s Adult Treatment Panel III; cadjusted for age, sex, smoking, alcohol consumption, physical activity, education and history of family cancer. HR: hazard ratio; CI: confidence interval.

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| Table 5: Association of metabolic syndrome (IDFa or/and ATP IIIb definitions) with risk of colorectal adenocarcinoma by anatomical locations |
| Metabolic syndrome definition | Colorectum | Proximal Colon | Distal Colon | Rectum |
| No. | HRc | 95%CIc | No. | HRc | 95%CIc | No. | HRc | 95%CIc | No. | HRc | 95%CIc |
| 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.