**Inflammatory potential of the diet and risk of Crohn's disease and ulcerative colitis**

**Short title:** ISD & IBD

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**Funding**: This study was supported by The Sir Halley Stewart Trust, Crohn's and Colitis UK and The UK National Health Service Executive Eastern Region. The coordination of EPIC-Europe is financially supported by International Agency for Research on Cancer (IARC) and also by the Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London which has additional infrastructure support provided by the NIHR Imperial Biomedical Research Centre (BRC). The national cohorts are supported by: Danish Cancer Society (Denmark); Ligue Nationale Contre le Cancer, Institut Gustave Roussy, Mutuelle Générale de l'Education Nationale (MGEN), Institut National de la Santé et de la Recherche Médicale (INSERM), French National Research Agency (ANR, reference ANR-10- COHO- 0006), French Ministry for Higher Education (subsidy 2102918823, 2103236497 and 2103586016) (France); German Cancer Aid, German Cancer Research Center (DKFZ), German Institute of Human Nutrition Potsdam-Rehbruecke (DIfE), Federal Ministry of Education and Research (BMBF) (Germany); Associazione Italiana per la Ricerca sul Cancro-AIRC-Italy, Italian Ministry of Health, Italian Ministry of University and Research (MUR), Compagnia di San Paolo (Italy); Dutch Ministry of Public Health, Welfare and Sports (VWS), the Netherlands Organisation for Health Research and

Development (ZonMW), World Cancer Research Fund (WCRF) (The Netherlands); UiT The Arctic University of Norway; Health Research Fund (FIS)—Instituto de Salud Carlos III (ISCIII), Regional Governments of Andalucía, Asturias, Basque Country, Murcia and Navarra and the Catalan Institute of Oncology – ICO (Spain); Swedish Cancer Society, Swedish Research Council and County Councils of Skåne and Västerbotten (Sweden); Cancer Research UK (C864/A14136 to EPIC-Norfolk (DOI 10.22025/2019.10.105.00004); C8221/A29017 to EPIC-Oxford), Medical Research Council (MR/N003284/1, MC-UU_12015/1 and MC_UU_00006/1 to EPIC-Norfolk; MR/Y013662/1 to EPIC- Oxford) (United Kingdom). Previous support has come from 'Europe against Cancer' Programme of the European Commission (DG SANCO). The funders had no role in the study design or in the collection, analysis, interpretation of data, writing of the report or decision to submit the article for publication. The funders had no role in the study design or in the collection, analysis, interpretation of data, writing of the report, or decision to submit the article for publication.

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**Data**: EPIC data and biospecimens are available for investigators who seek to answer important questions on health and disease in the context of research projects that are consistent with the legal and ethical standard practices of the International Agency for Research on Cancer (IARC), WHO, and the EPIC centres. The primary responsibility for accessing the data, obtained in the frame of the present publication, belongs to the EPIC centres that provided them. Access to EPIC data can be requested to the EPIC Steering Committee, as detailed in the EPIC-Europe Access Policy

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tion, visualization, writing – review and editing, validation. Anne Tjønneland: data curation, writing – review and editing, visualization, validation. Cecilie Kyrø: data curation, writing – review and editing, visualization, validation. Christina C. Dahm: data curation, validation, writing – review and editing, visualization. Verena A. Katzke: validation, visualization, writing – review and editing, data curation. Matthias B. Schulze: validation,

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**Acknowledgements:** We are grateful to all the participants who have been part of EPIC. The EPIC-Bilthoven study wish to thank the National Institute for Public Health and the Environment (RIVM), Bilthoven, the Netherlands, for their contribution and ongoing support. The EPIC-Norfolk study (DOI 10.22025/2019.10.105.00004) are grateful to all the participants who have been part of the project and to the many members of the study teams at the University of Cambridge who have enabled this research."

**Abstract**

**Background:** Association between dietary factors and the risk of developing inflammatory bowel disease (IBD) has been studied extensively. However, identification of deleterious dietary patterns merits further study**.**

**Aim:** To investigate the risk of developing Crohn's disease (CD) and ulcerative colitis (UC) according to the inflammatory score of the diet (ISD) in the multinational European Prospective Investigation into Cancer and Nutrition (EPIC) cohort.

**Methods:** We used validated food frequency questionnaires collected at baseline to compute ISD scores. We estimated the association between ISD score and risks of CD and UC risks using Cox models stratified by centre, sex and age. We adjusted for smoking status, BMI, physical activity, energy intake, educational level and alcohol intake.

**Results:** We included 394,255 individuals including 184 incident cases of CD and 459 of UC after median follow-up of 13.6 years (4,889,910 person-years). High ISD scores were associated with a higher risk of CD (fourth vs. first quartile-adjusted HR: 1.88, 95% CI: 1.14–3.10; p-trend < 0.01) but not of UC (adjusted HR: 0.85, 95% CI: 0.63–1.15; p-trend 0.21). For CD, this association was mainly observed for women (adjusted HR: 2.14, 95% CI: 1.17–3.91; p-trend < 0.01). On subgroup analyses, those differences were mainly driven by low intakes of fibre, mono-unsaturated fatty acids, vitamin C, magnesium, onion and alcohol.

**Conclusions:** A high ISD score is associated with a higher risk of developing CD but not UC. These results should be taken into account in high-risk populations.

**Keywords:** crohn's disease | diet | epidemiology | inflammatory bowel disease | ulcerative colitis

## Introduction

The importance of environmental factors in the aetiology of inflammatory bowel disease (IBD) is increasingly recognised. The association between lifestyle factors, including dietary factors, and risk of developing Crohn's disease (CD) and ulcerative colitis (UC), is being intensively studied within large prospective cohorts of healthy individuals [1, 2]. These studies have shown that the low intake of fruits, vegetables and fibre is associated with a higher risk of developing CD, while a high intake of red meat and n6 polyunsaturated fatty acids and low intake of n3 polyunsaturated fatty acids are associated with a higher risk of developing UC [3–5]. It is assumed that diet composition might contribute to create a pro-inflammatory microenvironment that increases the risk of developing IBD in genetically predisposed patients [6]. It has been shown that dietary patterns such as Mediterranean diet, ultra-processed foods or UK Food Standards Agency modified nutrient profiling system (FSAm-NPS-DI score) are associated with an increased risk of IBD [7–9]. However, these scores were developed primarily for cardiovascular diseases or to follow international dietary guidelines and used only subsequently for other conditions.

Several dietary scores are based on the inflammatory potential of foods. The inflammatory potential of the diet among the risk of IBD has been studied by the empirical dietary inflammatory pattern (EDIP) in two prospective cohorts of healthy individuals. The study by Lo et al. [10] based on three cohorts in the United States, included a total of 166,903 women and 41,931 men. Individuals in the highest EDIP quartile had a 51% increased risk of CD but not UC. Participants who moved from a low to high inflammatory diet score had a twofold higher risk of CD. The study by Narula et al., based upon the prospective urban rural epidemiology cohort, included a total of 28,428 participants in seven countries. There was no significant association between the EDIP score and the risks of CD and UC, although there was a numerical trend for CD [11].

It is important to better understand the association between the inflammatory potential of diets and the risk of IBD, among independent cohorts from different parts of the world. For this purpose, we decided to investigate this association within the European Prospective Investigation into Cancer and Nutrition (EPIC), a large prospective cohort of healthy volunteers, which uses a validated assessment of food intake. For this purpose, we used the inflammatory score of the diet (ISD), a modified version of the Dietary Inflammatory Index (DII).

## Methods

### Study population

The EPIC cohort was established in 1991 to investigate the role of dietary and lifestyle factors in various cancers and chronic diseases in middle-aged participants. EPIC includes about 520,000 men and women from 23 centres in 10 European countries (Denmark, France, Germany, Italy, the Netherlands, Norway, Spain, Sweden, Greece and the UK) [12]. Participants were prospectively included in the study between 1991 and 1999. Participants were recruited from the general population, except in France (women enrolled in a health insurance scheme for school and university employees) and Utrecht in the Netherlands (mammographic screening program). In addition, half of the Oxford cohort in the United Kingdom consisted of non-meat eaters due to targeted oversampling of this group.

The EPIC-IBD cohort is a subgroup of the EPIC cohort which includes EPIC centres which agreed to collect and certify new diagnoses of IBD which occurred after inclusion. The EPIC-IBD cohort includes 437,972 participants from eight European countries within the EPIC cohort (namely Denmark, France, Germany, Italy, the Netherlands, Spain, Sweden and the UK).

### Dietary intake assessment

Dietary data were collected at baseline using country- or centre- specific validated questionnaires (individual interviews or self-administered questionnaires). Food frequency questionnaires (FFQ) recorded average intakes of 98–2059 food items (depending on the centre) over the past 12 months and enabled computation of individual mean intakes of foods or food groups in grams per day. Total energy and nutrient intakes were estimated by using the FFQs and the standardised EPIC Nutrient Database [13]. Participants who did not complete the dietary questionnaire or with implausible dietary intakes, namely within the lowest and highest 1% of the cohort distribution of the ratio of reported total energy intake over energy requirement, were excluded.

### Inflammatory score of the diet

To characterise the inflammatory potential of the diet, we used the ISD score. The procedure to compute the ISD score in the EPIC cohort has been described elsewhere [14, 15]. Briefly, the procedure is similar to that of the Dietary Inflammatory Index (DII) but with some variations. The DII is computed using the intake of 45 food parameters which were identified as having anti-or pro-inflammatory properties based on an extensive literature review (Table S1) [16]. Each food parameter was assigned an inflammatory effect score according to its association with the biomarkers of inflammation (IL-1β, IL-4, IL-6, IL-10, TNF-α and C-reactive protein). Of the 45 possible items in the DII, after excluding the total fat to avoid redundancy with other fat components, 28 food parameters were available in the EPIC cohort. The intake of each item was standardised with the mean

and standard deviation of the EPIC cohort (unlike the DII that uses the mean and SD of a global composite data set). Then, in order to reduce the effect of right skewness, these standardised intakes were converted to centred percentile values by doubling the percentile and subtracting 1. These centred percentiles were multiplied by the corresponding inflammatory effect score to obtain a specific ISD for each food parameter, which were summed to produce the overall ISD score for each participant. Alcohol is considered to have an anti-inflammatory effect based on inflammatory cytokine levels, and therefore it is weighted negatively in the DII. However, as an inverse association with inflammatory markers has been found only in moderate consumers, in the ISD, we assigned a weight of zero for alcohol intakes higher than 40 g/day. Table S2 shows the ISD score for each food parameter in the EPIC population. When the ISD score has a positive value, it indicated a more pro-inflammatory potential of the diet, while a negative value corresponds to a more anti-inflammatory potential of the diet. The score has no unit and must be interpreted as a relative index to classify diets based on their inflammatory potential.

**Follow-up and case ascertainment**

Participants who developed incident IBD during follow-up were identified either by self-administered follow-up questionnaires or by national registries of cancers and chronic diseases, depending on centres. For each suspected case, local physicians ascertained the diagnosis of UC or CD by reviewing the medical, endoscopic, radiological and histological reports. Participants without follow-up after inclusion were excluded. Participants with previous diagnosis of IBD before inclusion were excluded. Participants with previous diagnosis of IBD before inclusion were excluded. Participants who developed indeterminate colitis or microscopic colitis were censored.

