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Inflammatory potential of the diet and risk of colorectal cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC) study

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Abbreviations list

CRC: Colorectal Cancer

EPIC: European Prospective Investigation into Cancer and Nutrition

ISD: Inflammatory Score of the Diet

IPS: Inflammatory Profile Score

DII: Dietary Inflammatory Index

HR: Hazard Ratio

IARC: International Agency for Research on Cancer

ICD-10: International Classification of Diseases

ICDO-2: International Classification of Disease for Oncology

NOS: Not Otherwise Specified

FFQ: Food Frequency Questionnaire

24hDR: 24-hour Dietary Recall

CRP: C-reactive Protein

TNF: Tumor Necrosis Factor

SD: Standard Deviation

CI: Confidence Intervals

BMI: Body Mass Index

LR: Likelihood Ratio

HRT: Hormone Replacement Therapy

NIH-AARP: National Institute of Health -American Association of Retired Persons study

RR: Relative Risk

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ABSTRACT

Pro-inflammatory diets are associated with risk of developing colorectal cancer (CRC), however inconsistencies exist in subsite- and sex-specific associations. The relationship between CRC and combined lifestyle-related factors that contribute towards a low-grade inflammatory profile has not yet been explored. We examined the association between the dietary inflammatory potential and an inflammatory profile and CRC risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. This cohort included 476,160 participants followed-up of 14 years and 5,991 incident CRC cases (3,897 colon and 2,094 rectal tumours). Dietary inflammatory potential was estimated using an Inflammatory Score of the Diet (ISD). An Inflammatory Profile Score (IPS) was constructed, incorporating the ISD, physical activity level and abdominal obesity. The associations between the ISD and CRC and IPS and CRC were assessed using multivariable regression models. More pro-inflammatory diets were related to a higher CRC risk, particularly for colon cancer; Hazar Ratio (HR) for highest versus lowest ISD quartile was 1.15 (95% confidence interval (CI) 1.04-1.27) for CRC, 1.24 (95% CI 1.09-1.41) for colon cancer and 0.99 (95% CI 0.83-1.17) for rectal cancer. Associations were more pronounced in men and not significant in women. The IPS was associated with CRC risk, particularly colon cancer among men; HRs for the highest versus lowest IPS were 1.62 (95% CI 1.31-2.01) for colon cancer overall and 2.11 (95% CI 1.50-2.97) for colon cancer in men. This study shows that more pro-inflammatory diets and a more inflammatory profile are associated with higher risk of CRC, principally colon cancer and in men.

Novelty and Impact Statement

This large prospective study strengthens the evidence that a diet with a high inflammatory potential is associated with increased risk of CRC. Our results also indicate that the inflammatory potential of the diet is predominantly related to colon cancer, particularly colon cancer in men. We report novel results showing that an overall low-grade inflammatory profile, incorporating the inflammatory potential of the diet, physical activity and abdominal obesity is a strong predictor of colon cancer.

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INTRODUCTION

Colorectal cancer (CRC) is the third most commonly occurring cancer globally, with an estimated 1.8 million new cases in 2018[1]. The incidence of CRC is much higher in men than women, with 324/100,000 compared to 253/100,000 new cases in 2018 in Europe, respectively[1]. The main lifestyle-related CRC risk factors are smoking, alcohol consumption, obesity, physical inactivity and certain dietary factors[2]. It has been estimated that approximately 70% of CRC cases could be avoided by following a healthy lifestyle[3] and diet is one of the key modifiable lifestyle factors[4].

Chronic inflammation has been implicated in the onset and progression of CRC[5], and diet plays an important role in modulating systemic inflammation. Therefore, the increased risk of CRC associated with certain dietary factors may be partly due to their effect on inflammatory biomarkers (cytokines/chemokines, acute-phase proteins, soluble adhesion molecules, etc)[6]. A high consumption of red and processed meat (foods shown to have pro-inflammatory properties) is strongly associated with a greater risk of CRC[7], whereas a high consumption of fibre and whole grains (foods shown to have anti-inflammatory properties) is strongly associated with risk[2]. Evidence also suggests that consumption of fruit and vegetables may decrease risk of CRC[2].

A widely applied tool designed to summarize the inflammatory potential of multiple dietary components is the Dietary Inflammatory Index (DII), which assigns inflammatory weights to different foods components according to their pro-inflammatory or anti-inflammatory properties[8,9]. The DII scores subjects along an inflammatory continuum; higher/ more positive DII scores reflect more pro-inflammation diets and lower/ more negative scores reflect more anti-inflammatory diets. Higher DII scores have been associated with higher levels of inflammatory biomarkers[8,10–12] and a higher risk of CRC[13–15], and several meta-analyses have reported around a 40% increased CRC risk for the highest versus lowest DII category. However, the risk estimates were substantially lower when analyses were restricted to prospective cohort studies and inconsistences between studies on gender- and site-specific associations warrant further investigation[13,15].

Adiposity and lack of physical activity are two other major factors that can contribute to chronic inflammation and they are highly interrelated with diet, and also recognised as causes of CRC[2]. The inflammatory effects of diet, physical activity and abdominal obesity may individually increase risk of CRC or act in combination. In terms of obesity, enlarged adipocytes in obese individuals lead to overexpression of a host of inflammatory mediators which then produces chronic systemic inflammation[16,17]. This is particularly relevant when the enlarged mass of adipose tissue accumulates in the abdomen as visceral fat[18]. Although the relationship between physical activity and inflammation is complex, evidence shows that in the long-term habitual exercise reduces inflammatory markers[19].

Therefore, the aim of this study was to assess the prospective association between the inflammatory potential of the diet and CRC, by anatomical sub-site and gender, in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study. In addition, the relationship between CRC and a low-grade inflammatory profile that considers the combined effect of the inflammatory potential of the diet along with abdominal obesity and physical activity was investigated.

MATERIALS AND METHODS

Study setting and population

EPIC is a large on-going multi-centric cohort study and the full methodological details for the recruitment procedure and data collection have been described previously[20]. In brief, between 1992 and 2000 a total of 521,324 subjects, mostly 30-70 years old, were recruited from 23 centres in 10 European countries. Participants were mainly recruited from the general population, with the exceptions detailed elsewhere[20]. All participants gave written informed consent. Ethical committees from the International Agency for Research on Cancer (IARC) and local centres approved the study. Participants were excluded if have had a prevalent cancer at baseline other than non-melanoma skin cancer (n=25,184), missing end of follow-up data (n=4,148), missing diet or lifestyle information (n=6,259) or extreme energy intake/expenditure (n=9,573), calculated as the top or bottom 1% of the distribution of the ratio of energy intake to energy requirement. Therefore, 476,160 participants (142,241 men and 333,919 women) were included in the final study population.

Follow-up and ascertainment of colorectal cancer cases

Incident CRC cases were identified via population cancer registries for Denmark, Italy, The Netherlands, Norway, Spain, Sweden and the United Kingdom. In France, Germany, Naples and Greece different methods was used, including health insurance records, cancer and pathology registries and active follow-up of participants and their next of kin, with a subsequent medical verification of the diagnosis. Vital status data was obtained from regional or national mortality registries. Censoring dates for the last complete follow-up varied by centre and ranged from 2005 to 2013. CRC cases were defined as tumours coded as C18-C20 in the 10th revision of the international classification of diseases (ICD-10), and the second revision of the International Classification of Disease for Oncology (ICDO-2). The CRC cases were further classified according to their anatomic location: proximal colon (C18.0–18.5), distal colon (C18.6–18.7), not otherwise specified (NOS) colon (C18.8–18.9) and rectum (C19–C20).

Assessment of lifestyle variables

At recruitment anthropometric data was collected using standardized procedures and a lifestyle questionnaire was used to obtain information on socio-demographic factors, level of education, physical activity, medical history and consumption of alcohol and tobacco consumption. Dietary data was also collected at baseline, using validated country/centre-specific questionnaires to record the usual diet during the previous year. Most countries used extensive quantitative food frequency questionnaires (FFQ) or semi-quantitative FFQ, although a combination of diet records and FFQ or diet-history questionnaires were also used in some countries/ centres[20,21]. Furthermore, standardised 24-hour dietary recall (24hDR) measurements were taken from a representative subsample of the EPIC cohort (5-12%) to correct for systematic differences between the dietary questionnaires and to minimize measurement error[22]. Country-specific food composition databases, which were standardised across EPIC countries, were used to calculate total energy, macro- and micronutrients and intake of other dietary parameters from the food consumption data[23].

The Inflammatory Score of the Diet

The diet's inflammatory potential was assessed using an Inflammatory Score of the Diet (ISD), which has been described previously[24,25]. The construction of the ISD is initially based on the DII[9], an index comprised of 45 food components which were identified after a comprehensive literature review and included because of their anti-

inflammatory or pro-inflammatory properties. Each food component has been given an inflammatory weighting according to its association with six well-known inflammatory biomarkers (IL-1b, IL-4, IL-6, IL-10, Tumor Necrosis Factor (TNF) and C-reactive Protein (CRP)); the weighting uses an algorithm that takes into account the level of evidence from the studies and numbers of articles that were reviewed. The construct of the DII has been validated by studying its relation to circulating levels of inflammatory biomarkers in many different populations and DII scores have been associated with level of CRP, as well as a summary score for low grade inflammation (derived from 6 key inflammatory biomarkers)[10–12].

