Metabolic Syndrome and Risks of Colon and Rectal Cancer: the European Prospective Investigation into Cancer and Nutrition Study

Running title: Metabolic Syndrome and Risks of Colon and Rectal Cancer

Krasimira Aleksandrova¹, Heiner Boeing¹, Mazda Jenab², H. Bas Bueno-de-Mesquita³,⁴, Eugene Jansen⁴, Fränzel J.B. van Diijnhoven⁴,⁵, Veronika Fedirko², Sabina Rinaldi², Isabelle Romieu², Elio Riboli⁶, Dora Romaguera⁶, Kim Overvad⁷, Jane Nautrup Østergaard⁷, Anja Olsen⁸, Anne Tjonneland⁸, Marie-Christine Boutron-Ruault⁹, Françoise Clavel-Chapelon⁹, Sophie Morois⁹, Giovanna Masala¹⁰, Claudia Agnoli¹¹, Salvatore Panico¹², Rosario Tumino¹³, Paolo Vineis¹⁴, Rudolf Kaaks¹⁵, Annekatrian Lukanova¹⁵, Antonia Trichopoulou¹⁶,¹⁷, Androniki Naska¹⁶, Christina Bamia¹⁶, Petra H. Peeters⁵, Laudina Rodriguez¹⁸, Genevieve Buckland¹⁹, María-José Sánchez²⁰, Miren Dorronsoro²¹, Jose-Maria Huerta²², Aurelio Barricarte²³, Göran Hallmans²⁴, Richard Palmqvist²⁵, Kay-Tee Khaw²⁶, Nicholas Wareham²⁷, Naomi E. Allen²⁸, Konstantinos K Tsilidis²⁸, Tobias Pischon¹,²⁹

¹Department of Epidemiology, German Institute of Human Nutrition Potsdam-Rehbrücke, Nuthetal, Germany;
²International Agency for Research on Cancer, Lyon, France;
³Department of Gastroenterology and Hepatology, University Medical Center, Utrecht, The Netherlands;
⁴National Institute for Public Health and the Environment (RIVM), Bilthoven, the Netherlands;
⁵Julius Center for Health Sciences and Primary Care, University Medical Center, Utrecht, the Netherlands;
⁶Division of Epidemiology, Public Health and Primary Care, Imperial College, London, United Kingdom;
7 Department of Epidemiology, Institute of Public Health, Aarhus University, Aarhus, Denmark;
8 Institute of Cancer Epidemiology, Danish Cancer Society, Copenhagen, Denmark;
9 Inserm, Centre for Research in Epidemiology and Population Health, U1018, Institut Gustave Roussy, F-94805, Villejuif, France and Paris South University, UMRS 1018, F-94805, Villejuif, France;
10 Molecular and Nutritional Epidemiology Unit, Cancer Research and Prevention Institute–ISPO, Florence, Italy;
11 Nutritional Epidemiology Unit, Fondazione IRCCS, Istituto Nazionale dei Tumori, Milan, Italy;
12 Department of Clinical and Experimental Medicine, Faculty of Medicine and Surgery, Federico II University, Naples, Italy;
13 Cancer Registry and Histopathology Unit, "M.P. Arezzo" Hospital, ASP 7 Ragusa, Italy;
14 MRC/HPA Centre for Environment and Health, School of Public Health, Imperial College London; HuGeF Foundation, Torino Italy;
15 Division of Cancer Epidemiology, German Cancer Research Centre, Heidelberg, Germany;
16 WHO Collaborating Center for Food and Nutrition Policies, Department of Hygiene, Epidemiology and Medical Statistics, University of Athens Medical School, Athens, Greece;
17 Hellenic Health Foundation, Athens, Greece;
18 Public Health and Participation Directorate, Health and Health Care Services Council, Asturias, Spain;
19 Unit of Nutrition, Environment and Cancer, Cancer Epidemiology Research Programme, Catalan Institute of Oncology (ICO-IDIBELL), Barcelona, Spain;
20 Andalusian School of Public Health and Centro de Investigación Biome’dica en Red de Epidemiología y Salud Pública (CIBERESP), Granada, Spain;
21 Public Health Division of Gipuzkoa, Basque Government, and CIBERESP, San Sebastian, Spain;
22 Department of Epidemiology, Murcia Regional Health Authority & CIBER Epidemiología y Salud Pública (CIBERESP), Spain;
23 Navarre Public Health Institute, Consortium for Biomedical Research in Epidemiology and Public Health (CIBER Epidemiología y Salud Pública-CIBERESP), Pamplona, Spain;
24 Division of Nutritional Research, Department of Public Health and Clinical Medicine, Faculty of Medicine, Umeå University, Umeå, Sweden;
25 Unit of Pathology, Department of Medical Biosciences, Faculty of Medicine, Umeå University, Umeå, Sweden;
26 Unit of Clinical Gerontology, Department of Public Health and Primary Care, School of Clinical Medicine, University of Cambridge, Cambridge, United Kingdom;
27 MRC Epidemiology Unit, Institute of Metabolic Science, Cambridge, United Kingdom;
28 Cancer Epidemiology Unit, Nuffield Department of Clinical Medicine, Medical Sciences Division, University of Oxford, Oxford, United Kingdom;
29 Molecular Epidemiology Group, Max Delbrück Center for Molecular Medicine (MDC), Berlin-Buch, Germany.

Correspondence:
Krasimira Aleksandrova, MPH, PhD
Department of Epidemiology
German Institute of Human Nutrition Potsdam-Rehbruecke
Arthur-Scheunert-Allee 114-116
14558 Nuthetal
Germany
Tel +49 33200 88 712
Fax +49 33200 88 721
e-mail: krasimira.aleksandrova@dife.de
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Abstract (n=250)

Metabolic syndrome (MetS) is purportedly related to risk of colorectal cancer, however the association of MetS, as defined according to recent international criteria, and colorectal cancer has not been yet evaluated. In particular, it remains unclear to what extent the MetS components individually account for such an association. We addressed these issues in a nested case-control study that included 1,093 incident cases matched (1:1) to controls using incidence-density sampling. Conditional logistic regression was used to estimate relative risks (RRs) and 95% confidence intervals (CIs). MetS was defined according to the criteria of the National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATPIII), the International Diabetes Federation and the 2009 harmonized definition. Among individual components, abdominal obesity (RR=1.51;95%CI:1.16-1.96) was associated with colon cancer; whereas abnormal glucose metabolism was associated with both colon (RR=2.05; 95%CI:1.57-2.68) and rectal cancer (RR=2.07;95%CI:1.45-2.96). MetS as defined by each of the definitions was similarly associated with colon cancer (e.g.RR=1.91;95%CI:1.47-2.42 for MetS by NCEP/ATPIII); whereas MetS by NCEP/ATPIII, but not IDF or harmonised definition was associated with rectal cancer (RR=1.45;95%CI:1.02-2.06). Overall, these associations were stronger in women compared with men. However, the association between MetS and colorectal cancer was accounted for by abdominal obesity and abnormal glucose metabolism, such that MetS did not provide risk information beyond these components (likelihood ratio test \( P=0.10 \) for MetS by NCEP/ATPIII). These data suggest that simple assessment of abnormal glucose metabolism and/or abdominal obesity to identify individuals at colorectal cancer risk may have higher clinical utility compared to applying more complex MetS definitions.
Introduction