**Assessment of other variables**

At baseline, standardized self-administered questionnaires were applied across centres to record information on smoking, physical activity, and educational level. Body mass indices (BMI) were calculated in $kg/m^2$ from the participants' weight and height measured at baseline except in France and Oxford (UK), where anthropometric data were self-reported at baseline and validated for a selected number of participants. Participants who did not complete lifestyle questionnaire were excluded.

**Statistical analysis**

Associations between the ISD score and risks of CD/UC were estimated using the Cox proportional hazard models to obtain hazard ratios (HR) and 95% confidence intervals (95% CI). Sex-specific quartiles of the ISD were used, the lowest quartile (i.e., lower inflammatory capacity) serving as the reference category. Age was used as the timescale, with the exit time as age at diagnosis of CD/UC, at death or at censoring date (last follow-up questionnaire retrieved or diagnosis of indeterminate colitis or microscopic colitis), whichever

occurred first. For the analysis concerning CD, patients were censored when they were diagnosed with UC, and vice versa. Models were stratified by centre, age and sex and adjusted for smoking status (never, former or current smoker), BMI (< 18.5, 18.5–24.9, 25.0–30.0, > 30.0 kg/m2), physical activity (active, moderately active, moderately inactive and inactive), educational level (primary school, secondary school and university degree), total energy intake (quartiles) and alcohol intake at recruitment (quartiles). As the total energy intake and alcohol intake are components included in the ISD, these variables were therefore included into the multivariable model as the residuals of a linear regression of each dietary variable on the ISD score. Linear trends were tested by using the median value for each category of the studied variables. Graphs based on the Schoenfeld residuals were used to assess the assumption of proportional hazards. Under the missing at random hypothesis, multiple imputation by chained equations with five imputations was used to address the three covariates with missing data: Smoking status (1.7% of missing data), educational level (3.7%) and physical activity (1.8%). We also modelled the ISD score as sex-specific deciles, as a continuous variable, and using cubic natural splines with four knots. In addition, we performed subgroup analyses according to sex. We conducted analyses of specific items included in the computation of the ISD score. Sensitivity analyses were also performed to assess the potential reverse causality due to delayed IBD diagnosis by excluding the first years of follow-up.

All tests were two-tailed with a limit of significance of $p < 0.05$. Analyses were performed with SAS software version 9.4 (SAS Institute, North Carolina, USA).

The EPIC study was approved by the ethical committees of the International Agency for Research on Cancer (IARC) and of all individual EPIC centres. The study data cannot be deposited publicly as these collaborative data originate from multiple research institutions across eight European countries with different legal frameworks. Information on submitting applications to access the EPIC data can be made to https://epic.iarc.fr/ access/index.php.

## Results

### Study population

Among 521,323 participants of the EPIC cohort, 394,255 were included in this study (Figure S1). The characteristics of participants are shown in Table 1. Women accounted for 68.1% of the studied population, and the mean age at recruitment was 52.1 years. The ISD score ranged from −6.36 to 4.94, and mean ISD scores were −1.92 (standard deviation: 0.91) in the first quartile and 2.55 (0.58) in the fourth quartile. A higher inflammatory score of the diet indicates a higher inflammatory potential. As expected, there were substantial differences among quartiles in each food parameter included in the ISD calculation (Table 2). For example, participants with a higher ISD score had a low daily intake of fibre (ISD score Q1: 31.1 g, Q4: 15.8 g), protein (ISD score Q1: 105.7 g, Q4: 69.4 g), vitamin C (ISD score Q1: 186.1 mg, Q4: 74.3 mg) and onion (ISD score Q1: 12.3 g, Q4: 2.9 g).

During a median follow-up duration of 13.6 years (4,889,910 person-years), there were 184 incident cases of CD and 459 incident cases of UC, yielding incidence rates of 3.8 and 9.4 per 100,000 person-years, respectively. The characteristics of participants per country are shown in Table S3. The highest mean ISD was seen in Sweden (1.40) and the lowest one in the United Kingdom (−0.92). The characteristics of cases and non-cases are shown in Table S4.

### Inflammatory score of the diet and risk of IBD

High ISD scores were associated with an increased risk of CD but not of UC (Table 3). Compared with the first quartile, the adjusted HRs for CD were 1.55 (95% CI: 0.97–2.49) for the second, 1.86 (95% CI: 1.16–2.98) for the third and 1.88 for the fourth quartile (95% CI: 1.14–3.10; *p*-trend < 0.01). Compared with the first quartile, the adjusted HRs for UC were 1.15 (95% CI: 0.89–1.49) for the second, 0.96 (95% CI: 0.73–1.27) for the third and 0.85 for the fourth quartile (95% CI: 0.63–1.15; *p*-trend 0.21), respectively. For CD, this association was observed in women (fourth vs. first quartile: aHR 2.14; 95% CI: 1.17–3.91) and not in men (fourth vs. first quartile: aHR 1.41; 95% CI: 0.56–3.56). However, women accounted for 68.1% of the participants, and interaction tests for ISD between women and men and the risk of developing CD were not significant ($p = 0.44$ for Q2, $p = 0.99$ for Q3, and $p = 0.66$ for Q4). Results were consistent in both sexes for UC.

We also divided the ISD score into sex-specific deciles. Compared with the first decile, the adjusted HRs for the tenth decile for CD was 2.14 (95% CI: 0.96–4.78) and 1.08 (95% CI: 0.67–1.72) for UC (Table S5). A one-unit increase in the ISD score was associated with a 12% increase in the risk of CD (aHR 1.12; 95% CI: 1.01–1.23) without association with the risk of UC (aHR 0.97; 95% CI: 0.91–1.03). Analyses with the ISD score modelled using cubic natural splines showed consistent results (Figure 1).

Among the food items included in the ISD computation, a higher risk of CD was observed for a lower intake of dietary fibre (aHR for fourth vs. first quartile 1.85; 95% CI: 1.12–3.04), mono-unsaturated fatty acids (aHR for fourth vs. first quartile 1.95; 95% CI: 1.08–3.52), vitamin C (aHR for fourth vs. first quartile 1.76; 95% CI: 1.09–2.85), magnesium (aHR for fourth vs. first quartile 1.67; 95% CI: 1.01–2.74), onion (aHR for fourth vs. first quartile 1.72; 95% CI: 1.01–2.95) and alcohol (aHR for fourth vs. first quartile 2.74; 95% CI: 1.05–7.14). No items among the ISD were associated with the risk of UC (Figure 2).

These results were unchanged in the sensitivity analyses excluding first year, first 2 years and first 5 years of follow-up to avoid reverse causality bias (Table S6). The effect of ISD remained at the same level of magnitude by excluding the 2 or 4 years of follow-up but decreased the statistical power of the analysis. These results were also unchanged in the sensitivity analyses excluding fibre in the ISD calculation (Table S7). The effect of ISD was unchanged.

**Discussion**

This study, based upon a prospective cohort of 394,255 healthy participants, investigated the inflammatory potential of the diet, as characterised by the ISD, and risks of CD and UC. We found that the risk of CD was roughly doubled in participants in the third and fourth ISD quartiles compared to the first ISD quartile. Among the items of the ISD, low intakes of dietary fibre, monounsaturated fatty acids, vitamin C, magnesium, onion and alcohol were associated with a higher risk of CD. There was no association with UC.

The link between dietary patterns and development of IBD have been previously studied in various prospective cohort studies [7, 10, 23, 24]. The risk of developing IBD was increased in individuals with Western dietary pattern, including higher intake of red meat, fat dairy, refined grains and n-6 fat. In contrast, Mediterranean dietary pattern with higher intake of fruits and vegetables, non-refined grains, fermented dairy products and n-3 fatty acids was found to be associated with a lower risk of CD[7].

Two studies have investigated the inflammatory potential of the diet and the risk of CD and UC, using the EDIP score. EDIP score is based on food groups [25] such as fish, for instance, which may include pro-inflammatory (e.g., vitamin B12 or protein) or anti-inflammatory nutrients (e.g., polyunsaturated fatty acids or vitamin D). Food groups may differ in nutrient composition and quality between countries and the ratio of ultra-processed food [5, 9, 26]. By contrast, ISD is mainly based upon nutrients and some specific food groups (garlic, ginger, onion, tea and pepper), and it may be more reproducible. The pro-and anti-inflammatory effects of each nutrient is computed by adding its pro-and anti-inflammatory effects [16, 27], as defined by their association with biomarkers of inflammation: IL-1β, IL-4, IL-6, IL-10, TNF-α and C-reactive protein. ISD is associated with the risk of breast, gastric and colorectal cancers [14, 15, 28]. Overall, our results are in accordance with those produced by Lo et al. and Narula et al., although the latter were not statistically significant.

The present study found a differential association of the nutritional quality of the diet with the risk of CD and UC. Aetiopathogenesis of CD differs from that of UC in several respects, namely genetic factors and smoking and also dietary factors. Indeed, a lower nutritional quality and ultra-processed foods are associated with the higher risk of CD, whereas high intakes of linoleic acid and red meat, as well as a low intake of docosohexaenoic acid have been reported to be associated with a higher risk of UC [4, 5, 8, 23, 29]. It is conceivable that the effect of diet on UC is mediated through other pathways.

Several dietary patterns have been shown to be associated with a lower risk of developing CD, all of which have a high intake of fibre, fruits and vegetables. The role of dietary fibre was confirmed in the present study, especially in the subpopulation with the highest intake of dietary fibre (aHR 1.85, 95% CI: 1.12–3.04). The protective effect of dietary fibre may be due to the production of short-chain fatty acids which have an immunoregulatory effect (aHR 1.72, 95% CI: 1.01–2.92) [30, 31]. Yet, dietary fibres also modulate various genes involved in the cell cycle control, apoptosis and intestinal inflammation [32–34]. Dietary fibres are

categorised by their sources, solubility and fermentability and include non-starch polysaccharides, oligosaccharides, lignin and associated plant substances obtained from cereals, legumes, fruit and vegetables and resistant starch obtained from milled grains and seeds, some cereals and cooked potatoes [35]. A previous EPIC study has shown that dietary fibre modulates differentially the risk of developing CD whether it comes from fruits, vegetables or cereals [36]. Further studies should focus on the effect of various types of dietary fibre upon the risk of developing IBD [37].

The impact of polyunsaturated fatty acids (PUFAs) has been reported on the risk of developing CD [4, 38]. In this matter, n-6 PUFAs are considered as pro-inflammatory whereas n-3 PUFAs as anti-inflammatory, resulting in a decreased risk of developing CD in patients with a high ratio of n-3 and n-6 PUFAs. Similarly, both a specific carbohydrate diet and the mediterranean diet, which is associated with a high ratio of n-3 and n-6 PUFAs, may be able to induce clinical remission in patients with mild-to-moderate CD [39]. In the present study, we found that low monounsaturated fatty-acids (MUFAs) dietary intake was associated with a higher risk of developing CD (aHR 1.95, 95% CI: 1.08–3.52). MUFAs are found in animal products but mainly in plant-based oils including olive oil and macadamia nuts. In contrast, Crohn's disease exclusion diet (CDED) which has demonstrated efficacy to treat active CD allows unlimited olive oil rich in MUFAs [37, 40, 41]. Similarly, Mediterranean diet which is rich in MUFAs has shown promising results in a prospective study [39]. The role of MUFAs should be wider investigated to better understand the impact of unsaturated fatty acids on the risk of developing IBD as well on the outcomes of IBD once diagnosed.