In the current study the ISD included 28 dietary components that were available in the EPIC datasets for all centres (listed in Supplementary Table 1). To calculate each participant's ISD their intake of each food item was first calibrated using data from the 24-hour recall (full methods are detailed in statistical analysis section) and then standardized using the mean and standard deviation (SD) of the study population. Each participant's z-score was then converted to a centred percentile value by transforming it to a percentile (of a standard normal distribution), doubling each percentile and then subtracting 1. To obtain the ISD for each item each percentile value was multiplied by the respective inflammatory effect score, using the item specific weights reported previously[9] (Supplementary Table 1). The separate ISD's obtained for the 28 dietary components for each participant were then summed to give their overall ISD. The overall ISD is a score without units and expresses an individual's diet, relative to the other participants, at a point along on a continuous scale ranging from below to above zero. The most negative value indicates the maximum anti-inflammatory diet in the cohort, while the highest positive value indicates the maximum pro-inflammatory diet.

The slightly different procedures used to construct the ISD, compared to the DII, have been described and justified previously[24]. In brief, total fat was not included as part of the ISD because the three separate components of dietary fat are already included, a different weight for alcohol was used due to its dose-dependent effect, so for subjects who consumed >40g/day the weight for alcohol was set as 0. Finally, each subject's intake for the 28 dietary components was standardized using the mean and SD of our study population to improve internal validity, as the aim of this study was to assess the association between the ISD and risk of CRC in this cohort, not to compare the inflammatory potential of the diet between populations.

The Inflammatory Profile Score

An overall inflammatory profile score (IPS)[25] was created to explore the potential relationship between CRC and low-grade inflammation linked to diet along with level of physical activity and abdominal obesity, two additional factors that modulate inflammation. Each subject's IPS is the sum of the three corresponding values obtained from i) the ISD (sex-specific tertiles; 1st tertile=0, 2nd tertile=1, 3rd tertile=2), ii) waist circumference defined using International Diabetes Federation cut-offs (men <94cm or women <80cm=0, and men ≥94cm or women ≥80cm=1) and iii) physical activity level (active or moderately active=0 and inactive or moderately inactive=1). Physical activity categories were derived by combining occupational and recreational activity levels and have been previously described and validated[26]. The IPS ranged from 0-4, with 0 reflecting less inflammation in terms of consuming an anti-inflammatory diet, not having abdominal obesity and being physically active. In contrast, an IPS of 4 reflects more inflammation in terms of eating a pro-inflammatory diet, having abdominal obesity and being physically inactive. Previous research in this population has shown that the ISD is associated with increased risk of gastric cancer and the ISD and IPS with higher mortality, in particular deaths by cardiovascular disease [24,25].

Statistical analysis

All analyses were carried out using R 3.2.1 software (R Foundation for Statistical Computing, Vienna, Austria). The ISD was described according to socio-demographic, lifestyle and dietary variables using the median, percentiles and age-, sex-, and energy-adjusted mean and SD using linear regression. Cox proportional hazard models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the association between ISD and risk of CRC, overall and for anatomical sub-sites (colon and rectal). Entry time was defined as age at recruitment and exit time was defined as age at diagnosis for cases, death or end of follow-up, whichever occurred first. Multivariable models were stratified by centre, sex and age at recruitment (1 year intervals) and adjusted by residuals of total energy intake on the ISD (quartiles), education (none and primary school, technical/professional school, secondary school, university or higher and not specified), smoking status and intensity (never, former quit <11 years, former quit 11–20 years, former quit >20 years, current ≤15 cigarettes/day, current 16–25 cigarettes/day, current >25 cigarettes/day, other smokers including occasional smokers and exclusive smokers of cigar or pipe, and smokers with unknown status or unknown amount), Cambridge physical activity index (inactive, moderately inactive, moderately active, active and not specified), Body Mass Index (BMI) (<25.0kg/m^2, 25-29.9 kg/m^2 and ≥30.0 kg/m^2) and the residuals of the intake of dietary variables including alcohol (quartiles, g/d), red meat (quartiles, g/d) processed meat (quartiles, g/d) and fibre (quartiles, g/d) intakes. The residuals of a linear regression of the dietary variables on the ISD were included in the multivariable models because these dietary factors are also a source of components included in the ISD.

The ISD was analysed as a categorical variable, using sex-specific quartiles and with the first quartile as the reference, and as a continuous variable for each increase in 1-SD of the ISD. Trend tests for the categorical variables were calculated by entering the categorical variable in the model as a continuous variable. All analyses were carried out on the whole study sample and by sex. Potential effect modification on the association between the ISD and CRC by the variables in the Cox models was evaluated by including interaction terms between the ISD and these variables, and the likelihood ratio (LR) test assessed the significance of the interaction. Schoenfeld residuals were used to assess that the assumptions of proportional hazards were met. The Wald statistic was applied to assess the homogeneity of the risk between the ISD and colon and rectal cancer. The association between the ISD as a continuous variable and risk of CRC and its subtypes was also examined in analyses stratified by EPIC European region (South, Middle and North), age, smoking status, physical activity, education level, BMI, weight circumference, alcohol consumption and intake of processed meat. The heterogeneity of HRs for the ISD across countries was explored with the use of a meta-analytic random- effects model.

The dietary data used to construct the ISD was calibrated to improve comparability of the dietary data across EPIC centres and to minimize measurement error. Country-and sex-specific linear regression calibration models were applied using the data from the subsample of subjects with 24hr dietary recalls (24hrDR)[22]. To obtain predicted (calibrated) values of dietary intake for all subjects, the 24hrDR measurements were regressed onto the dietary intakes from the questionnaires, while including in the following covariates; total energy intake, age at recruitment, centre, education, smoking, BMI and physical activity. The models were weighted by day of the week and season of the year in which the 24hrDR recall was administered. When zero consumption was reported on the main questionnaire, a zero was directly assigned as the calibrated intake. The calibrated values of each food item were used to calculate the ISD. A bootstrap sampling method (with 400 repetitions to ensure stability) was used to compute the mean and SD of the predicted intake of each food item in the ISD.

Adjusted HR and 95% CI for CRC were calculated for each of the 5 levels of the inflammatory profile. Subjects with unknown or missing information on physical activity level and waist circumference (112,654 subjects including 961 CRC cases) were put together in an IPS category labelled 'non-specified' to avoid excluding them from the inflammatory profile analysis. Sensitivity analyses were carried out to assess possible reverse causality caused by modifying habitual diet or lifestyle habits due to pre-existing subclinical conditions, by excluding cases with less than 2 years of follow-up (462 subjects). In addition, the Cox models were repeated using an ISD constructed without the alcohol component, due to its non-linear relationship with key inflammatory markers[27,28]. Finally, Cox models in women were repeated while additionally adjusting for hormonal factors: menopausal status (pre-menopausal, post-menopausal, peri-menopausal/unknown menopausal status or surgical post-menopausal), hormone replacement therapy (HRT) use (yes, no and unknown), and oral contraceptive use (yes, no and unknown), to evaluate their potential confounding effect in the association of interest.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

RESULTS

After following up 476,160 participants (70% women) for a mean of 13.9 years (SD 4.0 years), 5,991 incident primary CRC cases were diagnosed (1.02% of women and 1.82% of men developed CRC). Out of these cases, 3,897 were identified as having colon tumours (including 1,877 proximal, 1,743 distal and 277 not specified) and 2,094 as having rectal tumours.

The distribution of the baseline characteristics of the participants according to CRC cases and the ISD (mean and median) is shown in Table 1. At recruitment approximately half the participants were inactive or moderately inactive and overweight or obese. Almost a quarter of the participants were current smokers and a third had an education level only up to primary school. The ISD, reflecting the inflammatory potential of the diet, had a mean of 0.38 (SD 1.7) and ranged from -6.44 to 5.67, with a median of 0.53 (25th percentile -0.75 and 75th percentile 1.65) (data not tabulated). Figure 1 shows the mean ISD scores by EPIC country; the highest mean ISD (most pro-inflammatory) was in Norway and Sweden, while the United Kingdom and Spain had the lowest mean ISD (most anti-inflammatory). On average, women had a more pro-inflammatory diet than men and the inflammatory potential of the diet increased across age groups. Overall, the northern EPIC countries had more pro-inflammatory scores compared to other EPIC regions. The ISD values were higher among smokers and participants with a higher BMI and abdominal obesity, and lower in more physically active participants. The score tended to decrease across categories of alcohol consumption and fibre intake.

The multivariable HR for the association between the ISD and CRC overall and by sub-sites is shown in Table 2. For the whole population, there was a higher risk of CRC associated with higher values of the ISD (reflecting a more pro-inflammatory diet). The positive association was clear for both categorical and continuous ISD variables. In sex-specific models the higher risk of CRC across quartiles of ISD was evident in men but not in women; HR=1.23 (95% CI 1.05-1.44) and HR=1.09 (95% CI 0.95-1.25) respectively. In analyses by anatomical subsite we observed a strong association between the ISD and colon cancer, and this was more pronounced and only significant in men; HR=1.24 (95% CI 1.09-1.41) for colon cancer overall HR=1.44, 95% CI 1.18-

1.76) for colon cancer in men, for the highest versus lowest ISD quartile. Every 1-SD increase in ISD related to a 10% (HR=1.10, 95% CI 1.04-1.16) higher risk of colon cancer overall. In analysis of colon cancer subsites the magnitude of risk appeared higher for proximal compared to distal colon cancer; HR=1.29 (95% CI 1.07-1.55) and HR=1.14 (95% CI 0.94-1.37) respectively, for the highest versus the lowest ISD quartile (Table 2). No statistically significant associations were observed between the ISD and rectal cancer, overall or by sex. The Wald test indicated there was significant heterogeneity of the association by subsite overall and in men (p-value=0.01 in both), but not in women (p-value=0.18). There was no departure from linearity in any of the models, assessed using the likelihood ratio test.