The metabolic syndrome (MetS) is a cluster of metabolic abnormalities, including abdominal obesity, elevated blood pressure (BP), abnormal glucose metabolism, and dyslipidaemia, suggested to play a major role in the development of cardiovascular diseases and diabetes mellitus (1). Recent evidence shows that components of MetS may also be associated with risk of colorectal cancer (2, 3). In particular, high waist circumference (WC, a marker for abdominal obesity) (4), elevated levels of haemoglobin A1c (HbA1c, a marker for abnormal glucose metabolism) (5), and reduced levels of high-density lipoprotein cholesterol (HDL-C, a marker for dyslipidaemia)(6) were shown to be independently associated with risk of colorectal cancer. In line with these observations, a number of studies have reported that MetS may be associated with risk of colorectal cancer (7-12); however, a number of questions remain. First, studies defined MetS according to different criteria, mainly other than those originally proposed by a number of expert groups. Second, metabolic abnormalities, such as WC, may be more strongly related to risk of colon cancer than to rectal cancer, and results may differ between men and women (4); however, most studies on MetS published thus far have been relatively small, and incompletely defined results by sex (8, 11) or by colon/rectal cancer site (11-13).

Finally, MetS is a heterogeneous condition that may reflect various combinations of metabolic abnormalities, and it is not clear to what extent the components individually account for the potential association between MetS and colorectal cancer (14, 15). The answer to this question is crucial for understanding if complex assessment of MetS may be more useful for identifying subjects at risk of colorectal cancer compared to assessing certain MetS components.

We conducted a nested case-control study within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort with the aim to examine the association of components and definitions of MetS with risks of colon and rectal cancer. In particular, we
aimed to examine to what extent the components individually account for the potential association between MetS and colorectal cancer.

**Participants and Methods**

**Data Collection and Follow-up**

EPIC is a large prospective study with 519,978 participants, aged 25 to 70 years at period of enrollment (1992-2000) and recruited predominantly from the general population in 23 centers from 10 European countries. Participants gave written informed consent, underwent anthropometric measurements, and completed questionnaires on socio-demographic and lifestyle characteristics. Blood samples were collected according to a standardized protocol (16). Approval was obtained from ethics review board of the International Agency for Research on Cancer and local review boards. The present study includes subjects from Denmark, France, Germany, Greece, Italy, Spain, the Netherlands, and the United Kingdom. Excluded from the analysis were the subjects from Norway, where blood samples were only recently collected and few cases are diagnosed after blood donation, and the Malmö center of Sweden which did not provide blood samples. Incident cancer cases were identified through record linkage with regional cancer registries or based on a combination of methods, including health insurance records, cancer and pathology registries, and active follow-up through study subjects and their next-of-kin. Closure dates for the present study were defined as the latest date of complete follow-up for both cancer incidence and vital status, and ranged from December 1999 to June 2003 for centers using registry data, and from June 2000 to December 2002 for centers using active follow-up procedures. Colon and rectal cancers were defined according to the 10th Revision of the International Statistical Classification of Diseases, Injuries and Causes of Death (ICD-10), proximal colon tumors include tumors in the cecum appendix, ascending colon, hepatic flexure, transverse colon, and splenic flexure (ICD-10 codes C18.0–18.5); distal colon tumors include those in the descending colon (ICD-10 code C18.6) and sigmoid colon (ICD-10 code...
C18.7); and rectal tumors are those occurring at the rectosigmoid junction (ICD-10 code C19) or in the rectum (ICD-10 code C20). A total of 1093 incident cancer cases (689 colon, 404 rectum) with available baseline information for each of the MetS components were included in the analysis and were matched to same number of controls, selected with incidence density sampling procedure, such that controls could include subjects who became a case later in time; also each control subject could be sampled more than once. Matching characteristics were: the study center, sex, age at blood collection, follow-up time since blood collection, time of the day at blood collection, and fasting status; and among women, menopausal status. Premenopausal women were matched on phase of menstrual cycle at blood collection and postmenopausal women were matched on hormonal replacement therapy use.

**MetS Definitions**

We defined MetS using the 2005 revised criteria of the NCEP/ATPIII, the 2005 IDF criteria, and the latest harmonized definition published in 2009 (Table 1). In contrast to the other two definitions, the IDF definition requires abdominal obesity as an essential component of MetS. Further, the IDF and the harmonized criteria, but not the NCEP/ATPIII criteria use population specific cut-offs to define abdominal obesity. We slightly modified the above definitions, using baseline HbA1c instead of blood glucose as a surrogate marker for abnormal glucose metabolism (see below).

**MetS Components**

WC was measured either at the narrowest torso circumference or at the midpoint between the lower ribs and iliac crest (4). Abdominal obesity was defined as WC≥102 cm in men or ≥88 cm in women for the NCEP/ATPIII definition (17), or as WC ≥94 cm in men or ≥80 cm in women for the IDF and the harmonized definitions (18, 19).

Systolic and diastolic BP was measured by trained personnel at baseline. To avoid any possible white-coat effect, for the present analysis we primarily used the second reading (567 cases; 549 controls) and where unavailable, the first reading (379 cases; 375 controls).
Elevated BP was defined as systolic BP $\geq 130$ mm/Hg, diastolic BP $\geq 85$ mm/Hg, self-reported physician diagnosed hypertension or self-reported treatment for hypertension (17-19).

Serum HDL-C and TG were quantitatively determined by a colorimetric method, using a Synchron LX-20 Pro autoanalyser (Beckman-Coulter)(6). Reduced HDL-C concentrations were defined as $<40$ mg/dL (1.03 mmol/L) in men and $<50$ mg/dL (1.29 mmol/L) in women. Because 76% of the study participants provided non-fasting blood samples (time since last meal $<6h$), for the TG concentrations we subtracted the sex-specific geometric mean difference between non-fasting and fasting subjects from the individual levels of non-fasting subjects. Elevated TG levels were defined as $\geq 150$ mg/dL (1.7 mmol/L) (17-19).