The association of higher dietary intake of vitamin C and magnesium with a lower risk of developing CD is a new finding. In a Mendelian randomisation study including three large cohorts of patients with IBD and controls, higher genetically predicted magnesium, but not vitamin C levels, were positively associated with CD [42]. Yet, higher dietary vitamin C and magnesium might be associated to higher fruit and vegetable intake in a specific dietary pattern.

Our study has several strengths. First, its prospective design lowered the risk of recall bias. Second, lifestyle, sociodemographic and health-related indicators in EPIC allowed us to adjust for important confounders such as smoking, country of residence and educational level (a proxy for socioeconomic status). Third, IBD cases only included validated CD or UC cases.

Our study also has some limitations. First, diet was measured once at baseline, while it might change over time. In addition, this study relied on food frequency questionnaires rather than detailed 24 h dietary data, which may have limited our ability to fully grasp the variability in the dietary choices of the individuals (and variability within the food supply). Noteworthy, several centres did compare their food frequency questionnaires to 24 h food diaries for validation. Since it is a prospective study, any measurement error would be non-differential and thus underestimate potential associations [43]. Second, participants included in the

EPIC study (68% were women of middle age) might not be representative of dietary habits of the overall European populations. In addition, the median age at recruitment within the cohorts was approximately 50 years. Therefore, our results might not be generalisable to younger people. Third, as in all observational studies, we cannot rule out residual confounding from unmeasured factors.

In conclusion, we found that the inflammatory potential of the diet measured by the ISD was associated with an increased risk of CD but not UC. Low dietary fibre, onion and mono-unsaturated fatty acids might account for this association. Further studies are warranted to determine the impact of various types of fibre on the risk of developing CD. Implementation of anti-inflammatory diets should be encouraged in populations at high risk of IBD.

**Tables and figures legend**

**Figures legend**

**Figure 1:** Association between inflammatory score of the diet score and Crohn's disease or ulcerative colitis using a Cox model with inflammatory score of the diet modeled as cubic natural splines with four knots. A: CD: Crohn's disease; B: UC: ulcerative colitis. *Knots were placed at the 5$^{th}$, 35$^{th}$, 65$^{th}$ and 95$^{th}$ percentiles of the inflammatory score of the diet. Inflammatory score of the diet ranged from -6.4 to 4.9 (1$^{st}$ percentile: -3.8 and 99$^{th}$ percentile: 3.7).*

**Figure 2:** Risk of Crohn's disease and ulcerative colitis according to inflammatory score of the diet score items: *quartile 4 vs quartile 1 of the inflammatory score of diet. aHR: adjusted hazard ratio; CI: confidence interval; CD: Crohn's disease; UC: ulcerative colitis; ISD: inflammatory score of the diet score; MUFA: monounsaturated fatty acids; PUFA: polyunsaturated fatty acids. The inflammatory effect was literature-derived (10.1017/S1368980013002115).*

**Tables legend**

**Table 1:** Baseline characteristics of participants according to sex-specific quartiles of inflammatory score of the diet

**Table 2:** Baseline nutrients intake of participants according to sex-specific quartiles of inflammatory score of the diet

**Table 3:** Association between sex-specific quartiles of inflammatory score of the diet and Crohn's disease or ulcerative colitis (N=394,255)

**Supplementary materials**

**Supplementary Figure S1:** Flow-chart of participants included. *EPIC: European Prospective Investigation into Cancer and Nutrition. IBD: inflammatory bowel disease.*

**Supplementary Table S1:** Nutrients included in the inflammatory score of the diet

**Supplementary Table S2:** Items-specific scores for computation of the inflammatory score of the diet score according to sex-specific quartiles of inflammatory score of the diet

**Supplementary Table S3:** Characteristics of the cohort by country

**Supplementary Table S4:** Baseline characteristics of participants according to cases and non-cases

**Supplementary Table S5:** Association between sex-specific deciles of inflammatory score of the diet score and Crohn's disease or ulcerative colitis (N=394,255)

**Table S6:** Association between sex-specific quartiles of inflammatory score of the diet scores and Crohn's disease or ulcerative colitis: sensitivity analysis excluding the first years of follow-up to avoid inverse causality bias.

**References**

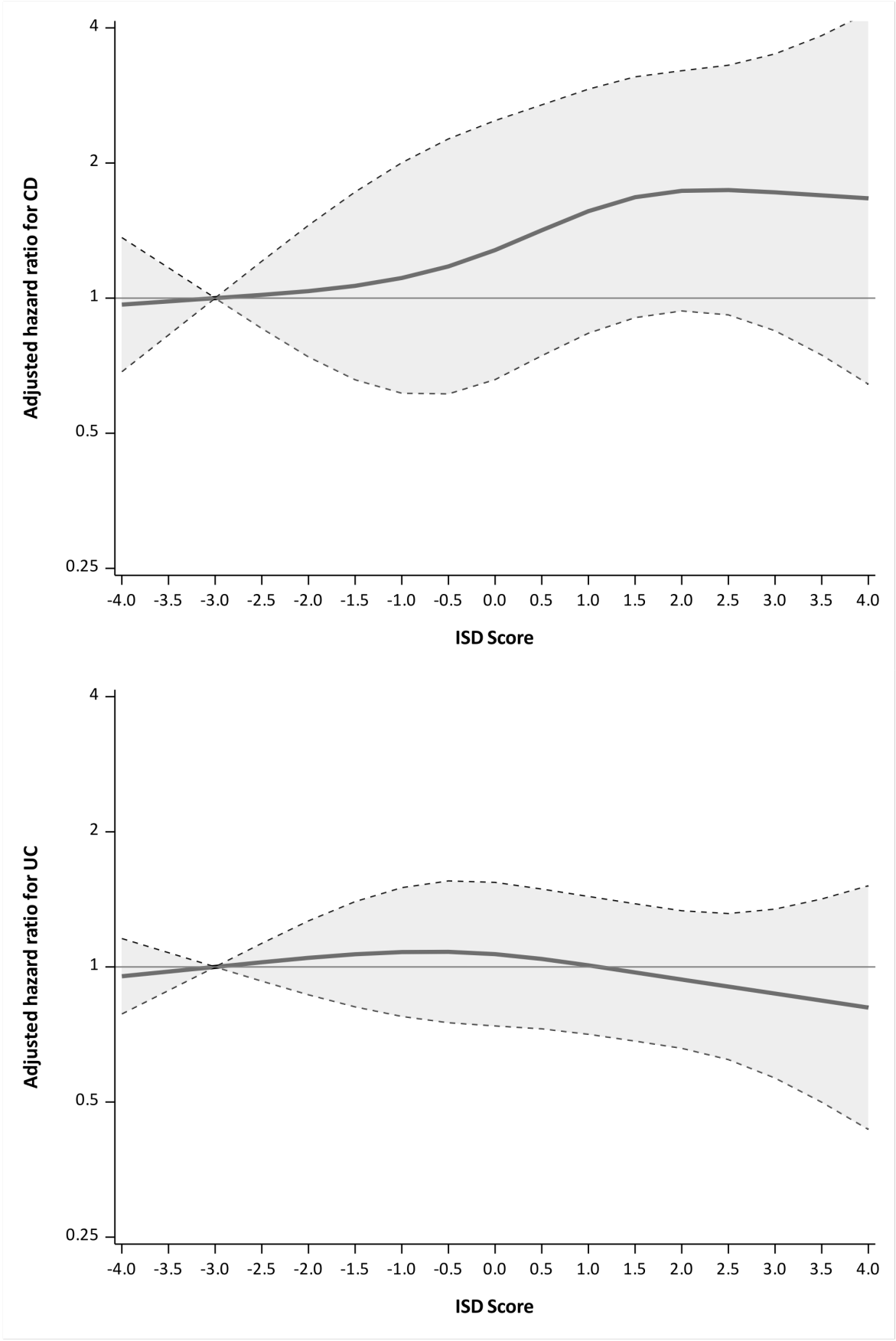

1. Lopes EW., Chan SSM., Song M., Ludvigsson JF., Håkansson N., Lochhead P., et al. Lifestyle factors for the prevention of inflammatory bowel disease. *Gut* 2022:gutjnl-2022-328174. Doi: 10.1136/gutjnl-2022-328174.
2. Sun Y., Yuan S., Chen X., Sun J., Kalla R., Yu L., et al. The Contribution of Genetic Risk and Lifestyle Factors in the Development of Adult-Onset Inflammatory Bowel Disease: A Prospective Cohort Study. *Am J Gastroenterol* 2023;**118**(3):511–22. Doi: 10.14309/ajg.0000000000002180.
3. Ananthakrishnan AN., Khalili H., Konijeti GG., Higuchi LM., de Silva P., Korzenik JR., et al. A prospective study of long-term intake of dietary fiber and risk of Crohn's disease and ulcerative colitis. *Gastroenterology* 2013;**145**(5):970–7. Doi: 10.1053/j.gastro.2013.07.050.
4. IBD in EPIC Study Investigators, Tjonneland A., Overvad K., Bergmann MM., Nagel G., Linseisen J., et al. Linoleic acid, a dietary n-6 polyunsaturated fatty acid, and the aetiology of ulcerative colitis: a nested case-control study within a European prospective cohort study. *Gut* 2009;**58**(12):1606–11. Doi: 10.1136/gut.2008.169078.
5. Narula N., Chang NH., Mohammad D., Wong ECL., Ananthakrishnan AN., Chan SSM., et al. Food Processing and Risk of Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis. *Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc* 2023;**21**(10):2483-2495.e1. Doi: 10.1016/j.cgh.2023.01.012.
6. Ng SC., Shi HY., Hamidi N., Underwood FE., Tang W., Benchimol EI., et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet Lond Engl* 2017;**390**(10114):2769–78. Doi: 10.1016/S0140-6736(17)32448-0.
7. Khalili H., Håkansson N., Chan SS., Chen Y., Lochhead P., Ludvigsson JF., et al. Adherence to a Mediterranean diet is associated with a lower risk of later-onset Crohn's disease: results from two large prospective cohort studies. *Gut* 2020;**69**(9):1637–44. Doi: 10.1136/gutjnl-2019-319505.
8. Meyer A., Dong C., Chan SSM., Touvier M., Julia C., Huybrechts I., et al. Dietary index based on the Food Standards Agency nutrient profiling system and risk of Crohn's disease and ulcerative colitis. *Aliment Pharmacol Ther* 2024;**59**(4):558–68. Doi: 10.1111/apt.17835.
9. Meyer A., Dong C., Casagrande C., Chan SSM., Huybrechts I., Nicolas G., et al. Food Processing and Risk of Crohn's Disease and Ulcerative Colitis: A European Prospective Cohort Study. *Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc* 2023;**21**(6):1607-1616.e6. Doi: 10.1016/j.cgh.2022.09.031.
10. Lo C-H., Lochhead P., Khalili H., Song M., Tabung FK., Burke KE., et al. Dietary Inflammatory Potential and Risk of Crohn's Disease and Ulcerative Colitis. *Gastroenterology* 2020;**159**(3):873-883.e1. Doi: 10.1053/j.gastro.2020.05.011.