Although the risk estimates varied in analyses stratified by potential effect modifiers (Table 3 shows p-values for interaction and Figure 1 shows the associations between the ISD and CRC by EPIC country), there was little evidence that the association between the ISD and risk of CRC was modified by these factors, except for a possible suggestion of interaction by sex (p-interaction 0.082), region (p-interaction 0.073) and processed meat (p-interaction 0.082). Within these respectively subgroups, the association was only observed in men, Northern EPIC regions and for individuals with a high intake of processed meat.

Table 4 shows the association between CRC and the IPS. Participants classified as having level 4 on the IPS had significantly higher risk of developing CRC compared to subjects classified in level 0 (HR=1.37, 95% 1.16-1.62). This association was more pronounced in men (HR 1.62 (95% CI 1.25-2.09 for highest versus lowest IPS) and was not significant in women. A similar pattern was observed in analyses of colon cancer, although the positive association was even stronger, especially in men.

In sensitivity analyses excluding participants with less than 2 years of follow-up, excluding the alcohol component from the ISD or additionally adjusting for hormone-related factors in women, the risk estimates did not change substantially (Table 5).

DISCUSSION

The results of this study shows that a pro-inflammatory diet, assessed using the ISD, was related to a higher risk of developing CRC in an adult European population. In this cohort, the diet's inflammatory potential was related to colon cancer but not rectal cancer and the association was more pronounced in men. When the inflammatory potential of the diet was combined with two other potential contributors to low-grade chronic inflammation to create an inflammatory profile, then the impact on risk of CRC, in particular colon cancer, was even greater. Individuals with a high inflammatory profile, defined as a more pro-inflammatory diet, a sedentary or moderately inactive lifestyle and also abdominal obesity, had a 37% higher risk of colon cancer compared to subjects with a low inflammatory profile (more anti-inflammatory diet, moderate or high physical activity levels and without abdominal obesity).

Overall, our results are in agreement with four recent meta-analyses of the association between CRC and the inflammatory potential of the diet, measured using the DII [13–15,29]. The meta-analyses including all study designs (up to five case-control and four prospective cohort studies) reported an approximately 40% increased risk of CRC associated with being in the highest compared to the lowest DII score category, which is much larger than the 15% increased risk of CRC observed in our study. However, when the meta-analyses were stratified by study design the summary risk estimate obtained from cohort studies was much lower than that from case-control studies[12,13]. Results from case-control studies may be less reliable due to their susceptibility to recall and selection bias, and so our results are more comparable to other prospective

studies. The summary relative risks for CRC derived from cohort studies for a 1-unit increment in the DII ranged from 3% (95% CI 2-4%)[14] to 4% (95% CI 3-5%)[29], that was fairly similar in magnitude to the 6% found in our study.

In analyses stratified by anatomical subsite, it was clear that the association between the ISD and risk of CRC was driven by the results for colon cancer; the highest category of the ISD significantly increased the risk of colon cancer by 24% while there was no association with rectal cancer. In addition, the Wald test results confirmed that the differential effect of the ISD by subsite was statistically significant. The magnitude of the association we observed is comparable to that reported in the Multi-ethnic cohort, where participants in the highest DII quartile were 20% more likely to develop colon cancer than participants in the lowest quartile.

The differing results by anatomical sites in our study are consistent with findings from two other prospective studies, the Iowa Women's Study[18] and Women's Health Initiative[20], which found evidence of an association between the DII and colon cancer, but not rectal cancer. In contrast, two other prospective studies, the NIH-AARP study and Multi-ethnic cohort, did observe that the DII was significantly related to risk of rectal cancer. The explanation for these disparities is unclear, but could partly relate to differences in cohort characteristics or methodological issues between studies, such as adjustment for confounding factors or which dietary components were used to calculate the diet's inflammatory potential. In addition, although CRC is often considered a single tumour entity in research and clinical practice, the two anatomical sub-sites differ in numerous epidemiological features, their molecular carcinogenesis[31] and their risk factors[5,32,33]. In terms of dietary risk factors, a meta-analysis of the evidence on red and processed meat, whole-grains and dairy products found that the summary relative risks were significant for colon cancer but not rectal cancer[2]. Such aetiological differences between sub-sites may also extend to the differential impact of the inflammatory potential of the diet on developing colon and rectal cancer.

In our population the positive association between the ISD and colon cancer was more pronounced and only statistically significant in men. These findings are in line with the NIH-AARP study[34] which found that the association between the DII and CRC was also only statistically significant in men, and in the Multi-ethnic cohort[35] where the effect size was larger for men than women. In addition, a meta-analysis of both case-control and cohort studies reported that the pooled relative risk (RR) of CRC in men was double of that in women[14]. The explanation why some studies, including ours, observe weaker and/or non-significant associations in women is unclear, but several theories can be considered. CRC is strongly influenced by gender, illustrated by substantial differences between sexes in incidence, survival and various clinical and pathological characteristics[36]. This has been partly attributed to sex differences in biological and environmental risk factors[37]. In terms of hormonal influences, oestrogen plays an important protective role in the pathogenesis of CRC in women[38], therefore menopause-related changes in oestrogen levels and HRT might be potential confounders of the ISD-CRC association[38,39]. However, in sensitivity analyses the lack of association in women remained identical after additionally adjusting for menopausal status, HRT and oral contraceptive pill use. Nevertheless, other hormonal-related factors might not have been accounted for. Alternatively, because the incidence of CRC is higher in men[37], the inflammatory potential of the diet might have a greater impact in men due to a higher background risk. In line with our findings, the World Cancer Research Fund/American Institute for Cancer Research 2017 CRC report presents meta-analyses of several foods that were significantly related to increased/ decreased risk of CRC in men (red and processed meat/fruit and non-starch vegetables) but did not reach statistical significance in women[2]. Finally, we cannot rule out gender differences in unmeasured risk factors, or in dietary intake reporting[40]

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and social desirability[41] that could introduce measurement error in estimating the ISD and confounding variables.

A novel aspect of our work was the construction of an inflammatory profile score, a combination of the inflammatory potential of the diet, physical activity and abdominal obesity. Low-grade chronic inflammation, a state of persistent and unresolved inflammation, is characterised by modest elevated levels of pro-inflammatory markers. The DII has been associated with higher concentrations of inflammatory biomarkers such as CRP, Interleukin (IL)-6, and homocysteine[10,11], as well as a low-grade inflammation summary score[12]. The abundance of inflammatory cells in visceral adipose tissue lead to systemic inflammation[18] and abdominal obesity is associated with elevated levels of tumour necrosis factor-α and high-sensitivity C-reactive protein (CRP)[42]. On the other hand, regular physical exercise is associated with lower levels of inflammatory markers such as IL-6 and CRP[43]. In our study, a pro-inflammatory profile, characterised by a more pro-inflammatory diet, lower levels of physical activity and abdominal obesity was a strong predictor of CRC, particularly colon cancer and in men. The differences by anatomical site probably reflect the strong evidence that physical activity protects against colon but not rectal cancer and that obesity may have a stronger negative impact on colon cancer[2]. The differential association between the ISD and the IPS and risk of colon and rectal cancer supports the fact that CRC is a heterogeneous group of diseases that should be investigated separately[44].

The biological plausibility behind these findings is supported by the fact that chronic inflammation is a well-documented pathological feature of colon cancer[5,45]. This is supported by the evidence that prolonged use of aspirin and other non-steroidal anti-inflammatory drugs reduces risk of colon cancer[2], whereas inflammatory bowel disease is a known cause of colon cancer[46]. In addition, a meta-analysis of 18 studies showed that a 1-unit increase in the natural logarithm (ln) of CRP related to a 13% increased risk of colon cancer, while no significant association was found with rectal cancer or in women[47]. The speculated inflammatory pathways could involve the effect of pro-inflammatory diets, abdominal obesity or low levels of physical activity on systemic inflammation, which can lead to insulin resistance[48]. Another hypothesis is related to the anti-inflammatory effects on local mircrobiota from omega-3 fatty acids and antioxidant components in certain foods (i.e. fruit, vegetables, tea and coffee)[49]. In addition, dietary factors can affect local inflammation and oxidation in the colon which leads to focal proliferation, angiogenesis and mutagenesis[48].

Strengths of the study are its large sample size, prospective and population-based design, extended follow-up and a large number of cases, allowing sufficient statistical power to explore gender- and site-specific associations and additional subgroup analyses. We also adjusted for multiple potential confounding factors, including the residuals of red meat, processed meat and fibre. These dietary factors are important sources of items included in the calculation of the ISD, and therefore including them directly in the model, along with the ISD, could result in over-adjustment or collinearity. However, excluding them could produce residual confounding because they are strongly related to CRC, operating through mechanisms other than inflammation[2]. To resolve these issues we calculated the residuals of a linear regression of the ISD on each dietary variable to use in the multivariable model. This ensured that the HR of the ISD was solely due to the inflammatory potential of the diet and that confounding by other dietary factors via non-inflammatory mechanisms was still controlled for.

There are also several limitations that should be considered when interpreting the results, mainly due to methodological issues relating to the construction of the ISD score, Firstly, only 28 of the original 45 items included in the DII were used to create the ISD. This was due to the availability of dietary data in the EPIC database and our

exclusion of total fat. However, a previous cohort study found that seven components, all of which were included in the ISD, explained 91% of the inter-individual variance in the DII[12]. Therefore, the fewer number of dietary components included in the ISD is likely to have had minimal influence on the estimations of the diet's total inflammatory potential. Secondly, since the construction of the ISD is based on the DII, it has similar inherent methodological limitations[8], one of which is that the ISD is constructed using inflammatory weights derived from data from other studies and so does not directly relate to inflammatory biomarkers measured in our specific population. Thus, further studies that assess the inflammatory potential of the diet based on alternative methods from DII would help corroborate our findings. Thirdly, potential measurement error derived from self-reported country-specific dietary questionnaires could have led to systematic and random errors in the dietary data used to construct the ISD. However, subjects with implausible dietary intake were excluded from the analyses and we adjusted for total energy intake. We also used models stratified by country/centre to account for potential systematic between-country differences in dietary assessment and used calibrated dietary intakes (from the 24hDR) to calculate the ISD. In addition, comparability of nutrient intakes across the EPIC countries has been improved through harmonising nutrient databases[23]. A further limitation is that diet and lifestyle variables were only assessed at recruitment, so any potential changes during follow-up were not taken into account. Potential reverse causality due to modification of diet during the early pre-diagnostic period of the disease is also possible, however in sensitivity analyses the associations did not materially change when we excluded incident cases diagnosed in the first two years of follow-up. We also lacked information on use of anti-inflammatory drugs[50] and supplements.