Subjects were determined as having abnormal glucose metabolism based on self-reported diabetes (57 cases; 42 controls) or HbA$_1c$ $\geq 5.7\%$ (572 cases; 433 controls) which corresponds to fasting plasma glucose levels of 100 mg/dl, as proposed by the American Diabetes Association. Measurements of HbA$_1c$ in erythrocyte hemolysate were done using high-performance liquid chromatography with a Bio-Rad Variant IIITM instrument (5).

**Statistical Analyses**

Case-control differences were assessed using Student’s paired t-test or Wilcoxon’s signed rank test for continuous variables, and by McNemar’s test or Bowker’s test of symmetry for categorical variables. The association of MetS and its components, as defined based on the NCEP/ATPIII, IDF, and the harmonized criteria, with risks of colorectal cancer was analyzed using multivariable-adjusted conditional logistic regression, adjusted for confounders other than those controlled for by matching, including smoking status (never, former, current, or missing), education (no school degree/primary school, technical/professional school, secondary school, university degree, or missing), physical activity (inactive, moderately inactive, moderately active, active, or missing), alcohol (g/d), fiber (g/d), red and processed meat (g/d), fruits and vegetables (g/d), fish and shellfish (g/d).

In the same model, we estimated the relative risks (RRs) for the mutually-adjusted
components of MetS. We present the results in terms of estimated RRs, under the assumption that with risk-set sampling, the odds ratio derived from the conditional logistic regression directly estimates the hazard ratio as a measure of the relative risk (20). We performed the main multivariable-adjusted analysis separately for men and women and for colon (proximal/distal) and rectal cancer. We examined whether the associations differ by sex and cancer site (colon/rectum; proximal/distal colon) by using interaction terms of MetS definitions and components (both dichotomous), respectively, multiplied by the stratum variable in the main multivariable-adjusted model. To study the potential effect of various combinations of MetS components, we estimated the multivariable-adjusted risks of colon cancer associated with combinations of MetS components, relative to the absence of the respective combinations. To examine to what extent the association between MetS and colorectal cancer is statistically explained by single components, we added those components that showed to be significantly associated with risk (abdominal obesity, abnormal glucose metabolism and reduced HDL-C) individually and in combinations into the multivariable-adjusted model for each MetS definition. To explore if MetS may be more useful to assess colon cancer risk compared to its individual components, we used likelihood ratio test (LRT), a standard statistical test for comparing nested models, and compared the fit of a multivariable-adjusted model, including only abnormal glucose metabolism and abdominal obesity to a model also including the metabolic syndrome variable (21).

To distinguish any potential effect of diagnosed diabetes we repeated the analyses using a cut-off point for HbA1c ≥ 6.5% (95 cases; 47 controls) and excluding people with reported diabetes at baseline (35 cases; 18 controls). To account for the high proportion of non-fasting participants, we repeated the multivariable-adjusted analyses after excluding non-fasting cases and their corresponding controls (830 case-control sets). To test the possibility of reverse causation, we repeated the main multivariable-adjusted analyses after exclusion of cases diagnosed within the first two years of recruitment (284 cases). All P values were two-
tailed, and P values below 0.05 were considered to indicate statistical significance. Data were analysed using the Statistical Analysis System (SAS) software package, version 9.2 (SAS Institute Inc, North Carolina).

Results

The median time between study recruitment and cancer diagnosis among cases was 3.7 years; the average follow-up time among controls was 9.3 years. Colon cancer cases had a higher number of metabolic abnormalities and a higher prevalence of MetS by any of the three definitions at baseline compared to controls; while rectal cancer cases had a higher prevalence for MetS as defined by NCEP/ATPIII but not for the other two definitions (Table 2).

In multivariable-adjusted conditional logistic regression, abdominal obesity, reduced HDL-C and abnormal glucose metabolism, but not elevated TG or BP, were each associated with colon cancer risk, whereas abnormal glucose metabolism was the only component associated with risk of rectal cancer (Table 3). When the components were mutually adjusted, abdominal obesity by IDF (RR = 1.51; 95% CI: 1.16-1.96) and abnormal glucose metabolism (RR = 2.05; 95% CI = 1.57-2.68), but not abdominal obesity by NCEP/ATPIII and reduced HDL-C, remained statistically significantly related to risk of colon cancer (Figure 1A). For rectal cancer, abnormal glucose metabolism remained strongly associated with risk after adjustment for all other components (Figure 1B).

The analysis on the association of different combinations of the MetS components with colon cancer risk showed that the strength of the association of a certain combination was highly reflecting the strength of the association of the components included in that combination (Table 4). For example, a combination of abdominal obesity and abnormal glucose metabolism, each of which was significantly associated with colon cancer risk, resulted in a RR of 2.29 (95%CI: 1.72-3.03), while the combination of elevated BP and elevated TG, both of which were not associated with risk, expectedly produced non-significant risk estimates (RR = 1.33; 95% CI: 0.97-1.84).
MetS as determined based on each of the three original definitions was statistically significantly associated with colon cancer risk. The multivariable-adjusted RRs were: 1.91 (95% CI: 1.47-2.42) for the NCEP/ATPIII definition, 1.91 (95% CI: 1.48-2.46) for the IDF definition and 2.00 (95% CI: 1.56-2.56) for the harmonized definition; with no statistically significant differences between sexes ($P = 0.49$, $P = 0.84$, $P = 0.73$ for difference between sexes for each respective definition). For rectal cancer, there was an association with MetS by NCEP/ATPIII (RR = 1.45; 95% CI: 1.02-2.06), but not with the other two definitions (Table 3). When stratified by sex, this association was statistically present in women (RR = 2.03; 95% CI: 1.14-3.62), but not in men (RR = 1.35; 95% CI: 0.83-2.21, $P$ for difference between sexes = 0.80; Table 3). The differences between colon and rectal cancer were statistically significant for MetS by IDF ($P = 0.04$) and harmonised definition ($p=0.03$), but not for MetS by NCEP/ATPIII ($P = 0.17$). The association with MetS was somewhat stronger for distal colon cancer (e.g. RR = 2.27; 95% CI: 1.51-3.41 for MetS by NCEP/ATPIII), compared to proximal colon cancer (RR = 1.83; 95% C: 1.21-2.75; $P$ for difference by cancer sub-site = 0.21; Supplementary Table 1, Appendix). However, the interpretation of these findings is hampered due to the small number of cases in these analyses (281 proximal colon cases and 314 distal colon cases) which may have lowered the precision of the risk estimates.