11. Narula N., Wong ECL., Dehghan M., Marshall JK., Moayyedi P., Yusuf S. Does a High-inflammatory Diet Increase the Risk of Inflammatory Bowel Disease? Results From the Prospective Urban Rural Epidemiology (PURE) Study: A Prospective Cohort Study. *Gastroenterology* 2021;**161**(4):1333-1335.e1. Doi: 10.1053/j.gastro.2021.06.007.
12. Riboli E., Hunt KJ., Slimani N., Ferrari P., Norat T., Fahey M., et al. European Prospective Investigation into Cancer and Nutrition (EPIC): study populations and data collection. *Public Health Nutr* 2002;**5**(6B):1113–24. Doi: 10.1079/PHN2002394.
13. Slimani N., Deharveng G., Unwin I., Southgate D a. T., Vignat J., Skeie G., et al. The EPIC nutrient database project (ENDB): a first attempt to standardize nutrient databases across the 10 European countries participating in the EPIC study. *Eur J Clin Nutr* 2007;**61**(9):1037–56. Doi: 10.1038/sj.ejcn.1602679.
14. Agudo A., Cayssials V., Bonet C., Tjønneland A., Overvad K., Boutron-Ruault M-C., et al. Inflammatory potential of the diet and risk of gastric cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. *Am J Clin Nutr* 2018;**107**(4):607–16. Doi: 10.1093/ajcn/nqy002.
15. Castro-Espin C., Agudo A., Bonet C., Katzke V., Turzanski-Fortner R., Aleksandrova K., et al. Inflammatory potential of the diet and risk of breast cancer in the European Investigation into Cancer and Nutrition (EPIC) study. *Eur J Epidemiol* 2021;**36**(9):953–64. Doi: 10.1007/s10654-021-00772-2.
16. Shivappa N., Steck SE., Hurley TG., Hussey JR., Hébert JR. Designing and developing a literature-derived, population-based dietary inflammatory index. *Public Health Nutr* 2014;**17**(8):1689–96. Doi: 10.1017/S1368980013002115.
17. Shah SC., Khalili H., Gower-Rousseau C., Olen O., Benchimol EI., Lynge E., et al. Sex-Based Differences in Incidence of Inflammatory Bowel Diseases-Pooled Analysis of Population-Based Studies From Western Countries. *Gastroenterology* 2018;**155**(4):1079-1089.e3. Doi: 10.1053/j.gastro.2018.06.043.
18. Peyrin-Biroulet L., Loftus EV., Tremaine WJ., Harmsen WS., Zinsmeister AR., Sandborn WJ. Perianal Crohn's disease findings other than fistulas in a population-based cohort. *Inflamm Bowel Dis* 2012;**18**(1):43–8. Doi: 10.1002/ibd.21674.
19. Severs M., Spekhorst LM., Mangen M-JJ., Dijkstra G., Löwenberg M., Hoentjen F., et al. Sex-Related Differences in Patients With Inflammatory Bowel Disease: Results of 2 Prospective Cohort Studies. *Inflamm Bowel Dis* 2018;**24**(6):1298–306. Doi: 10.1093/ibd/izy004.
20. Wagtmans MJ., Verspaget HW., Lamers CB., van Hogezand RA. Gender-related differences in the clinical course of Crohn's disease. *Am J Gastroenterol* 2001;**96**(5):1541–6. Doi: 10.1111/j.1572-0241.2001.03755.x.
21. Cosnes J. Tobacco and IBD: relevance in the understanding of disease mechanisms and clinical practice. *Best Pract Res Clin Gastroenterol* 2004;**18**(3):481–96. Doi: 10.1016/j.bpg.2003.12.003.

22. Sutherland LR., Ramcharan S., Bryant H., Fick G. Effect of cigarette smoking on recurrence of Crohn's disease. *Gastroenterology* 1990;**98**(5 Pt 1):1123–8. Doi: 10.1016/0016-5085(90)90324-t.
23. Cosnes J., Nion-Larmurier I., Afchain P., Beaugerie L., Gendre J-P. Gender differences in the response of colitis to smoking. *Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc* 2004;**2**(1):41–8. Doi: 10.1016/s1542-3565(03)00290-8.
24. Racine A., Carbonnel F., Chan SSM., Hart AR., Bueno-de-Mesquita HB., Oldenburg B., et al. Dietary Patterns and Risk of Inflammatory Bowel Disease in Europe: Results from the EPIC Study. *Inflamm Bowel Dis* 2016;**22**(2):345–54. Doi: 10.1097/MIB.0000000000000638.
25. D'Souza S., Levy E., Mack D., Israel D., Lambrette P., Ghadirian P., et al. Dietary patterns and risk for Crohn's disease in children. *Inflamm Bowel Dis* 2008;**14**(3):367–73. Doi: 10.1002/ibd.20333.
26. Tabung FK., Smith-Warner SA., Chavarro JE., Fung TT., Hu FB., Willett WC., et al. An Empirical Dietary Inflammatory Pattern Score Enhances Prediction of Circulating Inflammatory Biomarkers in Adults. *J Nutr* 2017;**147**(8):1567–77. Doi: 10.3945/jn.117.248377.
27. Huang Y., Burgoine T., Theis DR., Adams J. Differences in energy and nutrient content of menu items served by large chain restaurants in the USA and the UK in 2018. *Public Health Nutr* 2022;**25**(10):1–9. Doi: 10.1017/S1368980022001379.
28. Hébert JR., Shivappa N., Tabung FK., Steck SE., Wirth MD., Hurley TG. On the use of the dietary inflammatory index in relation to low-grade inflammation and markers of glucose metabolism in the Cohort study on Diabetes and Atherosclerosis Maastricht (CODAM) and the Hoorn study. *Am J Clin Nutr* 2014;**99**(6):1520. Doi: 10.3945/ajcn.113.079095.
29. Jakszyn P., Cayssials V., Buckland G., Perez-Cornago A., Weiderpass E., Boeing H., et al. Inflammatory potential of the diet and risk of colorectal cancer in the European Prospective Investigation into Cancer and Nutrition study. *Int J Cancer* 2020;**147**(4):1027–39. Doi: 10.1002/ijc.32870.
30. Walker AW., Duncan SH., McWilliam Leitch EC., Child MW., Flint HJ. pH and peptide supply can radically alter bacterial populations and short-chain fatty acid ratios within microbial communities from the human colon. *Appl Environ Microbiol* 2005;**71**(7):3692–700. Doi: 10.1128/AEM.71.7.3692-3700.2005.
31. Fernández-Jalao I., Balderas C., Calvo MV., Fontecha J., Sánchez-Moreno C., De Ancos B. Impact of High-Pressure Processed Onion on Colonic Metabolism Using a Dynamic Gastrointestinal Digestion Simulator. *Metabolites* 2021;**11**(5):262. Doi: 10.3390/metabo11050262.
32. Hamer HM., Jonkers D., Venema K., Vanhoutvin S., Troost FJ., Brummer R-J. Review article: the role of butyrate on colonic function. *Aliment Pharmacol Ther* 2008;**27**(2):104–19. Doi: 10.1111/j.1365-2036.2007.03562.x.
33. Scheppach W., Weiler F. The butyrate story: old wine in new bottles? *Curr Opin Clin Nutr Metab Care* 2004;**7**(5):563–7. Doi: 10.1097/00075197-200409000-00009.

34. Pajak B., Orzechowski A., Gajkowska B. Molecular basis of sodium butyrate-dependent proapoptotic activity in cancer cells. *Adv Med Sci* 2007;**52**:83–8.
35. Mudgil D., Barak S. Composition, properties and health benefits of indigestible carbohydrate polymers as dietary fiber: a review. *Int J Biol Macromol* 2013;**61**:1–6. Doi: 10.1016/j.ijbiomac.2013.06.044.
36. Andersen V., Chan S., Luben R., Khaw K-T., Olsen A., Tjonneland A., et al. Fibre intake and the development of inflammatory bowel disease: A European prospective multi-centre cohort study (EPIC-IBD). *J Crohns Colitis* 2018;**12**(2):129–36. Doi: 10.1093/ecco-jcc/jjx136.
37. Levine A., Rhodes JM., Lindsay JO., Abreu MT., Kamm MA., Gibson PR., et al. Dietary Guidance From the International Organization for the Study of Inflammatory Bowel Diseases. *Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc* 2020;**18**(6):1381–92. Doi: 10.1016/j.cgh.2020.01.046.
38. Hou JK., Abraham B., El-Serag H. Dietary intake and risk of developing inflammatory bowel disease: a systematic review of the literature. *Am J Gastroenterol* 2011;**106**(4):563–73. Doi: 10.1038/ajg.2011.44.
39. Lewis JD., Sandler RS., Brotherton C., Brensinger C., Li H., Kappelman MD., et al. A Randomized Trial Comparing the Specific Carbohydrate Diet to a Mediterranean Diet in Adults With Crohn's Disease. *Gastroenterology* 2021;**161**(3):837-852.e9. Doi: 10.1053/j.gastro.2021.05.047.
40. Yanai H., Levine A., Hirsch A., Boneh RS., Kopylov U., Eran HB., et al. The Crohn's disease exclusion diet for induction and maintenance of remission in adults with mild-to-moderate Crohn's disease (CDED-AD): an open-label, pilot, randomised trial. *Lancet Gastroenterol Hepatol* 2022;**7**(1):49–59. Doi: 10.1016/S2468-1253(21)00299-5.
41. Levine A., Wine E., Assa A., Sigall Boneh R., Shaoul R., Kori M., et al. Crohn's Disease Exclusion Diet Plus Partial Enteral Nutrition Induces Sustained Remission in a Randomized Controlled Trial. *Gastroenterology* 2019;**157**(2):440-450.e8. Doi: 10.1053/j.gastro.2019.04.021.
42. Chen J., Ruan X., Yuan S., Deng M., Zhang H., Sun J., et al. Antioxidants, minerals and vitamins in relation to Crohn's disease and ulcerative colitis: A Mendelian randomization study. *Aliment Pharmacol Ther* 2023;**57**(4):399–408. Doi: 10.1111/apt.17392.
43. Kipnis V., Freedman LS. Impact of Exposure Measurement Error in Nutritional Epidemiology. *JNCI J Natl Cancer Inst* 2008;**100**(23):1658–9. Doi: 10.1093/jnci/djn408.