In summary, our results show that a diet with a higher inflammatory potential is associated with increased risk of CRC, particularly colon cancer among men. In addition, an inflammatory profile incorporating the inflammatory potential of the diet, physical activity and abdominal obesity, was a strong predictor of colon cancer. Public health initiatives that jointly target these modifiable risk factors may be particularly effective for preventing colon cancer. Future research should identify specific dietary patterns that are related to plasma levels of inflammatory biomarkers in the same population (using reduced rank regression). Studying biomarker patterns and CRC risk[51] also takes into account complex interactions between biomarkers and would help clarify pathways involved.

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Table 1. Main baseline characteristics, number of CRC cases and mean and median of the ISD in the EPIC study.

Baseline Characteristics				Inflammatory Score of the Diet (ISD)		
	n	%	CRC (RC / CC)	Median (P25, P75)	Mean (95% CI)[1]	p-value
Sex						
Men	142241	29.9	2589 (1032 / 1557)	-0.46 (-1.56, 0.61)	-0.30 (-0.31, -0.29)	<0.001
Women	333919	70.1	3402 (1062 / 2340)	0.94 (-0.24, 1.93)	0.67 (0.67, 0.68)	
European Region[2]						
Northern	137663	28.9	2454 (912 / 1542)	1.43 (0.32, 2.31)	1.26 (1.25, 1.27)	
Middle	199891	42.0	2136 (754 / 1382)	-0.15 (-1.38, 0.91)	-0.34 (-0.35, -0.33)	<0.001
Southern	138606	29.1	1401 (428 / 973)	0.64 (-0.59, 1.68)	0.56 (0.55, 0.56)	
Age at recruitment, years						
<55	306429	64.4	2328 (898 / 1430)	0.47 (-0.88, 1.64)	0.29 (0.28, 0.30)	
55 to <65	137863	29.0	2848 (964 / 1884)	0.56 (-0.58, 1.63)	0.53 (0.52, 0.53)	<0.001
≥65	31868	6.7	815 (232 / 583)	0.86 (-0.34, 1.84)	0.66 (0.64, 0.67)	
Smoking status						
Never	233096	49.0	2446 (805 / 1641)	0.43 (-0.83, 1.48)	0.11 (0.10, 0.12)	
Former	126822	26.6	2029 (721 / 1308)	0.20 (-1.07, 1.43)	0.24 (0.23, 0.25)	<0.001
Current	106564	22.4	1425 (545 / 880)	1.06 (-0.20, 2.18)	1.08 (1.08, 1.09)	
Pipe/cigar/occasional/other	9678	2.0	91 (23 / 68)	1.40 (0.28, 2.24)	1.07 (1.04, 1.10)	
Physical activity						
Inactive	99861	21.0	1487 (457 / 1030)	1.04 (-0.21, 2.01)	0.74 (0.71, 0.75)	
Moderately Inactive	156796	32.9	1954 (662 / 1292)	0.47 (-0.76, 1.57)	0.29 (0.29, 0.30)	
Moderately Active	125488	26.4	1334 (490 / 844)	0.50 (-0.75, 1.59)	0.34 (0.33, 0.35)	<0.001
Active	85191	17.9	1110 (447 / 663)	-0.07 (-1.29, 1.16)	0.09 (0.08, 0.10)	
Unknown	8824	1.9	106 (38 / 68)	1.49 (0.27, 2.48)	1.40 (1.37, 1.43)	
Educational level						
None/Primary	142782	30.0	2187 (739 / 1448)	1.17 (-0.08, 2.17)	1.00 (0.99, 1.01)	
Technical/professional	105864	22.2	1483 (545 / 938)	0.60 (-0.68, 1.78)	0.48 (0.47, 0.49)	
Secondary	97204	20.4	935 (325 / 610)	0.60 (-0.49, 1.53)	0.33 (0.32, 0.34)	<0.001
Higher education	113379	23.8	1108 (390 / 718)	-0.32 (-1.51, 0.82)	-0.33 (-0.34, -0.32)	
Unknown	16931	3.6	278 (95 / 183)	0.01 (-1.30, 1.11)	-0.30 (-0.33, -0.28)	
BMI, Kg/m²						
<25.0	246060	51.7	2486 (877 / 1609)	0.44 (-0.84, 1.53)	0.16 (0.15, 0.16)	
25.0 to <30.0	166134	34.9	2503 (898 / 1605)	0.53 (-0.73, 1.72)	0.58 (0.57, 0.59)	<0.001
≥30.0	63966	13.4	1002 (319 / 683)	0.87 (-0.44, 1.93)	0.74 (0.73, 0.76)	
Waist circumference (cm)						
<80 women , <94 men	195633	41.1	2170 (776 / 1394)	0.00 (-1.34, 1.28)	-0.03 (-0.04, -0.02)	
≥80 women , ≥94 men	174659	36.7	2944 (1005 / 1939)	0.56 (-0.68, 1.70)	0.54 (0.54, 0.55)	<0.001
Unknown	105868	22.2	877 (313 / 564)	1.15 (0.26, 2.01)	0.88 (0.87, 0.89)	
Alcohol consumption, g/day[3]						
Non-consumers	60724	12.8	718 (221 / 497)	1.35 (0.27, 2.22)	0.87 (0.86, 0.89)	
Low-moderate	322940	67.8	3821 (1330 / 2491)	0.48 (-0.82, 1.62)	0.31 (0.31, 0.32)	<0.001
Moderate-high	92496	19.4	1452 (543 / 909)	0.14 (-1.00, 1.22)	0.32 (0.31, 0.33)	

Table 1.Continued….

Baseline Characteristics				Inflammatory Score of the Diet (ISD)		
	n	%	CRC (RC / CC)	Median (P25, P75)	Mean (95% CI)[1]	p-value
Fibre intake g/d (quartiles)						
<17.4	119040	25.0	1556 (505 / 1051)	1.73 (0.76, 2.49)	1.59 (1.58, 1.60)	
17.4 - 21.8	119040	25.0	1492 (533 / 959)	0.96 (-0.03, 1.80)	0.81 (0.80, 0.82)	<0.001
21.8 - 27.0	119040	25.0	1493 (514 / 979)	0.25 (-0.76, 1.16)	0.13 (0.12, 0.14)	
≥27.0	119040	25.0	1450 (542 / 908)	-0.96 (-2.01, 0.08)	-0.99 (-1.00, -0.98)	
Red meat intake, g/d (quartiles)						
<16.1	119108	25.0	1166 (384 / 782)	0.22 (-1.48, 1.58)	-0.29 (-0.30, -0.28)	
16.1 - 34.9	118974	25.0	1413 (477 / 936)	0.79 (-0.45, 1.85)	0.48 (0.47, 0.49)	<0.001
34.9 - 63.1	119038	25.0	1634 (553 / 1081)	0.73 (-0.43, 1.78)	0.65 (0.64, 0.66)	
≥63.1	119040	25.0	1778 (680 / 1098)	0.32 (-0.77, 1.34)	0.70 (0.69, 0.70)	
Processed meat intake, g/d (quartiles)						
<10.5	119040	25.0	1168 (379 / 789)	0.15 (-1.47, 1.48)	-0.32 (-0.32, -0.31)	
10.5 - 24.3	119040	25.0	1620 (548 / 1072)	0.72 (-0.47, 1.80)	0.42 (0.41, 0.43)	<0.001
24.3 - 43.9	119063	25.0	1623 (588 / 1035)	0.73 (-0.40, 1.77)	0.65 (0.64, 0.66)	
≥43.9	119017	25.0	1580 (579 / 1001)	0.39 (-0.75, 1.52)	0.78 (0.77, 0.79)	

Abbreviations: CRC (RC / CC): Colorectal cancer (rectal cancer / colon cancer)

[1]Age, sex, and energy-adjusted means (95 Confidence Levels) obtained from linear regression models. [2]European regions defined as Northern (Norway, Denmark and Sweden), Middle (United Kingdom, Germany, Holland and EPIC centers in northern France) and Southern (Spain, Italy, Greece and EPIC centers in southern France). [3]Alcohol consumption: Non-consumers (<0.1g/d), Low-moderate (<15g/d women, <30g/d men), Moderate-high (≥15g/d women , ≥30 g/d men)

Table 2. Adjusted HRs and 95% CI for colorectal cancer, by tumour subsite, according to the Inflammatory Score of the Diet (ISD) in the EPIC study.