To examine to what extent the components may explain the association between MetS and colorectal cancer, we next adjusted the multivariable-adjusted model containing the MetS variable with each of the single components, individually and in combinations. In this analysis, abdominal obesity and abnormal glucose metabolism most strongly attenuated the association towards unity for both colon and rectal cancer. For example, when MetS was defined by the NCEP/ATPIII criteria, the RR was 1.44 (95% CI: 0.94-2.20) for colon cancer and 1.02 (95% CI: 0.65-1.60) for rectal cancer.

Thereafter, we tested if MetS improves colorectal cancer risk assessment beyond abdominal obesity and abnormal glucose metabolism by comparing models containing only
abdominal obesity and abnormal glucose metabolism to models also including the MetS variable. In this analysis, addition of the MetS did not statistically significantly improve the multivariable-adjusted model (likelihood ratio test; colorectal cancer, \( P = 0.10 \), colon cancer, \( P = 0.18 \); rectal cancer \( P = 0.22 \) for MetS by NCEP/ATPIII).

When, we repeated the main analyses using a cut-off point for HbA1c \( \geq 6.5\% \) and excluding people with reported diabetes, MetS by any of the three definitions was similarly associated with colon cancer risk (e.g. RR = 1.69; 95% CI: 1.23-2.31 for MetS by NCEP/ATPIII), but not with risk of rectal cancer (RR = 1.26; 95% CI: 0.85-1.85). In this analysis, none of the components was associated with risk of rectal cancer (data not shown). After excluding non-fasting subjects, the risk estimates did not substantially change (e.g. RR = 2.25; 95% CI: 1.26-4.00 for MetS by NCEP/ATPIII). After exclusion of cases that occurred during the first two years of the follow-up, the studied associations remained unaltered (e.g. RR = 1.77; 95% CI: 1.29-2.40 for the association of MetS by NCEP/ATPIII and colon cancer).

**Discussion**

In this large population-based study, abdominal obesity, reduced HDL-C and abnormal glucose metabolism, but not elevated TG or BP, were each associated with colon cancer risk; while abnormal glucose metabolism was associated with both colon and rectal cancer risk. However, abdominal obesity and abnormal glucose metabolism, but not reduced HDL-C, remained associated with colorectal cancer risk independently from the other components. Furthermore, the association of MetS as defined here and colorectal cancer risk was largely accounted for by abdominal obesity and abnormal glucose metabolism. To our knowledge, this is the first study documenting that MetS did not add information for the assessment of colorectal cancer risk beyond these two metabolic abnormalities.

To date, several prospective studies investigated the association of MetS with risk of colorectal cancer, predominantly reporting positive associations (7-12). However, the
comparison of the results from these prior studies is hampered due to the fact that each of them defined MetS according to different criteria, and that most studies did not distinguish between colon and rectal cancer (7, 11, 12) or between men and women (8, 11). To address these gaps in the previous research, for defining MetS, we applied three different definitions recently proposed by international expert groups and studied the association separately for colon and rectal cancer. MetS as defined according to the NCEP/ATPIII, IDF, or the harmonized criteria, was similarly associated with colon cancer risk, and when based on the NCEP/ATPIII criteria, was associated also with risk of rectal cancer. Overall, the results showing stronger associations of MetS components and definitions for colon than for rectal cancer in our study are consistent with previous studies on other metabolic factors (4, 22), suggesting that colon and rectum may differ in their susceptibility to risks associated with the metabolic abnormalities and justify the need to distinguish between these cancer sites in future epidemiological research.

Our findings that MetS is somewhat more strongly related to risk of colorectal cancer in women compared to men, are in contradiction to some prior studies (7, 9, 12). However, compared to those studies our data provide much higher number of cases. Further, previous reports had higher proportion of men than women, which may have led to a higher power to detect associations in men, while our study population was equally distributed by sex. Although, in our study the differences by sex were not statistically significant, the question whether men and women may potentially have different susceptibility to metabolic abnormalities in terms of colorectal cancer risk warrant further investigation.

Interestingly, we observed an association for MetS by NCEP/ATPIII definition and rectal cancer risk which was no longer statistically significant when abnormal glucose metabolism was defined using a cut-off point for HbA1c of 6.5% instead of 5.7%. These differences in the associations by using different cut-off point levels may be explained by that applying a lower cut-off point increased the number of exposed individuals and thus increased
also the power to detect statistically significant associations. Nevertheless, previous evidence suggests hyperglycemia to be associated with colorectal cancer incidence and mortality (5, 12) and plausible biological mechanisms to explain its role in colorectal cancer risk include direct involvement insulin resistance, as well as acting as an energy depot for cancer cell growth(12).

We studied the association between abdominal obesity and colorectal cancer according to cut-off points defined specifically for European populations (IDF definition) and were able to judge upon its relative performance, compared to the cut-off points suggested for the American populations (NCEP/ATPIII definition). The prevalence of abdominal obesity when defined according to the IDF criteria was approximately twice higher compared to the NCEP/ATPIII criteria. In parallel, abdominal obesity by IDF, but not abdominal obesity by NCEP/ATP III was independently associated with colon cancer, suggesting that the lower cut-off point of the IDF definition might be more appropriate to assess the risk in European population, compared to the cut-off point of the NCEP/ATPIII definition. These results, however, should be confirmed by other studies and additional reclassification analyses are needed to draw meaningful recommendations.

It should be noted that the detection of an association with risk of colorectal cancer in our study may depend on the categorization of the metabolic markers according to the different set of cut-off points. Thus, any insignificant associations may not necessarily imply the absence of a true biological relationship. For example, in our analysis reduced HDL-C as defined according the MetS criteria was not associated with colon cancer independently from the other components. However, a previous report on same data showed that high concentrations of serum HDL-C (continuously) were associated with a decreased risk of colon cancer independently from markers of systemic inflammation, insulin resistance and oxidative stress, as well as from the other MetS components(6). To overcome the limitations of using
arbitrary cut-off points, other analytical approaches might be further explored such as development of risk scores composed by metabolic markers.