Figure 1


Adjusted hazard ratio for CD
4
2
1
0.5
0.25
-4.0 -3.5 -3.0 -2.5 -2.0 -1.5 -1.0 -0.5 0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0
ISD Score
Adjusted hazard ratio for UC
4
2
1
0.5
0.25
-4.0 -3.5 -3.0 -2.5 -2.0 -1.5 -1.0 -0.5 0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0
ISD Score

| Items of the ISD | Inflammatory effect | CD, aHR (95% CI) | UC, aHR (95% CI) |
|---|---|---|---|
| **A higher intake means a lower risk of IBD** | | | |
| Fibre (g) | −0.663 | 1.85 (1.12−3.04) | 0.86 (0.64−1.15) |
| Flavones (mg) | −0.616 | 1.44 (0.90−2.32) | 0.84 (0.62−1.13) |
| Isoflavonoids (mg) | −0.593 | 0.66 (0.39−1.14) | 1.10 (0.78−1.56) |
| B−carotene (ug) | −0.584 | 1.29 (0.79−2.11) | 0.85 (0.65−1.13) |
| Mg (mg) | −0.484 | 1.67 (1.01−2.74) | 0.78 (0.57−1.07) |
| Flavonols (mg) | −0.467 | 0.91 (0.55−1.51) | 0.99 (0.72−1.36) |
| Vitamin D (ug) | −0.446 | 1.00 (0.60−1.67) | 0.98 (0.71−1.35) |
| Vitamin C (mg) | −0.424 | 1.76 (1.09−2.85) | 0.88 (0.67−1.15) |
| Vitamin E (mg) | −0.419 | 1.23 (0.76−1.99) | 0.89 (0.65−1.20) |
| Flavan−3−ol (mg) | −0.415 | 0.85 (0.51−1.41) | 0.83 (0.61−1.14) |
| Vitamin A (Retinol Eq) | −0.401 | 1.27 (0.78−2.06) | 0.89 (0.65−1.21) |
| Vitamin B6 (mg) | −0.365 | 1.58 (0.97−2.58) | 0.76 (0.56−1.03) |
| PUFA (g) | −0.337 | 1.47 (0.92−2.37) | 0.87 (0.64−1.17) |
| Onion (g) | −0.301 | 1.72 (1.01−2.95) | 1.09 (0.78−1.52) |
| Alcohol (g) | −0.278 | 2.74 (1.05−7.14) | 0.99 (0.56−1.78) |
| Flavanones (mg) | −0.250 | 1.41 (0.92−2.18) | 0.91 (0.70−1.18) |
| Folic acid (ug) | −0.190 | 1.38 (0.83−2.31) | 0.93 (0.68−1.28) |
| Anthocyanidins (mg) | −0.131 | 1.51 (0.91−2.50) | 0.97 (0.72−1.32) |
| Thiamin (mg) | −0.098 | 1.25 (0.75−2.09) | 0.90 (0.65−1.26) |
| Riboflavin (mg) | −0.068 | 1.40 (0.85−2.30) | 1.03 (0.75−1.43) |
| MUFA (g) | −0.009 | 1.95 (1.08−3.52) | 0.93 (0.64−1.34) |
| **A higher intake means a higher risk of IBD** | | | |
| Protein (g) | 0.021 | 1.06 (0.61−1.86) | 1.25 (0.89−1.77) |
| Fe (mg) | 0.032 | 0.99 (0.60−1.62) | 1.34 (0.98−1.83) |
| Carbohydrate (g) | 0.097 | 0.73 (0.42−1.27) | 1.36 (0.98−1.90) |
| Vitamin B12 (ug) | 0.106 | 0.80 (0.51−1.27) | 0.99 (0.73−1.33) |
| Cholesterol (mg) | 0.110 | 1.20 (0.68−2.14) | 1.35 (0.94−1.93) |
| Energy (kcal) | 0.180 | 0.63 (0.33−1.22) | 1.18 (0.79−1.77) |
| Saturated fat (g) | 0.373 | 1.12 (0.59−2.10) | 0.80 (0.54−1.18) |

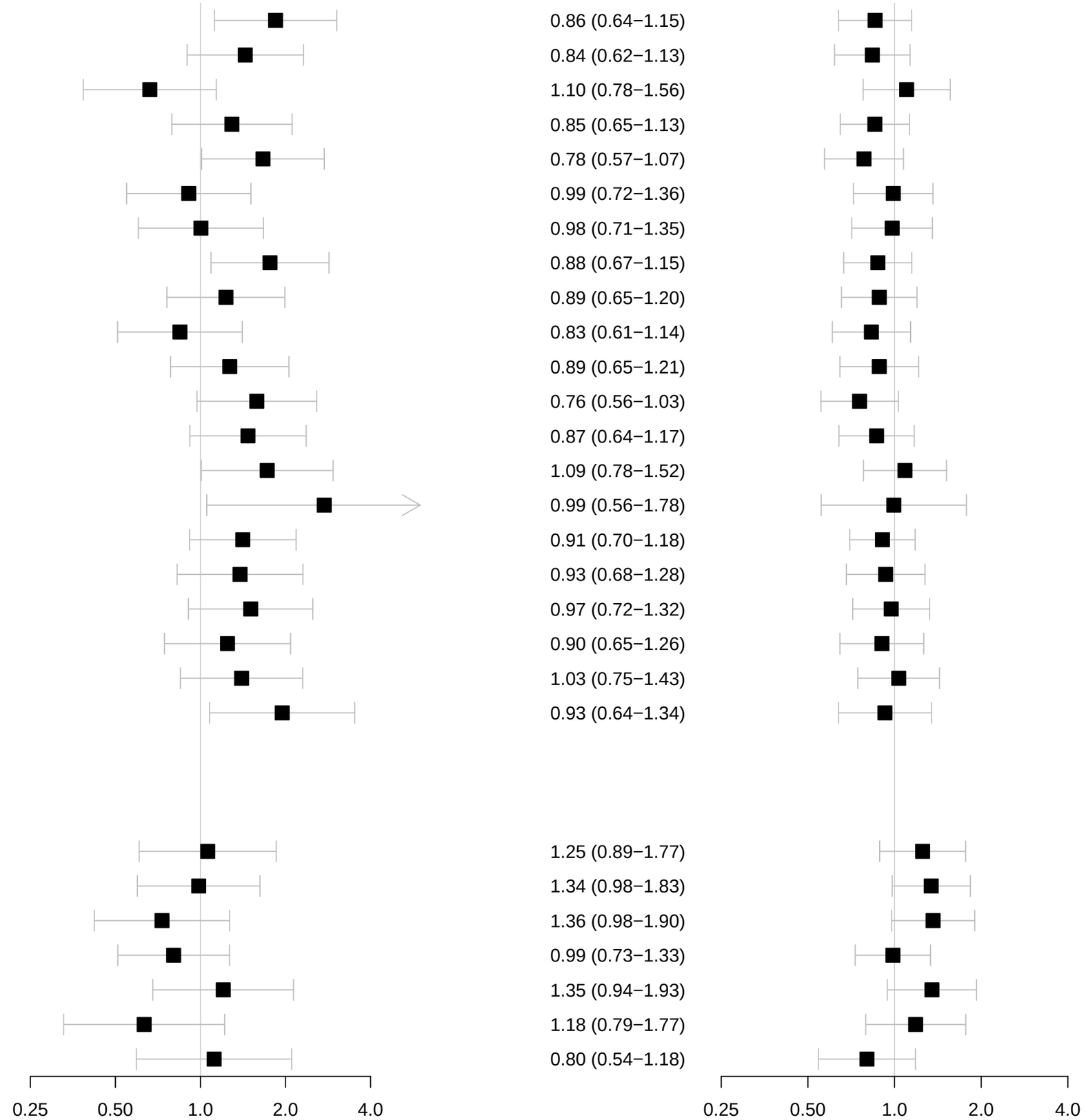


**Table 1. Baseline characteristics of participants according to sex-specific quartiles of inflammatory potential of the diet score**

| | All | Sex-specific quartiles of inflammatory score of the diet | | | |
|---|---|---|---|---|---|
| | | Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 |
| **Number of participant, n** | 394 255 | 98 564 | 98 564 | 98 564 | 98 563 |
| **Person-years, n** | 4 889 910 | 1 134 512 | 1 234 978 | 1 257 376 | 1 263 044 |
| **Inflammatory score of the diet, mean (SD)** | 0.44 (1.75) | -1.92 (0.91) | -0.05 (0.39) | 1.16 (0.35) | 2.55 (0.58) |
| Male | 0.31 (1.71) | -1.98 (0.87) | -0.19 (0.37) | 1.01 (0.34) | 2.41 (0.59) |
| Female | 0.49 (1.76) | -1.89 (0.93) | 0.01 (0.39) | 1.23 (0.34) | 2.62 (0.56) |
| **Female, n (%)** | 268 599 (68.1) | 67 150 (68.1) | 67 150 (68.1) | 67 150 (68.1) | 67 149 (68.1) |
| **Age at recruitment (years), mean (SD)** | 52.1 (9.6) | 52.0 (10.3) | 52.3 (9.5) | 52.2 (9.4) | 52.1 (9.4) |
| **Body mass index at inclusion (kg/m²), mean (SD)** | 25.3 (4.2) | 25.1 (4.1) | 25.2 (4.1) | 25.3 (4.2) | 25.5 (4.3) |
| **Smoking status†, n (%)** | | | | | |
| Never | 194 303 (50.2) | 52 237 (54.2) | 49 694 (51.4) | 47 511 (48.9) | 44 861 (46.1) |
| Former | 109 097 (28.2) | 29 198 (30.3) | 27 936 (28.9) | 27 358 (28.2) | 24 605 (25.3) |
| Current | 83 985 (21.7) | 14 879 (15.5) | 19 079 (19.7) | 22 208 (22.9) | 27 819 (28.6) |
| **Educational level†, n (%)** | | | | | |
| Primary school | 109 413 (28.8) | 21 225 (23.1) | 24 932 (26.3) | 28 091 (29.2) | 35 165 (36.2) |
| Secondary school | 170 473 (44.9) | 40 953 (44.6) | 43 347 (45.7) | 43 677 (45.5) | 42 496 (43.8) |
| Longer education | 99 865 (26.3) | 29 633 (32.3) | 26 531 (28.0) | 24 326 (25.3) | 19 375 (20.0) |
| **Physical activity†, n (%)** | | | | | |
| Inactive | 79 304 (20.5) | 17 557 (18.1) | 18 370 (19.0) | 19 679 (20.4) | 23 698 (24.4) |
| Moderately inactive | 135 012 (34.9) | 32 096 (33.1) | 33 251 (34.4) | 34 560 (35.8) | 35 105 (36.2) |
| Moderately active | 97 112 (25.1) | 25 594 (26.4) | 24 871 (25.8) | 24 247 (25.1) | 22 400 (23.1) |
| Active | 75 745 (19.6) | 21 758 (22.4) | 20 043 (20.8) | 18 192 (18.8) | 15 752 (16.3) |

*A higher inflammatory potential of the diet score indicates a higher inflammatory potential.*
*†Missing values: smoking status: 1.7%, educational level: 3.7%, physical activity: 1.8%.*
*SD: standard deviation; IQR: interquartile range.*

**Table 2. Baseline food intake of participants according to sex-specific quartiles of inflammatory potential of the diet score**