| | Inflammatory Score of the Diet (ISD), HR (95% CI)[1] | | | | | ISD continuous[2] |
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	p-trend	HR (95% CI)
Colorectal cancer, n	1,167	1,439	1,517	1,868		
All	Referent	1.09 (1.00, 1.18)	1.12 (1.03, 1.23)	1.15 (1.04, 1.27)	0.009	1.06 (1.01, 1.10)
Men	Referent	1.13 (0.99, 1.29)	1.23 (1.07, 1.41)	1.23 (1.05, 1.44)	0.006	1.08 (1.01, 1.15)
Women	Referent	1.05 (0.95, 1.18)	1.05 (0.93, 1.19)	1.09 (0.95, 1.25)	0.279	1.03 (0.98, 1.10)
Colon cancer, n	756	925	952	1,264		
All	Referent	1.09 (0.98, 1.21)	1.11 (0.99, 1.24)	1.24 (1.09, 1.41)	0.001	1.10 (1.04, 1.16)
Men	Referent	1.17 (0.99, 1.40)	1.29 (1.07, 1.54)	1.44 (1.18, 1.76)	<0.001	1.16 (1.07, 1.26)
Women	Referent	1.05 (0.92, 1.20)	1.02 (0.88, 1.18)	1.14 (0.96, 1.35)	0.188	1.06 (0.99, 1.14)
Proximal colon cancer, n	350	452	451	624		
All	Referent	1.14 (0.98, 1.32)	1.14 (0.96, 1.34)	1.29 (1.07, 1.55)	0.012	1.13 (1.04, 1.22)
Distal colon cancer, n	353	395	438	557		
All	Referent	0.99 (0.84, 1.15)	1.07 (0.91, 1.27)	1.14 (0.94, 1.37)	0.113	1.08 (1.00, 1.17)
Rectal cancer, n	411	514	565	604		
All	Referent	1.08 (0.94, 1.24)	1.14 (0.99, 1.33)	0.99 (0.83, 1.17)	0.997	0.98 (0.91, 1.05)
Men	Referent	1.08 (0.88, 1.32)	1.16 (0.94, 1.43)	0.98 (0.77, 1.25)	0.970	0.98 (0.88, 1.08)
Women	Referent	1.07 (0.88, 1.30)	1.13 (0.91, 1.39)	0.98 (0.76, 1.26)	0.983	0.98 (0.88, 1.08)

[1]Multivariate model: stratified by age, sex and center, and adjusted for energy intake (residual), tobacco smoking, physical activity, educational level, BMI, alcohol consumption, and intake of red meat, processed meat, and fibre.

[2]Hazard ratio (HR) per each increase in one standard deviation (SD) of the ISD.

Table 3. Adjusted HR and 95% CI for CRC according to cohort subgroups in relation to the Inflammatory Score of the Diet (ISD) in the EPIC study.

Cohort Subgroup	Colorectal Cancer			Colon Cancer			Rectal Cancer		
	n, cases	ISD continuous[1] HR (95% CI)	p-value[2]	n, cases	ISD continuous[1] HR (95% CI)	p-value[2]	n, cases	ISD continuous[1] HR (95% CI)	p-value[2]
Sex									
Male	2589	1.08 (1.01, 1.15)	0.159	1557	1.16 (1.07, 1.26)	0.082	1032	0.98 (0.88, 1.08)	0.758
Female	3402	1.03 (0.98, 1.10)		2340	1.06 (0.99, 1.14)		1062	0.98 (0.88, 1.08)	
Age, yr									
<55	2328	1.02 (0.95, 1.09)		1430	1.08 (0.98, 1.18)		898	0.94 (0.84, 1.05)	
55-65	2848	1.09 (1.03, 1.16)	0.465	1884	1.14 (1.06, 1.23)	0.444	964	1.01 (0.91, 1.12)	0.453
65+	815	1.02 (0.90, 1.14)		583	1.01 (0.88, 1.16)		232	1.04 (0.83, 1.30)	
European region									
North	2454	1.09 (1.02, 1.17)		1542	1.17 (1.07, 1.28)		912	0.98 (0.88, 1.09)	
Middle	2136	1.02 (0.95, 1.09)	0.067	1382	1.05 (0.97, 1.15)	0.073	754	0.97 (0.87, 1.09)	0.199
South	1401	1.11 (0.99, 1.24)		973	1.10 (0.96, 1.26)		428	1.14 (0.93, 1.40)	
Smoking status									
Never	2446	1.00 (0.93, 1.08)		1641	1.03 (0.94, 1.13)		805	0.96 (0.85, 1.08)	
Former	2029	1.12 (1.04, 1.20)	0.482	1308	1.14 (1.05, 1.25)	0.918	721	1.07 (0.95, 1.20)	0.309
Smoker	1425	1.03 (0.95, 1.12)		880	1.15 (1.03, 1.29)		545	0.86 (0.75, 0.99)	
Physical activity									
Inactive	1487	1.02 (0.93, 1.12)		1030	1.04 (0.93, 1.16)		457	1.00 (0.85, 1.18)	
Moderately Inactive	1954	1.05 (0.97, 1.14)	0.761	1292	1.14 (1.03, 1.25)	0.847	662	0.92 (0.80, 1.05)	0.285
Moderately Active	1334	1.08 (0.98, 1.19)		844	1.16 (1.03, 1.30)		490	0.98 (0.84, 1.14)	
Active	1110	1.07 (0.97, 1.17)		663	1.09 (0.96, 1.22)		447	1.04 (0.90, 1.21)	
Educational level									
None/Primary	2187	1.02 (0.94, 1.10)		1448	1.06 (0.96, 1.17)		739	0.95 (0.83, 1.08)	
Technical/professional	1483	1.04 (0.95, 1.13)	0.287	938	1.13 (1.01, 1.26)	0.184	545	0.92 (0.80, 1.05)	0.520
Secondary	935	1.00 (0.89, 1.13)		610	1.03 (0.89, 1.19)		325	0.95 (0.79, 1.16)	
Higher education	1108	1.19 (1.08, 1.32)		718	1.20 (1.06, 1.36)		390	1.18 (1.00, 1.40)	

Table 3. Continued…

Cohort Subgroup	Colorectal Cancer			Colon Cancer			Rectal Cancer		
	n, cases	ISD continuous[1] HR (95% CI)	*p-value[2]*	*n*, cases	ISD continuous[1] HR (95% CI)	*p-value[2]*	*n*, cases	ISD continuous[1] HR (95% CI)	*p-value[2]*
BMI, Kg/m^2									
<25.0	2486	1.01 (0.94, 1.08)	0.187	1609	1.06 (0.97, 1.15)	0.250	877	0.92 (0.82, 1.03)	0.535
≥25.0	3505	1.11 (1.05, 1.17)		2288	1.15 (1.08, 1.24)		1217	1.03 (0.93, 1.13)	
Waist circumference (cm)									
<80 women , <94 men	2170	1.03 (0.96, 1.10)	0.520	1394	1.06 (0.97, 1.16)	0.847	776	0.97 (0.86, 1.09)	0.55
≥80 women , ≥94 men	2944	1.09 (1.03, 1.16)		1939	1.14 (1.05, 1.22)		1005	1.01 (0.91, 1.12)	
Alcohol consumption, g/day[3]									
Non-consumers	718	0.98 (0.86, 1.12)		497	0.99 (0.85, 1.16)		221	0.96 (0.76, 1.21)	
Low-moderate	3821	1.04 (0.98, 1.09)	0.232	2491	1.09 (1.02, 1.16)	0.317	1330	0.95 (0.87, 1.04)	0.648
Moderate-high	1452	1.12 (1.03, 1.21)		909	1.15 (1.03, 1.28)		543	1.06 (0.93, 1.22)	
Processed meat intake, g/day									
Low, <25	2856	1.03 (0.97, 1.10)		1905	1.08 (1.00, 1.16)		951	0.95 (0.86, 1.05)	
Moderate, 25 - 50	1860	1.08 (1.00, 1.17)	0.368	1185	1.09 (0.99, 1.21)	0.082	675	1.07 (0.94, 1.22)	0.568
High, ≥50	1275	1.07 (0.97, 1.18)		807	1.19 (1.05, 1.36)		468	0.90 (0.76, 1.06)	

[1]Hazard ratio (HR) per each increase in one standard deviation (SD) of the ISD. [2]Significance level for the interaction between participant's characteristics and the ISD. [3]Alcohol consumption: Non-consumers (<0.1g/d), Low-moderate (<15g/d women, <30g/d men), Moderate-high (≥15g/d women , ≥30g/d men)

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Table 4. Adjusted HR and 95% CI for CRC according to the Inflammatory Profile Score (IPS).

Colorectal Cancer	Inflammatory Profile Score (IPS)[1]					p-value trend
	Level 0 HR (95% CI)	Level 1 HR (95% CI)	Level 2 HR (95% CI)	Level 3 HR (95% CI)	Level 4 HR (95% CI)	
Colorectal cancer	352	1020	1445	1423	790	
All	Referent	1.13 (1.00, 1.28)	1.20 (1.05, 1.37)	1.28 (1.11, 1.48)	1.37 (1.16, 1.62)	<0.001
Men	Referent	1.20 (0.99, 1.45)	1.30 (1.07, 1.58)	1.47 (1.18, 1.82)	1.62 (1.25, 2.09)	<0.001
Women	Referent	1.06 (0.90, 1.26)	1.11 (0.93, 1.33)	1.11 (0.92, 1.36)	1.17 (0.93, 1.48)	0.195
Colon cancer	200	664	918	945	553	
All	Referent	1.27 (1.08, 1.49)	1.30 (1.09, 1.54)	1.45 (1.20, 1.74)	1.62 (1.31, 2.01)	<0.001
Men	Referent	1.41 (1.09, 1.83)	1.50 (1.14, 1.97)	1.80 (1.34, 2.41)	2.11 (1.50, 2.97)	<0.001
Women	Referent	1.16 (0.94, 1.43)	1.15 (0.92, 1.44)	1.21 (0.95, 1.55)	1.32 (0.99, 1.74)	0.102
Rectal cancer	152	356	527	478	237	
All	Referent	0.95 (0.78, 1.15)	1.07 (0.87, 1.32)	1.04 (0.83, 1.31)	1.02 (0.78, 1.35)	0.612
Men	Referent	0.99 (0.75, 1.30)	1.10 (0.82, 1.46)	1.13 (0.82, 1.55)	1.12 (0.76, 1.65)	0.543
Women	Referent	0.91 (0.68, 1.21)	1.05 (0.78, 1.41)	0.94 (0.68, 1.32)	0.91 (0.61, 1.37)	0.903

[1]Inflammatory profile score calculated as Inflammatory Score of the Diet (sex-specific tertile 1=0; tertile 2=1; tertile 3=2) + waist circumference (men<94cm and women<80cm=0; men≥94cm n d women≥80cm=1) + physical activity (active or moderately active=0; inactive or moderately inactive=1).