Over the recent years there has been controversy surrounding the concept of MetS, and its clinical usefulness for assessing the risk of cardiovascular diseases and diabetes mellitus has been questioned. Thus, it was discussed that the ‘cardio-vascular risk associated with the syndrome may be no greater than the sum of its parts’ (23) and that ‘a simple fasting plasma glucose measurement may serve as a much better predictor of future diabetes than the expense and inconvenience necessary to diagnose the syndrome’ (24). Recently, the World Health Organization (WHO) expert consultation concluded that the MetS has little utility as a diagnostic or management tool (25). Our results suggest that abdominal obesity and abnormal glucose metabolism may have an independent effect on colorectal cancer risk. Furthermore, these two factors statistically explained to the highest extent the observed association between MetS definitions and colon cancer. In fact, MetS did not did not provide risk information beyond its individual components. Thus, our data highlight the role of abdominal fatness and the subsequent hyperinsulinemia among the rest of the metabolic consequences of the insulin resistance state in the aetiology of colorectal cancer. Hyperinsulinemia is suggested to stimulate proliferation and promote metastasis of malignant colonic epithelial cells by elevating the bioactivity of insulin-like growth factor (IGF) I and reducing IGF-binding protein-3 (26). While future research to shed light on the underlying pathophysiology that links metabolic factors with colorectal cancer risk is still warranted, the clinical and cancer-preventive implications of assessing abnormal glucose metabolism and abdominal obesity might be timely considered.

Among the main strengths of our study are the prospective design and the largest number of cases to date, which allowed analysis by cancer sub-site and sex. Availability of detailed information about dietary and lifestyle factors allowed sufficient control for potential residual confounding. To be more objective and complete, we defined MetS according to
three different international criteria, including the most recent definitions, which were not studied before in the same context. Finally, we addressed a question that has not been answered so far, but being of both clinical and public health importance, namely whether MetS improves colorectal cancer risk assessment beyond its components.

Some limitations need to be taken into account when interpreting the results. More than 70% of the study participants provided non-fasting blood samples, which may have affected the TG levels; however, we accounted for fasting status and found essentially the same results after excluding non-fasting participants. A single assessment of metabolic indicators may be susceptible to short-term variation, which would bias the results towards the null; however, the parameters assessed in our study were shown to be relatively stable over time (27). Use of non-steroidal anti-inflammatory drugs (NSAIDs) may be inversely related to MetS components and may reduce colorectal cancer risk; however, information about NSAID use is not available in EPIC. Similarly, information about family history of colorectal cancer is not recorded in EPIC. However prior studies do not suggest that NSAID use and family history are strong confounders of the association of metabolic markers with colorectal cancer risk (7).

Despite excluding participants with cancer at baseline, we cannot exclude the possibility that some individuals had, yet, undiagnosed cancer, although results were similar when cancer cases diagnosed during the first two years of follow-up were excluded from our analysis.

In conclusion, our findings illustrate the heterogeneity of MetS reflecting various combinations of metabolic abnormalities, and expand the previous literature showing that the association of MetS and colorectal cancer is largely accounted for by abdominal obesity and abnormal glucose metabolism, but not the rest of the MetS components. In terms of primary prevention, these results suggest that simple assessment of these factors to identify individuals at colorectal cancer risk may have higher clinical utility, compared to the complex assessment
of MetS. From a public health perspective, prevention strategies through nutritional and lifestyle modifications aiming to alleviate the metabolic abnormalities may have profound cancer-protective effects and should be further prioritised.

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Figure legends:

Figure 1: Multivariable-adjusted* relative risks (95% CI) of colon (Panel A) and rectal (Panel B) cancers for the MetS components mutually adjusted for the other components

Footnote:

Abbreviations: RR, relative risks; CI, confidence interval; WC, waist circumference; AO, abdominal obesity; AGM, abnormal glucose metabolism; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; BP, blood pressure;

Results based on conditional logistic regression (matching factors: age, sex, study center, follow-up time since blood collection, time of the day at blood collection and fasting status; women were further matched by menopausal status, phase of menstrual cycle at blood collection and postmenopausal women were matched by HRT use) with adjustment for smoking status, education, alcohol consumption, physical activity, fiber intake, consumption of fruits and vegetables, red and processed meat, fish and shellfish.

Note: AO as defined based on the NCEP/ATPIII definition was used in the mutually adjusted models presented at the figure. The RRs (95%CI) when the IDF criteria to define AO was used instead of NCEP/ATPIII criteria were as follows: for colon cancer: AGM, 2.05 (1.57-2.68), reduced HDL-C, 1.24 (0.93 - 1.65); elevated BP, 1.15 (0.91 - 1.52); elevated TG, 1.04 (0.76 - 1.42). For rectal cancer: AGM, 2.07 (1.45 - 2.95), reduced HDL-C, 0.91 (0.61 - 1.35); elevated BP, 1.04 (0.73 - 1.48); elevated TG, 0.97 (0.66 - 1.44). RRs are plotted on a logarithmic scale.
Table 1. Definitions of MetS

|-----------------------------|--------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| Abdominal obesity (high WC) | Three or more of the following: High population specific WC, \(\geq 94\) cm in men, \(\geq 80\) cm in women  
\(\text{for European population}\) plus any 2 of the following: \(\geq 94\) cm in men, \(\geq 80\) cm in women  
\(\text{for European population}\)  
\(\geq 102\) cm in men,  
\(\geq 88\) cm in women  
Elevated TG \(\geq 150\) mg/dL (1.7 mmol/L)  
Reduced HDL-C  <40 mg/dL (1.03 mmol/L) in men  <50 mg/dL (1.29 mmol/L) in women  
Elevated BP  systolic \(\geq 130\), diastolic \(\geq 85\) mmHg or treatment of previously diagnosed hypertension  
Abnormal glucose metabolism\(^b\)  fasting glucose levels \(\geq 100\) mg/dL (\(\geq 5.6\) mmol/L) or previously diagnosed type 2 diabetes  
                                                                                     | \(\geq 150\) mg/dL (1.7 mmol/L) or specific treatment for lipid metabolism  
\(\geq 150\) mg/dL (1.7 mmol/L) or specific treatment for lipid metabolism  
Elevated TG \(\geq 150\) mg/dL (1.7 mmol/L) or specific treatment for lipid metabolism  
Reduced HDL-C  <40 mg/dL (1.03 mmol/L) in men  <50 mg/dL (1.29 mmol/L) in women  
Elevated BP  systolic \(\geq 130\), diastolic \(\geq 85\) mmHg or treatment of previously diagnosed hypertension  
Abnormal glucose metabolism\(^b\)  fasting glucose levels \(\geq 100\) mg/dL (\(\geq 5.6\) mmol/L) or drug treatment of elevated glucose  
                                                                                     | \(\geq 94\) cm in men, \(\geq 80\) cm in women  
\(\text{for European population}\)  
\(\geq 102\) cm in men,  
\(\geq 88\) cm in women  
Elevated TG \(\geq 150\) mg/dL (1.7 mmol/L) or specific treatment for lipid metabolism  
Reduced HDL-C  <40 mg/dL (1.03 mmol/L) in men  <50 mg/dL (1.29 mmol/L) in women  
Elevated BP  systolic \(\geq 130\), diastolic \(\geq 85\) mmHg or treatment of previously diagnosed hypertension  
Abnormal glucose metabolism\(^b\)  fasting glucose levels \(\geq 100\) mg/dL (\(\geq 5.6\) mmol/L) or drug treatment of elevated glucose  
                                                                                     | \(\geq 94\) cm in men, \(\geq 80\) cm in women  
\(\text{for European population}\)  
\(\geq 102\) cm in men,  
\(\geq 88\) cm in women  
Elevated TG \(\geq 150\) mg/dL (1.7 mmol/L) or specific treatment for lipid metabolism  
Reduced HDL-C  <40 mg/dL (1.03 mmol/L) in men  <50 mg/dL (1.29 mmol/L) in women  
Elevated BP  systolic \(\geq 130\), diastolic \(\geq 85\) mmHg or treatment of previously diagnosed hypertension  
Abnormal glucose metabolism\(^b\)  fasting glucose levels \(\geq 100\) mg/dL (\(\geq 5.6\) mmol/L) or drug treatment of elevated glucose  
                                                                                     |