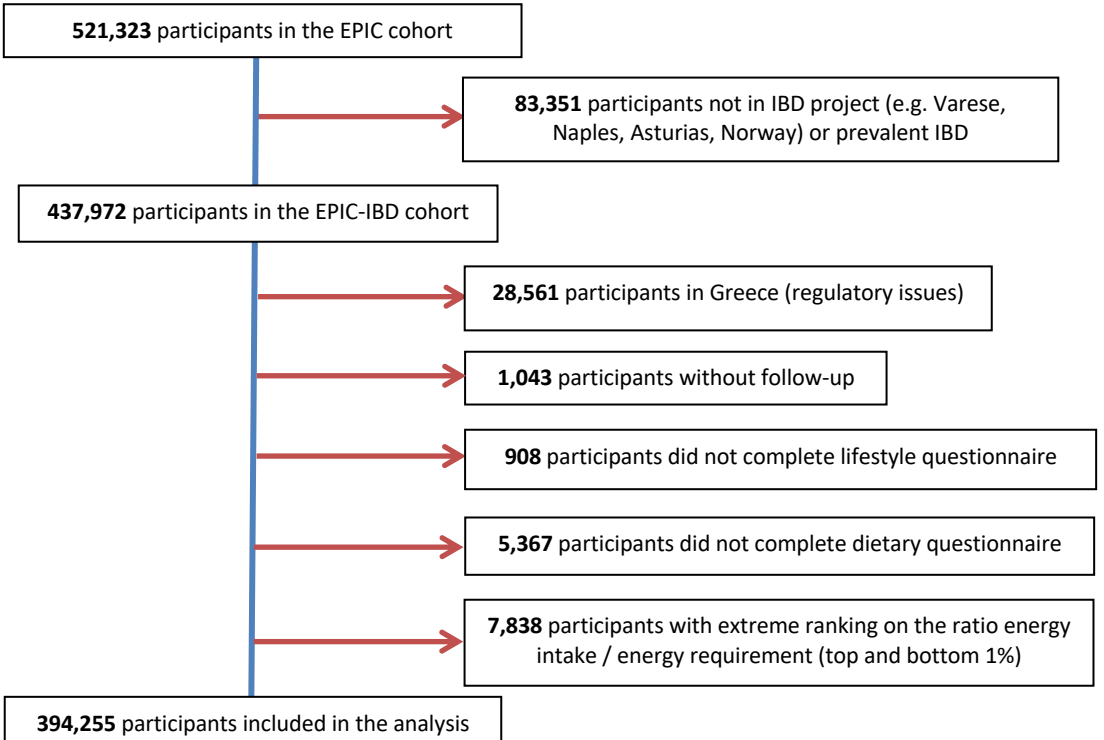
| | All | Sex-specific quartiles of inflammatory potential of the diet score | | | |
|---|---|---|---|---|---|
| | | Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 |
| **Number of participant, n** | 394 255 | 98 564 | 98 564 | 98 564 | 98 563 |
| Energy (kcal), mean (SD) | 2 111 (620) | 2 534 (647) | 2 227 (554) | 1 999 (485) | 1 685 (438) |
| Carbohydrate (g), mean (SD) | 232.7 (75.2) | 283.2 (78.8) | 245.3 (68.2) | 218.5 (59.7) | 183.7 (53.7) |
| Protein (g), mean (SD) | 87.8 (27.8) | 105.7 (29.8) | 93.0 (24.7) | 83.0 (21.8) | 69.4 (20.0) |
| Fibre (g), mean (SD) | 22.9 (7.8) | 31.1 (7.5) | 24.4 (5.2) | 20.5 (4.3) | 15.8 (4.0) |
| Saturated fat (g), mean (SD) | 32.3 (13.2) | 36.5 (14.9) | 33.9 (13.1) | 31.3 (11.9) | 27.6 (10.9) |
| MUFA (g), mean (SD) | 29.3 (12.1) | 34.8 (14.3) | 30.8 (11.8) | 27.9 (10.3) | 23.8 (8.8) |
| PUFA (g), mean (SD) | 13.6 (6.0) | 18.2 (6.8) | 14.5 (5.3) | 12.3 (4.4) | 9.5 (3.5) |
| Cholesterol (mg), mean (SD) | 328.0 (154.4) | 380.0 (183.0) | 347.8 (150.8) | 316.0 (134.3) | 268.3 (119.3) |
| Alcohol (g), median [IQR] | 6.6 [1.4-17.1] | 8.1 [1.9-19.0] | 7.4 [1.7-18.3] | 6.7 [1.4-17.4] | 4.4 [0.7-13.4] |
| Vitamin A (Retinol Equivalents), mean (SD) | 871.3 (763.8) | 1 022.3 (917.6) | 920.9 (783.4) | 837.9 (697.4) | 704.0 (580.6) |
| β-carotene (µg), mean (SD) | 3 565.8 (2 834.9) | 5 695.4 (3 786.4) | 3 832.3 (2 361.8) | 2 854.7 (1 703.2) | 1 880.9 (1 174.5) |
| Thiamin (mg), mean (SD) | 1.4 (0.5) | 1.8 (0.5) | 1.4 (0.4) | 1.2 (0.3) | 1.0 (0.3) |
| Riboflavin (mg), mean (SD) | 1.9 (0.8) | 2.5 (0.8) | 2.0 (0.6) | 1.8 (0.6) | 1.4 (0.5) |
| Vitamin B6 (mg), mean (SD) | 1.9 (0.6) | 2.5 (0.6) | 2.0 (0.4) | 1.7 (0.4) | 1.4 (0.4) |
| Folic acid (µg), mean (SD) | 312.3 (116.6) | 446.3 (118.0) | 329.8 (61.0) | 269.8 (49.7) | 203.2 (47.9) |
| Vitamin B12 (µg), mean (SD) | 6.8 (4.2) | 8.3 (5.3) | 7.2 (4.2) | 6.3 (3.5) | 5.2 (2.9) |
| Vitamin C (mg), mean (SD) | 124.9 (63.8) | 186.1 (73.1) | 133.3 (45.5) | 105.9 (35.9) | 74.3 (28.7) |
| Vitamin D (µg), mean (SD) | 4.0 (2.6) | 4.8 (3.0) | 4.1 (2.6) | 3.7 (2.3) | 3.2 (2.0) |
| Vitamin E (mg), mean (SD) | 11.9 (5.4) | 16.4 (6.0) | 12.7 (4.4) | 10.5 (3.6) | 7.9 (2.8) |
| Fe (mg), mean (SD) | 13.2 (4.2) | 16.6 (4.2) | 14.0 (3.4) | 12.2 (2.9) | 9.8 (2.7) |
| Mg (mg), mean (SD) | 369.0 (113.6) | 461.0 (113.0) | 391.8 (94.4) | 343.3 (82.7) | 279.8 (73.8) |
| Onion (g), median [IQR] | 5.0 [2.0-14.6] | 12.3 [3.7-26.7] | 5.6 [2.4-15.3] | 4.3 [1.9-10.2] | 2.9 [1.3-6.7] |
| Flavan-3-ol (mg), median [IQR] | 53.3 [22.4-198.8] | 162.3 [47.0-342.6] | 68.6 [28.3-247.3] | 43.7 [21.1-136.0] | 24.0 [12.9-57.8] |
| Flavones (mg), median [IQR] | 9.2 [5.8-14.1] | 13.2 [8.9-19.0] | 9.9 [6.6-14.5] | 8.3 [5.5-12.3] | 6.4 [4.0-9.6] |
| Flavonols (mg), median [IQR] | 30.6 [17.7-57.9] | 61.6 [37.6-94.4] | 35.7 [23.6-61.4] | 25.8 [17.0-41.9] | 15.6 [10.1-24.7] |
| Flavanones (mg), median [IQR] | 23.8 [10.1-54.0] | 47.8 [22.4-82.7] | 28.1 [12.6-59.1] | 20.0 [9.3-42.2] | 12.2 [5.5-25.0] |
| Anthocyanidins (mg), median [IQR] | 26.8 [12.8-56.2] | 34.6 [16.5-75.7] | 33.4 [15.3-64.4] | 27.2 [13.2-53.6] | 18.2 [8.5-36.7] |
| Isoflavonoids (mg), median [IQR] | 0.0 [0.0-0.1] | 0.1 [0.0-0.5] | 0.0 [0.0-0.1] | 0.0 [0.0-0.1] | 0.0 [0.0-0.0] |

*A higher inflammatory potential of the diet score indicates a higher inflammatory potential.*
*Quantitative normal variable are described as mean and standard deviation (SD) and non-normal variable are described as median and interquartile range (IQR).*

**Table 3. Association between sex-specific quartiles of inflammatory potential of the diet scoreand Crohn's disease or ulcerative colitis (N=394,255)**

| | Sex-specific quartiles of inflammatory potential of the diet score | | | | |
|---|---|---|---|---|---|
| | **Quartile 1** | **Quartile 2** | **Quartile 3** | **Quartile 4** | **p-trend†** |
| **Number of participants** | 98 564 | 98 564 | 98 564 | 98 563 | |
| Female | 67 150 | 67 150 | 67 150 | 67 149 | |
| Male | 31 414 | 31 414 | 31 414 | 31 414 | |
| **Crohn's disease** | | | | | |
| **Cases, n** | 29 | 46 | 55 | 54 | |
| Female | 20 | 28 | 39 | 41 | |
| Male | 9 | 18 | 16 | 13 | |
| **Sex, age, and center stratified Cox models, aHR (95%CI)** | | | | | |
| Overall | 1 (Ref) | 1.52 (0.95-2.44) | 1.81 (1.13-2.88) | 1.77 (1.10-2.87) | 0.02 |
| **Multi-adjusted Cox models, aHR (95%CI)‡** | | | | | |
| Overall | 1 (Ref) | 1.55 (0.97-2.49) | 1.86 (1.16-2.98) | 1.88 (1.14-3.10) | <0.01 |
| Female | 1 (Ref) | 1.34 (0.75-2.41) | 1.89 (1.07-3.32) | 2.14 (1.17-3.91) | <0.01 |
| Male | 1 (Ref) | 2.01 (0.89-4.55) | 1.82 (0.78-4.28) | 1.41 (0.56-3.56) | 0.55 |
| **Ulcerative colitis** | | | | | |
| **Cases, n** | 110 | 133 | 114 | 102 | |
| Female | 62 | 65 | 61 | 61 | |
| Male | 48 | 68 | 53 | 41 | |
| **Sex, age, and center stratified Cox models, aHR (95%CI)** | | | | | |
| Overall | 1 (Ref) | 1.17 (0.91-1.52) | 1.01 (0.77-1.32) | 0.94 (0.70-1.25) | 0.51 |
| **Multi-adjusted Cox models, aHR (95%CI)‡** | | | | | |
| Overall | 1 (Ref) | 1.15 (0.89-1.49) | 0.96 (0.73-1.27) | 0.85 (0.63-1.15) | 0.21 |
| Female | 1 (Ref) | 1.01 (0.70-1.44) | 0.89 (0.61-1.30) | 0.82 (0.54-1.24) | 0.30 |
| Male | 1 (Ref) | 1.33 (0.91-1.93) | 1.06 (0.71-1.59) | 0.89 (0.57-1.39) | 0.48 |