Table 5. Sensitivity analyses for the association between colorectal cancer, by tumour subsite, according to the Score of the Diet (ISD) in the EPIC study.

	Inflammatory Score of the Diet (ISD), HR (95% CI)[1]					ISD continuous[2]
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	p-trend	HR (95% CI)
Excluding first 2yr follow-up[3]						
Colorectal cancer	Referent	1.08 (0.99, 1.18)	1.12 (1.02, 1.23)	1.16 (1.04, 1.29)	0,007	1.06 (1.02, 1.11)
Colon cancer	Referent	1.11 (0.99, 1.23)	1.12 (0.99, 1.26)	1.26 (1.11, 1.44)	0,001	1.11 (1.05, 1.17)
Rectal cancer	Referent	1.03 (0.89, 1.20)	1.12 (0.96, 1.31)	0.98 (0.82, 1.18)	0,925	0.98 (0.91, 1.06)
ISD excluding alcohol[4]						
Colorectal cancer	Referent	1.08 (1.00, 1.18)	1.10 (1.01, 1.21)	1.15 (1.04, 1.27)	0,012	1.05 (1.01, 1.10)
Colon cancer	Referent	1.09 (0.98, 1.21)	1.10 (0.98, 1.23)	1.25 (1.11, 1.42)	0,001	1.10 (1.04, 1.16)
Rectal cancer	Referent	1.08 (0.94, 1.24)	1.12 (0.96, 1.29)	0.97 (0.81, 1.15)	0,756	0.98 (0.91, 1.05)
Additional adjustment in women[5]						
Colorectal cancer	Referent	1.05 (0.94, 1.17)	1.05 (0.93, 1.18)	1.08 (0.94, 1.24)	0,328	1.03 (0.97, 1.09)
Colon cancer	Referent	1.04 (0.92, 1.19)	1.02 (0.88, 1.17)	1.13 (0.95, 1.33)	0,224	1.06 (0.99, 1.14)
Rectal cancer	Referent	1.07 (0.88, 1.30)	1.12 (0.91, 1.39)	0.98 (0.76, 1.26)	0,955	0.97 (0.88, 1.08)

[1]Multivariate model: stratified by age, sex and center, and adjusted for energy intake (residual), tobacco smoking, physical activity, educational level, BMI, alcohol consumption, and intake of red meat, processed meat, and fibre.
[2]Hazard ratio (HR) per each increase in one standard deviation (SD) of the ISD.

[3]Multivariate model excluding incident cases occurring during the first 2 years of follow-up.

[4]Multivariate model with the ISD calculated without including the alcohol component.

[5]Multivariate model in women with additional adjustment for hormone replacement therapy, menopausal status and contraceptive pill use.

Table 1. Main baseline characteristics, number of CRC cases and mean and median of the ISD in the EPIC study.

Baseline Characteristics	n	%	CRC (RC / CC)	Inflammatory Score of the Diet (ISD)		
				Median (P25, P75)	Mean (95% CI)[1]	p-value
Sex						
Men	142241	29.9	2589 (1032 / 1557)	-0.46 (-1.56, 0.61)	-0.30 (-0.31, -0.29)	<0.001
Women	333919	70.1	3402 (1062 / 2340)	0.94 (-0.24, 1.93)	0.67 (0.67, 0.68)	
European Region[2]						
Northern	137663	28.9	2454 (912 / 1542)	1.43 (0.32, 2.31)	1.26 (1.25, 1.27)	
Middle	199891	42.0	2136 (754 / 1382)	-0.15 (-1.38, 0.91)	-0.34 (-0.35, -0.33)	<0.001
Southern	138606	29.1	1401 (428 / 973)	0.64 (-0.59, 1.68)	0.56 (0.55, 0.56)	
Age at recruitment, years						
<55	306429	64.4	2328 (898 / 1430)	0.47 (-0.88, 1.64)	0.29 (0.28, 0.30)	
55 to <65	137863	29.0	2848 (964 / 1884)	0.56 (-0.58, 1.63)	0.53 (0.52, 0.53)	<0.001
≥65	31868	6.7	815 (232 / 583)	0.86 (-0.34, 1.84)	0.66 (0.64, 0.67)	
Smoking status						
Never	233096	49.0	2446 (805 / 1641)	0.43 (-0.83, 1.48)	0.11 (0.10, 0.12)	
Former	126822	26.6	2029 (721 / 1308)	0.20 (-1.07, 1.43)	0.24 (0.23, 0.25)	<0.001
Current	106564	22.4	1425 (545 / 880)	1.06 (-0.20, 2.18)	1.08 (1.08, 1.09)	
Pipe/cigar/occasional/other	9678	2.0	91 (23 / 68)	1.40 (0.28, 2.24)	1.07 (1.04, 1.10)	
Physical activity						
Inactive	99861	21.0	1487 (457 / 1030)	1.04 (-0.21, 2.01)	0.74 (0.71, 0.75)	
Moderately Inactive	156796	32.9	1954 (662 / 1292)	0.47 (-0.76, 1.57)	0.29 (0.29, 0.30)	
Moderately Active	125488	26.4	1334 (490 / 844)	0.50 (-0.75, 1.59)	0.34 (0.33, 0.35)	<0.001
Active	85191	17.9	1110 (447 / 663)	-0.07 (-1.29, 1.16)	0.09 (0.08, 0.10)	
Unknown	8824	1.9	106 (38 / 68)	1.49 (0.27, 2.48)	1.40 (1.37, 1.43)	
Educational level						
None/Primary	142782	30.0	2187 (739 / 1448)	1.17 (-0.08, 2.17)	1.00 (0.99, 1.01)	
Technical/professional	105864	22.2	1483 (545 / 938)	0.60 (-0.68, 1.78)	0.48 (0.47, 0.49)	
Secondary	97204	20.4	935 (325 / 610)	0.60 (-0.49, 1.53)	0.33 (0.32, 0.34)	<0.001
Higher education	113379	23.8	1108 (390 / 718)	-0.32 (-1.51, 0.82)	-0.33 (-0.34, -0.32)	
Unknown	16931	3.6	278 (95 / 183)	0.01 (-1.30, 1.11)	-0.30 (-0.33, -0.28)	
BMI, Kg/m²						
<25.0	246060	51.7	2486 (877 / 1609)	0.44 (-0.84, 1.53)	0.16 (0.15, 0.16)	
25.0 to <30.0	166134	34.9	2503 (898 / 1605)	0.53 (-0.73, 1.72)	0.58 (0.57, 0.59)	<0.001
≥30.0	63966	13.4	1002 (319 / 683)	0.87 (-0.44, 1.93)	0.74 (0.73, 0.76)	
Waist circumference (cm)						
<80 women , <94 men	195633	41.1	2170 (776 / 1394)	0.00 (-1.34, 1.28)	-0.03 (-0.04, -0.02)	
≥80 women , ≥94 men	174659	36.7	2944 (1005 / 1939)	0.56 (-0.68, 1.70)	0.54 (0.54, 0.55)	<0.001
Unknown	105868	22.2	877 (313 / 564)	1.15 (0.26, 2.01)	0.88 (0.87, 0.89)	
Alcohol consumption, g/day[3]						
Non-consumers	60724	12.8	718 (221 / 497)	1.35 (0.27, 2.22)	0.87 (0.86, 0.89)	
Low-moderate	322940	67.8	3821 (1330 / 2491)	0.48 (-0.82, 1.62)	0.31 (0.31, 0.32)	<0.001
Moderate-high	92496	19.4	1452 (543 / 909)	0.14 (-1.00, 1.22)	0.32 (0.31, 0.33)	

Table 1.Continued….

Baseline Characteristics				Inflammatory Score of the Diet (ISD)		
	n	%	CRC (RC / CC)	Median (P25, P75)	Mean (95% CI)[1]	*p*-value
Fibre intake g/d (quartiles)						
<17.4	119040	25.0	1556 (505 / 1051)	1.73 (0.76, 2.49)	1.59 (1.58, 1.60)	
17.4 - 21.8	119040	25.0	1492 (533 / 959)	0.96 (-0.03, 1.80)	0.81 (0.80, 0.82)	<0.001
21.8 - 27.0	119040	25.0	1493 (514 / 979)	0.25 (-0.76, 1.16)	0.13 (0.12, 0.14)	
≥27.0	119040	25.0	1450 (542 / 908)	-0.96 (-2.01, 0.08)	-0.99 (-1.00, -0.98)	
Red meat intake, g/d (quartiles)						
<16.1	119108	25.0	1166 (384 / 782)	0.22 (-1.48, 1.58)	-0.29 (-0.30, -0.28)	
16.1 - 34.9	118974	25.0	1413 (477 / 936)	0.79 (-0.45, 1.85)	0.48 (0.47, 0.49)	<0.001
34.9 - 63.1	119038	25.0	1634 (553 / 1081)	0.73 (-0.43, 1.78)	0.65 (0.64, 0.66)	
≥63.1	119040	25.0	1778 (680 / 1098)	0.32 (-0.77, 1.34)	0.70 (0.69, 0.70)	
Processed meat intake, g/d (quartiles)						
<10.5	119040	25.0	1168 (379 / 789)	0.15 (-1.47, 1.48)	-0.32 (-0.32, -0.31)	
10.5 - 24.3	119040	25.0	1620 (548 / 1072)	0.72 (-0.47, 1.80)	0.42 (0.41, 0.43)	<0.001
24.3 - 43.9	119063	25.0	1623 (588 / 1035)	0.73 (-0.40, 1.77)	0.65 (0.64, 0.66)	
≥43.9	119017	25.0	1580 (579 / 1001)	0.39 (-0.75, 1.52)	0.78 (0.77, 0.79)	

Abbreviations: CRC (RC / CC): Colorectal cancer (rectal cancer / colon cancer)

[1]Age, sex, and energy-adjusted means (95 Confidence Levels) obtained from linear regression models. [2]European regions defined as Northern (Norway, Denmark and Sweden), Middle (United Kingdom, Germany, Holland and EPIC centers in northern France) and Southern (Spain, Italy, Greece and EPIC centers in southern France). [3]Alcohol consumption: Non-consumers (<0.1g/d), Low-moderate (<15g/d women, <30g/d men), Moderate-high (≥15g/d women , ≥30 g/d men)

Table 2. Adjusted HRs and 95% CI for colorectal cancer, by tumour subsite, according to the Inflammatory Score of the Diet (ISD) in the EPIC study.