Abbreviations: MetS, Metabolic Syndrome; NCEP/ATPIII, National Cholesterol Education Program/Adult Treatment Panel III; IDF, International Diabetes Federation; WC, waist circumference; AO, abdominal obesity; AGM, abnormal glucose metabolism; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; BP, blood pressure.

\(^a\)Based on a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity.

\(^b\)In this analysis HB\(A_1C\) \(\geq 5.7\)% was used instead of fasting glucose for defining abnormal glucose metabolism, according to the American Diabetes Association recommendations, 2010.
Table 2. Baseline Characteristics, Baseline Prevalence of MetS and Individual Components in Colon and Rectal Cancer Cases and Matched Controls, European Prospective Investigation into Cancer and Nutrition, 1992–2003

<table>
<thead>
<tr>
<th></th>
<th>Colon cancer</th>
<th>Rectal cancer</th>
<th>P Value&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Colon cancer</th>
<th>Rectal cancer</th>
<th>P Value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Socio-demographic and lifestyle characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women, %</td>
<td>54.7</td>
<td>54.7</td>
<td>0.97</td>
<td>45.8</td>
<td>45.8</td>
<td>0.74</td>
</tr>
<tr>
<td>Age, mean (SD), years</td>
<td>58.8 (7.3)</td>
<td>58.8 (7.3)</td>
<td>0.31</td>
<td>58.1 (7.0)</td>
<td>58.1 (7.0)</td>
<td>0.23</td>
</tr>
<tr>
<td>University degree, %</td>
<td>16.7</td>
<td>18.4</td>
<td>0.70</td>
<td>20.0</td>
<td>20.0</td>
<td>0.98</td>
</tr>
<tr>
<td>Postmenopausal women, %</td>
<td>72.2</td>
<td>70.8</td>
<td>0.79</td>
<td>69.2</td>
<td>69.7</td>
<td>0.32</td>
</tr>
<tr>
<td>Ever use of HRT, %</td>
<td>11.5</td>
<td>10.6</td>
<td>0.57</td>
<td>8.7</td>
<td>7.8</td>
<td>0.54</td>
</tr>
<tr>
<td>Not fasting overnight, %</td>
<td>48.2</td>
<td>48.7</td>
<td>0.42</td>
<td>27.7</td>
<td>28.2</td>
<td>0.87</td>
</tr>
<tr>
<td>Smokers, %</td>
<td>23.7</td>
<td>20.8</td>
<td>0.13</td>
<td>15.8</td>
<td>14.9</td>
<td>0.007</td>
</tr>
<tr>
<td>Alcohol intake (g/day), median (IQR)</td>
<td>7.9 (2.3-17.9)</td>
<td>7.5 (2.7-17.4)</td>
<td>0.20</td>
<td>11.9 (3.5-27.2)</td>
<td>10.6 (3.5-22.4)</td>
<td>0.009</td>
</tr>
<tr>
<td>Fruits and vegetables intake (g/day), median (IQR)</td>
<td>381.3 (244.1-549.7)</td>
<td>412.3 (259.7-564.2)</td>
<td>0.08</td>
<td>355.7 (247.8-522.6)</td>
<td>372.7 (256.9-541.9)</td>
<td>0.43</td>
</tr>
<tr>
<td><strong>Metabolic abnormalities</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WC, mean (SD)</td>
<td>90.5 (13.1)</td>
<td>88.0 (12.1)</td>
<td>&lt;0.001</td>
<td>90.5 (13.1)</td>
<td>89.9 (13.1)</td>
<td>0.58</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>26.9 (4.4)</td>
<td>26.3 (3.8)</td>
<td>0.02</td>
<td>26.6 (4.1)</td>
<td>26.5 (3.9)</td>
<td>0.55</td>
</tr>
<tr>
<td>TG (mmol/l), median (IQR)</td>
<td>1.13 (0.77-1.61)</td>
<td>1.05 (0.76-1.50)</td>
<td>0.02</td>
<td>1.14 (0.79-1.62)</td>
<td>1.14 (0.79-1.63)</td>
<td>0.99</td>
</tr>
<tr>
<td>HDL-C (mmol/l), median (IQR)</td>
<td>1.37 (1.12-1.66)</td>
<td>1.44 (1.19-1.75)</td>
<td>&lt;0.001</td>
<td>1.44 (1.16-1.71)</td>
<td>1.40 (1.14-1.70)</td>
<td>0.94</td>
</tr>
<tr>
<td>Systolic BP (mmHg), mean (SD)</td>
<td>137.1 (22.3)</td>
<td>135.3 (19.3)</td>
<td>0.11</td>
<td>136.6 (20.7)</td>
<td>137.9 (21.6)</td>
<td>0.17</td>
</tr>
<tr>
<td>Diastolic BP (mmHg), mean (SD)</td>
<td>83.0 (12.5)</td>
<td>81.8 (10.9)</td>
<td>0.22</td>
<td>82.9 (10.9)</td>
<td>83.0 (11.2)</td>
<td>0.46</td>
</tr>
<tr>
<td>HbA1c (%), median, IQR</td>
<td>5.8 (5.5-6.1)</td>
<td>5.7 (5.5-6.0)</td>
<td>0.02</td>
<td>5.7 (5.5-6.0)</td>
<td>5.7 (5.5-6.0)</td>
<td>0.93</td>
</tr>
<tr>
<td><strong>Components of the definitions of MetS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AO by NCEP/ATPIII definition, %</td>
<td>33.5</td>
<td>25.4</td>
<td>&lt;0.001</td>
<td>31.4</td>
<td>25.9</td>
<td>0.08</td>
</tr>
<tr>
<td>AO by IDF definition, %</td>
<td>63.6</td>
<td>52.8</td>
<td>&lt;0.001</td>
<td>59.2</td>
<td>57.2</td>
<td>0.56</td>
</tr>
<tr>
<td>Elevated TG, %</td>
<td>21.9</td>
<td>17.7</td>
<td>0.04</td>
<td>23.3</td>
<td>21.5</td>
<td>0.54</td>
</tr>
<tr>
<td>Reduced HDL-C, %</td>
<td>25.5</td>
<td>19.7</td>
<td>0.009</td>
<td>19.3</td>
<td>21.5</td>
<td>0.42</td>
</tr>
<tr>
<td>Elevated BP, %</td>
<td>64.2</td>
<td>59.9</td>
<td>0.08</td>
<td>64.6</td>
<td>62.1</td>
<td>0.43</td>
</tr>
<tr>
<td>AGM, %</td>
<td>51.7</td>
<td>38.3</td>
<td>&lt;0.001</td>
<td>50.7</td>
<td>39.9</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Number of MetS components&lt;sup&gt;b&lt;/sup&gt;, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 or 1</td>
<td>12.2</td>
<td>18.3</td>
<td>&lt;0.001</td>
<td>11.9</td>
<td>16.3</td>
<td>0.05</td>
</tr>
<tr>
<td>2 or more</td>
<td>54.6</td>
<td>60.8</td>
<td>0.02</td>
<td>58.2</td>
<td>60.4</td>
<td>0.51</td>
</tr>
<tr>
<td><strong>Definitions of MetS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MetS by NCEP/ATPIII definition, %</td>
<td>33.2</td>
<td>20.9</td>
<td>&lt;0.001</td>
<td>30.0</td>
<td>23.3</td>
<td>0.02</td>
</tr>
<tr>
<td>MetS by IDF definition, %</td>
<td>40.6</td>
<td>27.3</td>
<td>&lt;0.001</td>
<td>35.6</td>
<td>30.7</td>
<td>0.13</td>
</tr>
<tr>
<td>MetS by the harmonized definition, %</td>
<td>44.4</td>
<td>29.8</td>
<td>&lt;0.001</td>
<td>38.4</td>
<td>32.9</td>
<td>0.09</td>
</tr>
</tbody>
</table>
P-values for the difference between cases and controls were determined by Student’s paired t-test for variables expressed as means; by Wilcoxon’s signed rank test for variables expressed as medians, by McNemar’s test and Bowker’s test of symmetry for variables expressed as percentages.