*A higher inflammatory potential of the diet score indicates a higher inflammatory potential.*
*†p-trend was computed by modeling the median value for each quartile as a continuous variable.*
*‡Cox models stratified for center, sex, and age and adjusted for smoking status, body mass index, physical activity, educational level, residuals of total energy, and residuals of alcohol intake. aHR (95%CI): adjusted hazard ratio (95% confidence interval).*


**521,323** participants in the EPIC cohort
**83,351** participants not in IBD project (e.g. Varese, Naples, Asturias, Norway) or prevalent IBD
**437,972** participants in the EPIC-IBD cohort
**28,561** participants in Greece (regulatory issues)
**1,043** participants without follow-up
**908** participants did not complete lifestyle questionnaire
**5,367** participants did not complete dietary questionnaire
**7,838** participants with extreme ranking on the ratio energy intake / energy requirement (top and bottom 1%)
**394,255** participants included in the analysis

**Supplementary table S1: Nutrients included in the inflammatory score of the diet**

| Food parameter | Inflammatory score* |
|---|---|
| Fibre (g) | -0.663 |
| Flavones (mg) | -0.616 |
| Isoflavonoids (mg) | -0.593 |
| B-carotene (mg) | -0.584 |
| Mg (mg) | -0.484 |
| Flavonols (mg) | -0.467 |
| Vitamin D (mg) | -0.446 |
| Vitamin C (mg) | -0.424 |
| Vitamin E (mg) | -0.419 |
| Flavan-3-ol (mg) | -0.415 |
| Vitamin A (Retinol equivalent) | -0.401 |
| Vitamin B6 (mg) | -0.365 |
| PUFA (g) | -0.337 |
| Onion (g) | -0.301 |
| Alcohol (g) | -0.278 |
| Flavonones (mg) | -0.250 |
| Folic acid | -0.190 |
| Anthocyanidins (mg) | -0.131 |
| Thiamin (mg) | -0.098 |
| Riboflavin (mg) | -0.068 |
| MUFA (g) | -0.009 |
| Protein (g) | 0.021 |
| Fe (mg) | 0.032 |
| Carbohydrate (g) | 0.097 |
| Vitamin B12 (µg) | 0.106 |
| Cholesterol (mg) | 0,110 |
| Energy (kcal) | 0.180 |
| Saturated fat (g) | 0.373 |

*The effect is per unit amount noted for each food parameter.

**Supplementary table S2:** Items-specific scores for computation of the inflammatory score of the diet according to sex-specific quartiles of inflammatory score of the diet

| | All | Sex-specific quartiles of inflammatory score of the diet | | | |
|---|---|---|---|---|---|
| | | Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 |
| **Number of participant, n** | 394 255 | 98 564 | 98 564 | 98 564 | 98 563 |
| **Inflammatory score of the diet, median [interquartile range]** | 0.58 [-0.75-1.75] | -1.72 [-2.46--1.19] | -0.04 [-0.38-0.28] | 1.16 [0.87-1.45] | 2.45 [2.08-2.94] |
| **Items-specific scores, median [interquartile range]:** | | | | | |
| Energy | -0.01 [-0.08-0.08] | 0.08 [0.00-0.14] | 0.02 [-0.05-0.10] | -0.03 [-0.09-0.05] | -0.09 [-0.13--0.03] |
| Carbohydrate | -0.01 [-0.04-0.04] | 0.04 [0.00-0.08] | 0.01 [-0.03-0.05] | -0.02 [-0.05-0.02] | -0.05 [-0.07--0.01] |
| Protein | 0.00 [-0.01-0.01] | 0.01 [0.00-0.02] | 0.00 [-0.01-0.01] | 0.00 [-0.01-0.01] | -0.01 [-0.02-0.00] |
| Fibre | 0.05 [-0.28-0.32] | -0.42 [-0.58--0.20] | -0.08 [-0.29-0.12] | 0.16 [-0.02-0.32] | 0.41 [0.27-0.51] |
| Saturated fat | -0.02 [-0.17-0.16] | 0.06 [-0.12-0.25] | 0.02 [-0.14-0.20] | -0.04 [-0.17-0.13] | -0.11 [-0.22-0.04] |
| MUFA | 0.00 [0.00-0.00] | 0.00 [-0.01-0.00] | 0.00 [0.00-0.00] | 0.00 [0.00-0.00] | 0.00 [0.00-0.01] |
| PUFA | 0.04 [-0.12-0.16] | -0.14 [-0.27-0.01] | -0.01 [-0.15-0.11] | 0.08 [-0.04-0.17] | 0.17 [0.09-0.23] |
| Cholesterol | -0.01 [-0.05-0.05] | 0.02 [-0.03-0.08] | 0.01 [-0.04-0.06] | -0.01 [-0.05-0.04] | -0.04 [-0.07-0.01] |
| Alcohol | 0.07 [-0.01-0.13] | 0.05 [-0.03-0.12] | 0.06 [-0.02-0.12] | 0.07 [-0.01-0.13] | 0.09 [0.00-0.13] |
| Vitamin A | 0.07 [-0.11-0.17] | 0.03 [-0.19-0.16] | 0.05 [-0.14-0.16] | 0.07 [-0.09-0.17] | 0.11 [-0.02-0.19] |
| β-carotene | 0.12 [-0.14-0.27] | -0.19 [-0.45-0.01] | 0.03 [-0.17-0.20] | 0.18 [0.00-0.28] | 0.29 [0.19-0.36] |
| Thiamin | 0.01 [-0.04-0.05] | -0.06 [-0.08--0.02] | -0.01 [-0.04-0.03] | 0.03 [-0.01-0.05] | 0.05 [0.03-0.07] |
| Riboflavin | 0.00 [-0.03-0.03] | -0.04 [-0.06--0.01] | -0.01 [-0.03-0.02] | 0.01 [-0.01-0.03] | 0.03 [0.01-0.05] |
| Vitamin B6 | 0.03 [-0.16-0.17] | -0.22 [-0.31--0.10] | -0.03 [-0.16-0.08] | 0.09 [-0.02-0.18] | 0.21 [0.12-0.27] |
| Folic acid | 0.02 [-0.07-0.09] | -0.12 [-0.16--0.07] | -0.02 [-0.06-0.03] | 0.05 [0.02-0.08] | 0.12 [0.09-0.14] |
| Vitamin B12 | -0.01 [-0.05-0.03] | 0.01 [-0.03-0.07] | 0.00 [-0.04-0.04] | -0.02 [-0.05-0.02] | -0.04 [-0.06--0.01] |
| Vitamin C | 0.07 [-0.12-0.21] | -0.20 [-0.34--0.05] | 0.00 [-0.14-0.12] | 0.12 [0.01-0.21] | 0.24 [0.16-0.30] |
| Vitamin D | 0.08 [-0.08-0.18] | -0.01 [-0.18-0.12] | 0.07 [-0.08-0.16] | 0.11 [-0.04-0.19] | 0.14 [0.01-0.22] |
| Vitamin E | 0.08 [-0.12-0.21] | -0.16 [-0.32-0.01] | 0.02 [-0.14-0.14] | 0.12 [0.00-0.21] | 0.24 [0.15-0.30] |
| Fe | 0.00 [-0.02-0.01] | 0.02 [0.00-0.03] | 0.00 [-0.01-0.02] | -0.01 [-0.02-0.00] | -0.02 [-0.02--0.01] |
| Mg | 0.02 [-0.21-0.22] | -0.25 [-0.40--0.08] | -0.06 [-0.24-0.11] | 0.09 [-0.08-0.23] | 0.27 [0.13-0.35] |
| Onion | 0.11 [-0.05-0.16] | -0.01 [-0.22-0.13] | 0.10 [-0.06-0.15] | 0.13 [0.02-0.16] | 0.14 [0.09-0.17] |
| Flavan-3-ol | 0.13 [-0.16-0.19] | -0.09 [-0.35-0.14] | 0.10 [-0.24-0.18] | 0.15 [-0.04-0.19] | 0.19 [0.12-0.20] |
| Flavones | 0.13 [-0.14-0.30] | -0.09 [-0.37-0.14] | 0.09 [-0.16-0.26] | 0.18 [-0.04-0.31] | 0.27 [0.11-0.37] |
| Flavonols | 0.10 [-0.19-0.23] | -0.23 [-0.42-0.02] | 0.04 [-0.22-0.17] | 0.15 [-0.02-0.23] | 0.25 [0.16-0.29] |
| Flavanones | 0.07 [-0.06-0.12] | -0.03 [-0.16-0.07] | 0.05 [-0.08-0.11] | 0.08 [-0.01-0.12] | 0.11 [0.06-0.14] |

| | | | | | |
|---|---|---|---|---|---|
| Anthocyanidins | 0.03 [-0.03-0.05] | 0.01 [-0.06-0.04] | 0.01 [-0.05-0.05] | 0.02 [-0.03-0.05] | 0.04 [0.01-0.06] |
| Isoflavonoids | 0.09 [0.08-0.09] | 0.09 [0.06-0.09] | 0.09 [0.08-0.09] | 0.09 [0.09-0.09] | 0.09 [0.09-0.09] |

*Item-specific scores of the inflammatory score of the diet are summed to produce the overall inflammatory score of the diet for each participant. A higher inflammatory score of the diet indicates a higher inflammatory potential.*

## Supplementary table S3: Characteristics of the cohort by country

| | All | Country | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | France | Italy | Spain | United Kingdom Cambridge | United Kingdom Oxford | The Netherlands | Germany | Sweden | Denmark |
| **Cohort size, n** | 394 255 | 72 008 | 29 108 | 32 247 | 24 842 | 37 293 | 38 194 | 52 011 | 52 736 | 55 816 |
| **CD cases, n** | 184 | 30 | 7 | 20 | 18 | 6 | 18 | 20 | 35 | 30 |
| **UC cases, n** | 459 | 43 | 31 | 31 | 51 | 25 | 43 | 42 | 80 | 113 |
| **Inflammatory score of the diet, mean (SD)** | 0.44 (1.75) | 0.20 (1.62) | 0.97 (1.56) | 0.29 (1.80) | -0.54 (1.67) | -1.17 (1.77) | 0.86 (1.35) | 0.98 (1.49) | 1.40 (1.48) | 0.35 (1.65) |
| **Female, %** | 68.1 | 100.0 | 59.2 | 61.9 | 54.8 | 77.2 | 74.4 | 57.0 | 56.4 | 52.4 |
| **Age recruitment (years), mean (SD)** | 52.1 (9.6) | 52.9 (6.7) | 50.2 (7.8) | 49.5 (8.0) | 59.3 (9.3) | 47.5 (13.5) | 49.3 (11.9) | 50.7 (8.6) | 52.4 (10.8) | 56.7 (4.4) |
| **Recruitment period range years** | 1991-2001 | 1993-1997 | 1992-1998 | 1992-1996 | 1993-1999 | 1993-1999 | 1993-1997 | 1994-1998 | 1991-1996 | 1993-1997 |
| **Length of follow-up (years), median [IQR]** | 13.6 [11.3-14.9] | 14.9 [13.7-15.0] | 12.1 [8.7-14.5] | 14.8 [10.7-15.9] | 13.7 [12.5-14.9] | 5.2 [5.0-5.6] | 14.3 [13.1-15.5] | 11.9 [11.3-13.0] | 14.1 [12.6-15.3] | 13.6 [12.9-14.3] |
| **Energy (kcal/day), mean (SD)** | 2 111 (620) | 2 154 (576) | 2 331 (689) | 2 164 (680) | 2 043 (575) | 1 972 (539) | 2 047 (590) | 2 050 (643) | 2 040 (642) | 2 203 (596) |
| **Carbohydrates (g/day), mean (SD)** | 232.7 (75.2) | 226.3 (72.9) | 264.0 (92.4) | 219.3 (68.8) | 232.3 (74.2) | 233.9 (69.7) | 229.0 (71.8) | 228.0 (77.6) | 236.9 (75.7) | 234.2 (70.3) |
| **Fat (g/day), mean (SD)** | 82.1 (29.5) | 87.7 (27.7) | 87.1 (28.7) | 86.7 (32.0) | 77.6 (28.4) | 72.5 (26.9) | 78.5 (27.6) | 80.3 (30.3) | 81.4 (32.8) | 82.7 (27.7) |
| **Protein intake (g/day), mean (SD)** | 87.8 (27.8) | 94.1 (27.2) | 97.1 (29.2) | 102.9 (31.5) | 87.8 (22.9) | 78.3 (24.0) | 86.7 (23.9) | 76.1 (24.9) | 76.6 (24.8) | 94.6 (26.9) |
| **Alcohol (g/day), median [IQR]** | 6.6 [1.4-17.1] | 6.4 [1.4-16.3] | 7.4 [0.6-24.2] | 2.8 [0.0-18.1] | 4.5 [0.8-11.4] | 5.9 [1.5-12.6] | 5.0 [0.7-16.1] | 8.9 [2.9-21.5] | 3.9 [0.8-10.0] | 12.9 [5.9-30.7] |