	Inflammatory Score of the Diet (ISD), HR (95% CI)[1]					ISD continuous[2]
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	p-trend	HR (95% CI)
Colorectal cancer, n	1,167	1,439	1,517	1,868		
All	Referent	1.09 (1.00, 1.18)	1.12 (1.03, 1.23)	1.15 (1.04, 1.27)	0.009	1.06 (1.01, 1.10)
Men	Referent	1.13 (0.99, 1.29)	1.23 (1.07, 1.41)	1.23 (1.05, 1.44)	0.006	1.08 (1.01, 1.15)
Women	Referent	1.05 (0.95, 1.18)	1.05 (0.93, 1.19)	1.09 (0.95, 1.25)	0.279	1.03 (0.98, 1.10)
Colon cancer, n	756	925	952	1,264		
All	Referent	1.09 (0.98, 1.21)	1.11 (0.99, 1.24)	1.24 (1.09, 1.41)	0.001	1.10 (1.04, 1.16)
Men	Referent	1.17 (0.99, 1.40)	1.29 (1.07, 1.54)	1.44 (1.18, 1.76)	<0.001	1.16 (1.07, 1.26)
Women	Referent	1.05 (0.92, 1.20)	1.02 (0.88, 1.18)	1.14 (0.96, 1.35)	0.188	1.06 (0.99, 1.14)
Proximal colon cancer, n	350	452	451	624		
All	Referent	1.14 (0.98, 1.32)	1.14 (0.96, 1.34)	1.29 (1.07, 1.55)	0.012	1.13 (1.04, 1.22)
Distal colon cancer, n	353	395	438	557		
All	Referent	0.99 (0.84, 1.15)	1.07 (0.91, 1.27)	1.14 (0.94, 1.37)	0.113	1.08 (1.00, 1.17)
Rectal cancer, n	411	514	565	604		
All	Referent	1.08 (0.94, 1.24)	1.14 (0.99, 1.33)	0.99 (0.83, 1.17)	0.997	0.98 (0.91, 1.05)
Men	Referent	1.08 (0.88, 1.32)	1.16 (0.94, 1.43)	0.98 (0.77, 1.25)	0.970	0.98 (0.88, 1.08)
Women	Referent	1.07 (0.88, 1.30)	1.13 (0.91, 1.39)	0.98 (0.76, 1.26)	0.983	0.98 (0.88, 1.08)

[1]Multivariate model: stratified by age, sex and center, and adjusted for energy intake (residual), tobacco smoking, physical activity, educational level, BMI, alcohol consumption, and intake of red meat, processed meat, and fibre.

[2]Hazard ratio (HR) per each increase in one standard deviation (SD) of the ISD.

Table 3. Adjusted HR and 95% CI for CRC according to cohort subgroups in relation to the Inflammatory Score of the Diet (ISD) in the EPIC study.

Cohort Subgroup	Colorectal Cancer			Colon Cancer			Rectal Cancer		
	n, cases	ISD continuous[1] HR (95% CI)	p-value[2]	n, cases	ISD continuous[1] HR (95% CI)	p-value[2]	n, cases	ISD continuous[1] HR (95% CI)	p-value[2]
Sex									
Male	2589	1.08 (1.01, 1.15)	0.159	1557	1.16 (1.07, 1.26)	0.082	1032	0.98 (0.88, 1.08)	0.758
Female	3402	1.03 (0.98, 1.10)		2340	1.06 (0.99, 1.14)		1062	0.98 (0.88, 1.08)	
Age, yr									
<55	2328	1.02 (0.95, 1.09)		1430	1.08 (0.98, 1.18)		898	0.94 (0.84, 1.05)	
55-65	2848	1.09 (1.03, 1.16)	0.465	1884	1.14 (1.06, 1.23)	0.444	964	1.01 (0.91, 1.12)	0.453
65+	815	1.02 (0.90, 1.14)		583	1.01 (0.88, 1.16)		232	1.04 (0.83, 1.30)	
European region									
North	2454	1.09 (1.02, 1.17)		1542	1.17 (1.07, 1.28)		912	0.98 (0.88, 1.09)	
Middle	2136	1.02 (0.95, 1.09)	0.067	1382	1.05 (0.97, 1.15)	0.073	754	0.97 (0.87, 1.09)	0.199
South	1401	1.11 (0.99, 1.24)		973	1.10 (0.96, 1.26)		428	1.14 (0.93, 1.40)	
Smoking status									
Never	2446	1.00 (0.93, 1.08)		1641	1.03 (0.94, 1.13)		805	0.96 (0.85, 1.08)	
Former	2029	1.12 (1.04, 1.20)	0.482	1308	1.14 (1.05, 1.25)	0.918	721	1.07 (0.95, 1.20)	0.309
Smoker	1425	1.03 (0.95, 1.12)		880	1.15 (1.03, 1.29)		545	0.86 (0.75, 0.99)	
Physical activity									
Inactive	1487	1.02 (0.93, 1.12)		1030	1.04 (0.93, 1.16)		457	1.00 (0.85, 1.18)	
Moderately Inactive	1954	1.05 (0.97, 1.14)	0.761	1292	1.14 (1.03, 1.25)	0.847	662	0.92 (0.80, 1.05)	0.285
Moderately Active	1334	1.08 (0.98, 1.19)		844	1.16 (1.03, 1.30)		490	0.98 (0.84, 1.14)	
Active	1110	1.07 (0.97, 1.17)		663	1.09 (0.96, 1.22)		447	1.04 (0.90, 1.21)	
Educational level									
None/Primary	2187	1.02 (0.94, 1.10)		1448	1.06 (0.96, 1.17)		739	0.95 (0.83, 1.08)	
Technical/professional	1483	1.04 (0.95, 1.13)	0.287	938	1.13 (1.01, 1.26)	0.184	545	0.92 (0.80, 1.05)	0.520
Secondary	935	1.00 (0.89, 1.13)		610	1.03 (0.89, 1.19)		325	0.95 (0.79, 1.16)	
Higher education	1108	1.19 (1.08, 1.32)		718	1.20 (1.06, 1.36)		390	1.18 (1.00, 1.40)	

Table 3. Continued…

Cohort Subgroup	Colorectal Cancer			Colon Cancer			Rectal Cancer		
	n, cases	ISD continuous[1] HR (95% CI)	*p-value[2]*	*n*, cases	ISD continuous[1] HR (95% CI)	*p-value[2]*	*n*, cases	ISD continuous[1] HR (95% CI)	*p-value[2]*
BMI, Kg/m^2									
<25.0	2486	1.01 (0.94, 1.08)	0.187	1609	1.06 (0.97, 1.15)	0.250	877	0.92 (0.82, 1.03)	0.535
≥25.0	3505	1.11 (1.05, 1.17)		2288	1.15 (1.08, 1.24)		1217	1.03 (0.93, 1.13)	
Waist circumference (cm)									
<80 women <94 men	2170	1.03 (0.96, 1.10)	0.520	1394	1.06 (0.97, 1.16)	0.847	776	0.97 (0.86, 1.09)	0.55
≥80 women , ≥94 men	2944	1.09 (1.03, 1.16)		1939	1.14 (1.05, 1.22)		1005	1.01 (0.91, 1.12)	
Alcohol consumption, g/day[3]									
Non-consumers	718	0.98 (0.86, 1.12)		497	0.99 (0.85, 1.16)		221	0.96 (0.76, 1.21)	
Low-moderate	3821	1.04 (0.98, 1.09)	0.232	2491	1.09 (1.02, 1.16)	0.317	1330	0.95 (0.87, 1.04)	0.648
Moderate-high	1452	1.12 (1.03, 1.21)		909	1.15 (1.03, 1.28)		543	1.06 (0.93, 1.22)	
Processed meat intake, g/day									
Low, <25	2856	1.03 (0.97, 1.10)		1905	1.08 (1.00, 1.16)		951	0.95 (0.86, 1.05)	
Moderate, 25 - 50	1860	1.08 (1.00, 1.17)	0.368	1185	1.09 (0.99, 1.21)	0.082	675	1.07 (0.94, 1.22)	0.568
High, ≥50	1275	1.07 (0.97, 1.18)		807	1.19 (1.05, 1.36)		468	0.90 (0.76, 1.06)	

[1]Hazard ratio (HR) per each increase in one standard deviation (SD) of the ISD. [2]Significance level for the interaction between participant's characteristics and the ISD. [3]Alcohol consumption: Non-consumers (<0.1g/d), Low-moderate (<15g/d women, <30g/d men), Moderate-high (≥15g/d women , ≥30g/d men)

Table 4. Adjusted HR and 95% CI for CRC according to the Inflammatory Profile Score (IPS).