Note: Sex, age, menopausal status, fasting status and HRT use were among the matching criteria.

MetS components as defined according to the NCEP/ATPIII definition.
Table 3. Multivariable-adjusted\textsuperscript{a} Estimated Relative Risks of Colon and Rectal Cancer According to MetS Definitions and Individual MetS Components, Follow-up 1992–2003

<table>
<thead>
<tr>
<th>Components of MetS</th>
<th>RR (95%CI)</th>
<th>Colon cancer</th>
<th>Rectal cancer</th>
<th>P Value\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>N, Cases/Controls</td>
<td></td>
<td>All</td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>AO (high WC) by NCEP/ATPIII</td>
<td>1.55 (1.19-2.02)</td>
<td>106/67 125/108</td>
<td>127/105 73/61 54/44</td>
<td>0.06 1.34 1.21 1.68</td>
</tr>
<tr>
<td>N, Cases/Controls</td>
<td>438/364 208/165 230/199</td>
<td>1.68 (1.31-2.15)</td>
<td>1.78 1.63 0.53</td>
<td>0.67 1.07 1.16 1.09</td>
</tr>
<tr>
<td>Elevated TG</td>
<td>1.36 (0.95-1.68)</td>
<td>81/69 70/53</td>
<td>94/87 72/61 22/26</td>
<td>0.53 1.00 0.98 1.02</td>
</tr>
<tr>
<td>Reduced HDL-C</td>
<td>1.36 (1.04-1.77)</td>
<td>72/48 104/88</td>
<td>78/87 43/43 35/44</td>
<td>0.37 0.91 1.21 0.83</td>
</tr>
<tr>
<td>MetS by NCEP/ATPIII</td>
<td>1.91 (1.47-2.42)</td>
<td>108/74 121/70</td>
<td>121/94 75/60 46/34</td>
<td>0.49 1.45 1.35 2.03</td>
</tr>
<tr>
<td>Elevated BP</td>
<td>1.91 (1.48-2.46)</td>
<td>140/94 140/94</td>
<td>144/124 87/77 57/47</td>
<td>0.84 1.28 1.16 1.83</td>
</tr>
<tr>
<td>AGM</td>
<td>2.00 (1.48-2.88)</td>
<td>150/107 156/98</td>
<td>155/133 97/84 58/49</td>
<td>0.73 1.31 1.24 1.70</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Multivariable-adjusted for age, sex, smoking status, BMI, physical activity, history of diabetes, and family history of cancer.

\textsuperscript{b}P values were calculated using the Wald test.
Abbreviations: RR, relative risks; CI, confidence interval; N, number; MetS, Metabolic syndrome; WC, waist circumference; AO, abdominal obesity; AGM, abnormal glucose metabolism; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; BP, blood pressure; NCEP/ATPIII, National Cholesterol Education Program/ Adult Treatment Panel III; IDF, International Diabetes Federation.

*Results based on conditional logistic regression (matching factors: age, sex, study centre, follow-up time since blood collection, time of the day at blood collection and fasting status; women were further matched by menopausal status, phase of menstrual cycle at blood collection and postmenopausal women were matched by HRT use) with adjustment for smoking status, education, alcohol consumption, physical activity, fiber intake, consumption of fruits and vegetables, red and processed meat, fish and shellfish.*

*p for difference by sex calculated by using interaction terms of MetS definitions and components (categorical), multiplied by the stratum variable in the multivariable-adjusted model.

Note: For all RRs, reference category was no presence of the characteristic. The presented relative risk estimates refer to dichotomized variables. The numbers for the cases and controls refer to the presence of MetS component or definitions.