*CD: Crohn's disease; SD: standard deviation; IQR: interquartile range ; UC: ulcerative colitis.*

**Supplementary table S4:** Baseline characteristics of participants according to cases and non-cases

| | Non-cases | Crohn's disease | Ulcerative colitis |
|---|---|---|---|
| **Number, n** | 393 612 | 184 | 459 |
| **Person-years, n** | 4 885 691 | 1 195 | 3 024 |
| **Inflammatory score of the diet, mean (SD)** | 0.44 (1.75) | 0.76 (1.69) | 0.38 (1.70) |
| Male | 0.31 (1.72) | 0.41 (1.62) | 0.27 (1.56) |
| Female | 0.49 (1.76) | 0.91 (1.71) | 0.47 (1.80) |
| **Female, n (%)** | 268 222 (68.1) | 128 (69.6) | 249 (54.3) |
| **Age recruitment (years), mean (SD)** | 52.1 (9.6) | 51.3 (9.7) | 52.5 (9.6) |
| **Body mass index at inclusion (kg/m²), mean (SD)** | 25.3 (4.2) | 25.3 (4.3) | 25.7 (4.1) |
| **Smoking status†, n (%)** | | | |
| Never | 194 096 (50.2) | 72 (39.6) | 135 (29.9) |
| Former | 108 890 (28.2) | 40 (22.0) | 167 (37.0) |
| Current | 83 765 (21.7) | 70 (38.5) | 150 (33.2) |
| **Educational level†, n (%)** | | | |
| Primary school | 109 206 (28.8) | 51 (28.2) | 156 (34.8) |
| Secondary school | 170 175 (44.9) | 92 (50.8) | 206 (46.0) |
| Longer education | 99 741 (26.3) | 38 (21.0) | 86 (19.2) |
| **Physical activity†, n (%)** | | | |
| Inactive | 79 170 (20.5) | 37 (20.3) | 97 (21.5) |
| Moderately inactive | 134 793 (34.9) | 66 (36.3) | 153 (33.9) |
| Moderately active | 96 974 (25.1) | 38 (20.9) | 100 (22.2) |
| Active | 75 603 (19.6) | 41 (22.5) | 101 (22.4) |
| **Energy (kcal/day), mean (SD)** | 2 111 (620) | 2 156 (602) | 2 245 (677) |
| **Carbohydrates (g/day), mean (SD)** | 232.6 (75.2) | 233.1 (68.8) | 247.4 (80.1) |
| **Fat (g/day), mean (SD)** | 82.1 (29.5) | 87.2 (30.4) | 87.1 (32.0) |
| **Protein (g/day), mean (SD)** | 87.8 (27.8) | 90.5 (29.4) | 92.4 (28.9) |
| **Alcohol (g/day), median [IQR]** | 6.6 [1.4-17.1] | 5.0 [0.8-13.2] | 8.8 [1.7-17.8] |

*A higher inflammatory score of the diet indicates a higher inflammatory potential.*
*†Missing values: smoking status: 1.7%, educational level: 3.7%, physical activity: 1.8%.*
*SD: standard deviation; IQR: interquartile range.*

**Supplementary table S5:** Association between sex-specific deciles of inflammatory score of the diet score and Crohn's disease or ulcerative colitis (N=394,255)

| | Sex-specific deciles of inflammatory score of the diet | | | | | | | | | | Continuous inflammatory score of the diet | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Decile 1** | **Decile 2** | **Decile 3** | **Decile 4** | **Decile 5** | **Decile 6** | **Decile 7** | **Decile 8** | **Decile 9** | **Decile 10** | | **p-value** |
| **Crohn's disease** | | | | | | | | | | | | |
| Cases, n | 10 | 14 | 13 | 17 | 21 | 25 | 21 | 23 | 18 | 22 | 184 | |
| Multi-adjusted Cox model, aHR (95%CI)‡ | 1 (Ref) | 1.32 (0.58-2.98) | 1.24 (0.54-2.85) | 1.60 (0.72-3.53) | 1.99 (0.92-4.29) | 2.37 (1.11-5.03) | 1.99 (0.91-4.33) | 2.18 (1.01-4.72) | 1.77 (0.78-3.98) | 2.14 (0.96-4.78) | 1.12 (1.01-1.23) | 0.03 |
| **Ulcerative colitis** | | | | | | | | | | | | |
| Cases, n | 38 | 48 | 49 | 54 | 54 | 40 | 49 | 43 | 39 | 45 | 459 | |
| Multi-adjusted Cox model, aHR (95%CI)‡ | 1 (Ref) | 1.20 (0.78-1.84) | 1.21 (0.79-1.87) | 1.31 (0.86-2.01) | 1.31 (0.85-2.00) | 0.96 (0.61-1.52) | 1.17 (0.75-1.82) | 1.02 (0.65-1.62) | 0.93 (0.58-1.49) | 1.08 (0.67-1.72) | 0.97 (0.91-1.03) | 0.35 |

*‡Cox models stratified for center, sex, and age and adjusted for smoking status, body mass index, physical activity, educational level, residuals of total energy, and residuals of alcohol intake. aHR (95%CI): adjusted hazard ratio (95% confidence interval).*

**Supplementary table S6:** Association between sex-specific quartiles of inflammatory score of the diet and Crohn's disease or ulcerative colitis: sensitivity analysis excluding the first years of follow-up to avoid inverse causality bias

| | Sex-specific quartiles of inflammatory score of the diet score | | | | |
|---|---|---|---|---|---|
| | **Quartile 1** | **Quartile 2** | **Quartile 3** | **Quartile 4** | **p-trend†** |
| **Crohn's disease, Multi-adjusted Cox model, aHR (95%CI)‡** | | | | | |
| Excluding the first year of follow-up | | | | | |
| Overall | 1 (Ref) | 1.64 (1.00-2.68) | 1.87 (1.14-3.06) | 1.98 (1.18-3.34) | <0.01 |
| Female | 1 (Ref) | 1.32 (0.72-2.40) | 1.86 (1.04-3.33) | 2.16 (1.16-4.03) | <0.01 |
| Male | 1 (Ref) | 2.50 (1.03-6.08) | 1.93 (0.75-4.96) | 1.65 (0.61-4.48) | 0.52 |
| Excluding the first 2 years of follow-up | | | | | |
| Overall | 1 (Ref) | 1.46 (0.88-2.42) | 1.53 (0.92-2.56) | 1.62 (0.94-2.78) | 0.09 |
| Female | 1 (Ref) | 1.19 (0.65-2.20) | 1.49 (0.81-2.72) | 1.70 (0.89-3.25) | 0.08 |
| Male | 1 (Ref) | 2.19 (0.89-5.41) | 1.65 (0.63-4.35) | 1.40 (0.50-3.91) | 0.72 |
| Excluding the first 4 years of follow-up | | | | | |
| Overall | 1 (Ref) | 1.41 (0.79-2.49) | 1.47 (0.82-2.62) | 1.72 (0.95-3.13) | 0.08 |
| Female | 1 (Ref) | 1.19 (0.60-2.34) | 1.27 (0.64-2.51) | 1.61 (0.79-3.27) | 0.20 |
| Male | 1 (Ref) | 2.04 (0.70-5.96) | 2.04 (0.68-6.10) | 1.89 (0.60-5.96) | 0.33 |
| **Ulcerative colitis, Multi-adjusted Cox model, aHR (95%CI)‡** | | | | | |
| Excluding the first year of follow-up | | | | | |
| Overall | 1 (Ref) | 1.21 (0.93-1.58) | 0.99 (0.75-1.32) | 0.87 (0.64-1.19) | 0.27 |
| Female | 1 (Ref) | 1.07 (0.74-1.55) | 0.94 (0.64-1.40) | 0.84 (0.54-1.29) | 0.39 |
| Male | 1 (Ref) | 1.38 (0.94-2.04) | 1.05 (0.69-1.60) | 0.90 (0.57-1.43) | 0.49 |
| Excluding the first 2 years of follow-up | | | | | |
| Overall | 1 (Ref) | 1.30 (0.98-1.72) | 1.06 (0.78-1.43) | 0.92 (0.66-1.28) | 0.44 |
| Female | 1 (Ref) | 1.12 (0.75-1.66) | 1.05 (0.69-1.58) | 0.87 (0.55-1.38) | 0.57 |
| Male | 1 (Ref) | 1.52 (1.01-2.28) | 1.06 (0.68-1.67) | 0.97 (0.60-1.58) | 0.62 |
| Excluding the first 4 years of follow-up | | | | | |
| Overall | 1 (Ref) | 1.44 (1.04-1.99) | 1.11 (0.79-1.58) | 1.05 (0.72-1.53) | 0.90 |
| Female | 1 (Ref) | 1.37 (0.86-2.19) | 1.23 (0.76-1.99) | 1.12 (0.66-1.90) | 0.77 |
| Male | 1 (Ref) | 1.51 (0.96-2.39) | 1.01 (0.60-1.68) | 0.98 (0.57-1.70) | 0.64 |

*A higher inflammatory score of the diet indicates a higher inflammatory potential.*
*†p-trend was computed by modeling the median value for each quartile as a continuous variable.*
*‡Cox models stratified for center, sex, and age and adjusted for smoking status, body mass index, physical activity, educational level, residuals of total energy, and residuals of alcohol intake. aHR (95%CI): adjusted hazard ratio (95% confidence interval).*