Colorectal Cancer	Inflammatory Profile Score (IPS)[1]					p-value trend
	Level 0 HR (95% CI)	Level 1 HR (95% CI)	Level 2 HR (95% CI)	Level 3 HR (95% CI)	Level 4 HR (95% CI)	
Colorectal cancer	352	1020	1445	1423	790	
All	Referent	1.13 (1.00, 1.28)	1.20 (1.05, 1.37)	1.28 (1.11, 1.48)	1.37 (1.16, 1.62)	<0.001
Men	Referent	1.20 (0.99, 1.45)	1.30 (1.07, 1.58)	1.47 (1.18, 1.82)	1.62 (1.25, 2.09)	<0.001
Women	Referent	1.06 (0.90, 1.26)	1.11 (0.93, 1.33)	1.11 (0.92, 1.36)	1.17 (0.93, 1.48)	0.195
Colon cancer	200	664	918	945	553	
All	Referent	1.27 (1.08, 1.49)	1.30 (1.09, 1.54)	1.45 (1.20, 1.74)	1.62 (1.31, 2.01)	<0.001
Men	Referent	1.41 (1.09, 1.83)	1.50 (1.14, 1.97)	1.80 (1.34, 2.41)	2.11 (1.50, 2.97)	<0.001
Women	Referent	1.16 (0.94, 1.43)	1.15 (0.92, 1.44)	1.21 (0.95, 1.55)	1.32 (0.99, 1.74)	0.102
Rectal cancer	152	356	527	478	237	
All	Referent	0.95 (0.78, 1.15)	1.07 (0.87, 1.32)	1.04 (0.83, 1.31)	1.02 (0.78, 1.35)	0.612
Men	Referent	0.99 (0.75, 1.30)	1.10 (0.82, 1.46)	1.13 (0.82, 1.55)	1.12 (0.76, 1.65)	0.543
Women	Referent	0.91 (0.68, 1.21)	1.05 (0.78, 1.41)	0.94 (0.68, 1.32)	0.91 (0.61, 1.37)	0.903

[1]Inflammatory profile score calculated as Inflammatory Score of the Diet (sex-specific tertile 1=0; tertile 2=1; tertile 3=2) + waist circumference (men<94cm and women<80cm=0; men≥94cm n d women≥80cm=1) + physical activity (active or moderately active=0; inactive or moderately inactive=1).

Table 5. Sensitivity analyses for the association between colorectal cancer, by tumour subsite, according to the Score of the Diet (ISD) in the EPIC study.

	Inflammatory Score of the Diet (ISD), HR (95% CI)[1]					ISD continuous[2]
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*p*-trend	HR (95% CI)
Excluding first 2yr follow-up[3]						
Colorectal cancer	Referent	1.08 (0.99, 1.18)	1.12 (1.02, 1.23)	1.16 (1.04, 1.29)	0,007	1.06 (1.02, 1.11)
Colon cancer	Referent	1.11 (0.99, 1.23)	1.12 (0.99, 1.26)	1.26 (1.11, 1.44)	0,001	1.11 (1.05, 1.17)
Rectal cancer	Referent	1.03 (0.89, 1.20)	1.12 (0.96, 1.31)	0.98 (0.82, 1.18)	0,925	0.98 (0.91, 1.06)
ISD excluding alcohol[4]						
Colorectal cancer	Referent	1.08 (1.00, 1.18)	1.10 (1.01, 1.21)	1.15 (1.04, 1.27)	0,012	1.05 (1.01, 1.10)
Colon cancer	Referent	1.09 (0.98, 1.21)	1.10 (0.98, 1.23)	1.25 (1.11, 1.42)	0,001	1.10 (1.04, 1.16)
Rectal cancer	Referent	1.08 (0.94, 1.24)	1.12 (0.96, 1.29)	0.97 (0.81, 1.15)	0,756	0.98 (0.91, 1.05)
Additional adjustment in women[5]						
Colorectal cancer	Referent	1.05 (0.94, 1.17)	1.05 (0.93, 1.18)	1.08 (0.94, 1.24)	0,328	1.03 (0.97, 1.09)
Colon cancer	Referent	1.04 (0.92, 1.19)	1.02 (0.88, 1.17)	1.13 (0.95, 1.33)	0,224	1.06 (0.99, 1.14)
Rectal cancer	Referent	1.07 (0.88, 1.30)	1.12 (0.91, 1.39)	0.98 (0.76, 1.26)	0,955	0.97 (0.88, 1.08)

[1]Multivariate model: stratified by age, sex and center, and adjusted for energy intake (residual), tobacco smoking, physical activity, educational level, BMI, alcohol consumption, and intake of red meat, processed meat, and fibre.
[2]Hazard ratio (HR) per each increase in one standard deviation (SD) of the ISD.

[3]Multivariate model excluding incident cases occurring during the first 2 years of follow-up.

[4]Multivariate model with the ISD calculated without including the alcohol component.

[5]Multivariate model in women with additional adjustment for hormone replacement therapy, menopausal status and contraceptive pill use.

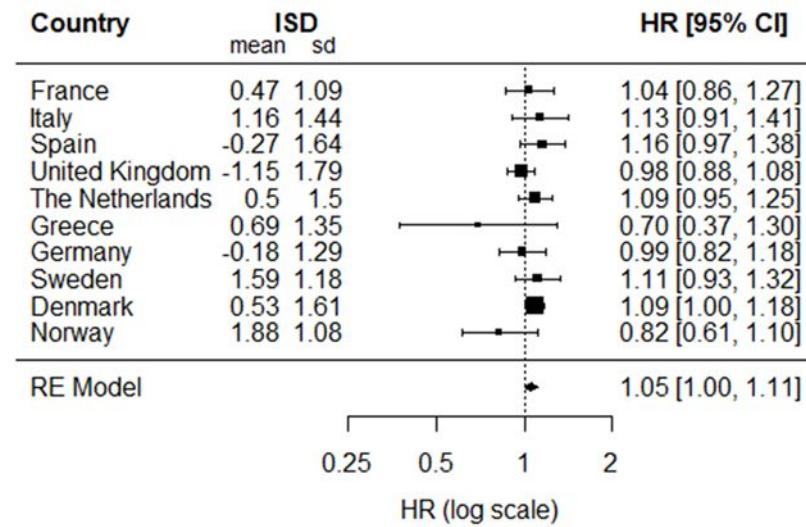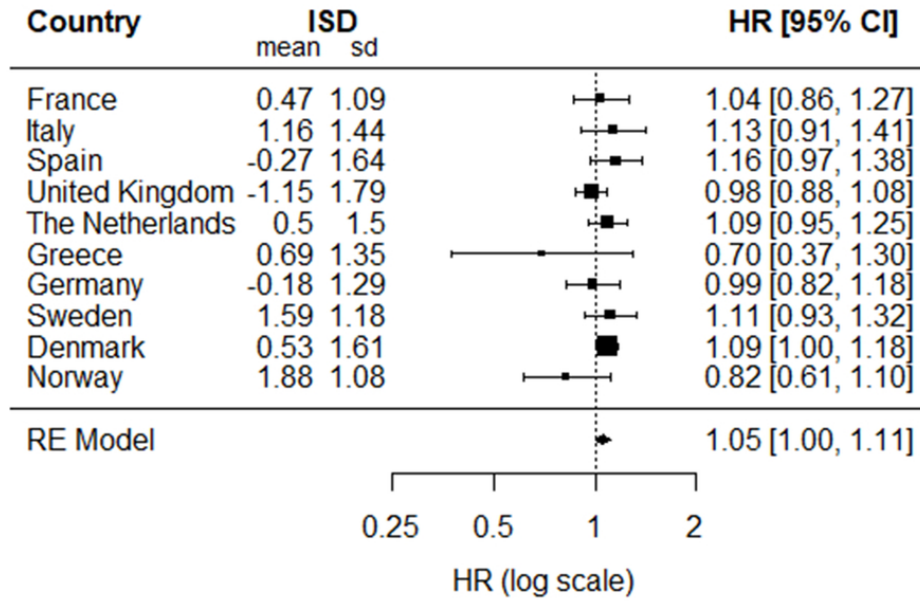| Country	ISD mean	sd	HR [95% CI]
France	0.47	1.09	1.04 [0.86, 1.27]
Italy	1.16	1.44	1.13 [0.91, 1.41]
Spain	-0.27	1.64	1.16 [0.97, 1.38]
United Kingdom	-1.15	1.79	0.98 [0.88, 1.08]
The Netherlands	0.5	1.5	1.09 [0.95, 1.25]
Greece	0.69	1.35	0.70 [0.37, 1.30]
Germany	-0.18	1.29	0.99 [0.82, 1.18]
Sweden	1.59	1.18	1.11 [0.93, 1.32]
Denmark	0.53	1.61	1.09 [1.00, 1.18]
Norway	1.88	1.08	0.82 [0.61, 1.10]
RE Model			1.05 [1.00, 1.11]

HR (log scale)

Figure 1. Association between Inflammatory Score of the Diet (ISD) and Colorectal Cancer and mean ISD (sd) by EPIC country. Hazards Ratio (HR) (95% Confidence Interval) for each 1-SD of the ISD, estimated from Cox model stratified by age, centre and sex and adjusted for energy intake (residual), tobacco smoking, physical activity, educational level, BMI, alcohol consumption, and intake of red meat, processed meat, and fibre. RE model: Overall effect from a random effects meta-analysis. Heterogeneity test: Q (9 df) = 9.705, p-value = 0.37

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80x52mm (300 x 300 DPI)