<table>
<thead>
<tr>
<th>RRs</th>
<th>(1.56-2.56)</th>
<th>(1.28-2.66)</th>
<th>(1.63-3.33)</th>
<th>(0.95-1.79)</th>
<th>(0.80-1.90)</th>
<th>(0.98-2.93)</th>
</tr>
</thead>
</table>

Cancer Research.


Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.
Table 4. Multivariable-adjusted Estimated Relative Risks of Colon Cancer associated with Specific Combinations of MetS Components, Follow-up 1992–2003

<table>
<thead>
<tr>
<th>Model</th>
<th>MetS components</th>
<th>% of all subjects</th>
<th>RR</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AGM Elevated TG AO by IDF Elevated BP Reduced HDL</td>
<td>(% of subjects among those with MetS by IDF)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 MetS component</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.1</td>
<td>x</td>
<td>45.0 (72.4)</td>
<td>2.14</td>
<td>1.64-2.77</td>
</tr>
<tr>
<td>1.2</td>
<td>x</td>
<td>19.8 (41.9)</td>
<td>1.36</td>
<td>0.95-1.68</td>
</tr>
<tr>
<td>1.3</td>
<td>x</td>
<td>58.2 (100.0)</td>
<td>1.68</td>
<td>1.31-2.15</td>
</tr>
<tr>
<td>1.4</td>
<td>x</td>
<td>62.1 (87.6)</td>
<td>1.26</td>
<td>0.98-1.61</td>
</tr>
<tr>
<td>1.5</td>
<td>x</td>
<td>22.6 (43.0)</td>
<td>1.36</td>
<td>1.04-1.77</td>
</tr>
<tr>
<td>2 MetS components</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.1</td>
<td>x</td>
<td>9.7 (22.7)</td>
<td>1.93</td>
<td>1.30-2.87</td>
</tr>
<tr>
<td>2.2</td>
<td>x</td>
<td>10.5 (23.5)</td>
<td>2.45</td>
<td>1.66-3.62</td>
</tr>
<tr>
<td>2.3</td>
<td>x</td>
<td>29.8 (72.4)</td>
<td>2.29</td>
<td>1.72-3.03</td>
</tr>
<tr>
<td>2.4</td>
<td>x</td>
<td>30.6 (63.0)</td>
<td>1.99</td>
<td>1.51-2.62</td>
</tr>
<tr>
<td>2.5</td>
<td>x</td>
<td>8.3 (21.6)</td>
<td>1.58</td>
<td>1.05-2.37</td>
</tr>
<tr>
<td>2.6</td>
<td>x</td>
<td>15.4 (41.9)</td>
<td>1.47</td>
<td>1.06-2.03</td>
</tr>
<tr>
<td>2.7</td>
<td>x</td>
<td>14.4 (34.0)</td>
<td>1.33</td>
<td>0.97-1.84</td>
</tr>
<tr>
<td>2.8</td>
<td>x</td>
<td>16.7 (43.0)</td>
<td>1.48</td>
<td>1.10-1.98</td>
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<tr>
<td>2.9</td>
<td>x</td>
<td>14.2 (32.7)</td>
<td>1.48</td>
<td>1.07-2.04</td>
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<td>2.10</td>
<td>x</td>
<td>40.1 (87.6)</td>
<td>1.67</td>
<td>1.31-2.12</td>
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<tr>
<td>3 MetS components</td>
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<td></td>
</tr>
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<td>3.1</td>
<td>x</td>
<td>7.7 (22.7)</td>
<td>1.92</td>
<td>1.23-2.99</td>
</tr>
<tr>
<td>3.2</td>
<td>x</td>
<td>8.0 (23.5)</td>
<td>2.57</td>
<td>1.64-4.01</td>
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<td>3.3</td>
<td>x</td>
<td>21.4 (63.0)</td>
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<td>1.80-3.35</td>
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<tr>
<td>3.4</td>
<td>x</td>
<td>4.0 (10.5)</td>
<td>2.46</td>
<td>1.32-4.58</td>
</tr>
<tr>
<td>3.5</td>
<td>x</td>
<td>7.3 (17.7)</td>
<td>2.06</td>
<td>1.31-2.32</td>
</tr>
<tr>
<td>3.6</td>
<td>x</td>
<td>7.3 (21.6)</td>
<td>1.66</td>
<td>1.07-2.57</td>
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<tr>
<td>3.7</td>
<td>x</td>
<td>11.5 (34.0)</td>
<td>1.69</td>
<td>1.17-2.43</td>
</tr>
<tr>
<td>3.8</td>
<td>x</td>
<td>7.6 (22.2)</td>
<td>1.47</td>
<td>0.96-2.26</td>
</tr>
<tr>
<td>3.9</td>
<td>x</td>
<td>4.9 (14.3)</td>
<td>1.65</td>
<td>0.99-2.76</td>
</tr>
<tr>
<td>3.10</td>
<td>x</td>
<td>0.0 (0.0)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Abbreviations: RR, relative risks; CI, confidence interval; N, number; MetS, Metabolic syndrome; AO, abdominal obesity; AGM, abnormal glucose metabolism; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; BP, blood pressure; NCEP/ATPIII, National Cholesterol Education Program/Adult Treatment Panel III; IDF, International Diabetes Federation.

Results based on conditional logistic regression (matching factors: age, sex, study centre, follow-up time since blood collection, time of the day at blood collection and fasting status; women were further matched by menopausal status, phase of menstrual cycle at blood collection and postmenopausal women were matched by HRT use) with adjustment for smoking status, education, alcohol consumption, physical activity, fiber intake, consumption of fruits and vegetables, red and processed meat, fish and shellfish.

MetS is defined here according to the criteria of the IDF.

Results are shown for AO by IDF as this is the factor that showed to be independently associated with risk of colon cancer in a model mutually adjusted for the other components.

Note: RRs are shown for persons with the metabolic syndrome combination specified compared with persons without that combination. Consequently, models 1.1–1.5, 2.1–2.10, and 3.10 do not define mutually exclusive groups, and the prevalence of trait combinations do not sum to 100%.
Figure 1A: Multivariable-adjusted relative risks (95% CI) of colon cancer for the individual MetS components mutually adjusted for the other components.
Figure 1B: Multivariable-adjusted relative risks (95% CI) of rectal cancer for the individual MetS components mutually adjusted for the other components.
Metabolic Syndrome and Risks of Colon and Rectal Cancer: the European Prospective Investigation into Cancer and Nutrition Study

Krasimira Aleksandrova, Heiner Boeing, Mazda Jenab, et al.

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