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Original Article

Meat Intake Is Associated with a Higher Risk of Ulcerative Colitis in a Large European Prospective Cohort Studyø

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Abstract

Background and Aims: We aimed to investigate the association between protein intake and risk of inflammatory bowel disease [IBD] in the European Prospective Investigation into Cancer and Nutrition.

Methods: A total of 413 593 participants from eight European countries were included. Dietary data were collected at baseline from validated food frequency questionnaires. Dietary data were calibrated to correct errors in measures related to each country-specific questionnaire. Associations between proteins [total, animal, and vegetable] or food sources of animal proteins, and IBD risk were estimated by Cox proportional hazard models.

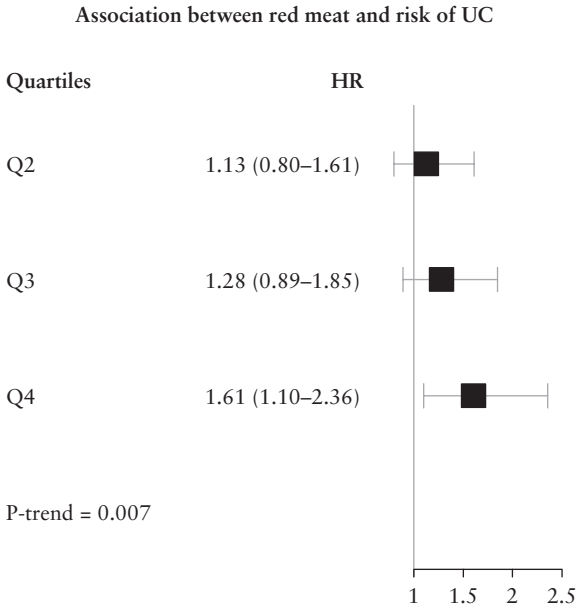
Results: After a mean follow-up of 16 years, 177 patients with Crohn's disease [CD] and 418 with ulcerative colitis [UC], were identified. There was no association between total protein, animal protein, or vegetable protein intakes and CD or UC risks. Total meat and red meat intakes were associated with UC risk (hazard ratio [HR] for the 4th vs 1st quartile = 1.40, 95% confidence interval [CI] = 0.99-1.98, *p*-trend = 0.01; and 1.61,

95% CI = 1.10-2.36, *p*-trend = 0.007, respectively]. There was no association between other food sources of animal protein [processed meat, fish, shellfish, eggs, poultry] and UC. We found no association between food sources of animal proteins and CD risk.

Conclusions: Meat and red meat consumptions are associated with higher risks of UC. These results support dietary counselling of low meat intake in people at high-risk of IBD.

Key Words: Diet; meat; inflammatory bowel disease

Graphical Abstract



1. Introduction

Incidence of inflammatory bowel disease [IBD] increased in North America and Europe during the 20th century, particularly during the latter half. More recently, it has increased in newly industrialised countries formerly unaffected by IBD, such as Asia, Middle East, and South America.[1] These temporal trends suggest the role of environmental factors in IBD aetiology. Industrialisation is associated with many lifestyle changes including urbanisation, health care, extensive use of antibiotics, exposure to different types of environmental pollution, physical inactivity, and a Western diet. A better understanding of the driving forces that act to increase the IBD incidence worldwide might help to develop prevention strategies. These are needed, particularly in large Asian countries such as India and China where a growing number of IBD patients is expected within the following decades.

Several studies, based on large prospective cohorts of healthy participants in Europe and in the USA, have investigated the association between nutrients or food patterns and the risk of IBD.[2–7] Two studies have previously investigated the association between protein intake and risk of IBD.[8,9] However, these studies were limited to a single sex or by a relatively small number of IBD cases. In a recent umbrella review of meta-analyses of environmental risk factors for IBD, the credibility of the association between protein intake and IBD was found to be weak.[10]

In this study, we sought to investigate the association between protein and sources of protein intakes and risk of IBD in the European Prospective Investigation into Cancer and Nutrition [EPIC], a large prospective cohort study of men and women in 10 European countries.

2. Materials and Methods

2.1. Study population

The EPIC cohort is a European cohort that was established in 1991 to investigate the role of environmental factors in various cancers and chronic diseases in middle-aged participants. EPIC includes about 520 000 men and women from 23 centres in 10 countries [Denmark, France, Germany, Greece, Italy, The Netherlands, Norway, Spain, Sweden, and the UK].[11] Participants were prospectively included in the study between 1991 and 1998. In this study, the follow-up for outcome ascertainment was completed until 2009.

In most centres, participants were recruited from the general population, except in France [where women were enrolled in a health insurance scheme for school and university employees], in The Netherlands [from a mammographic screening programme], and in Italy [from screening programme participants]. In addition, half of the Oxford cohort consisted of health-conscious individuals. The EPIC study was approved by the ethical committees of the International Agency for Research on Cancer and of all individual EPIC centres.

The EPIC-IBD cohort is a subgroup of the EPIC cohort, which includes all EPIC centres who agreed to collect and certify diagnoses of IBD. The EPIC-IBD cohort includes 413 593 participants from eight European countries, namely Denmark, France, Germany, Italy, The Netherlands, Spain, Sweden, and the UK. Participants were enrolled between 1991 and 2001; they were followed until 2009.

2.2. Dietary and lifestyle data

Dietary data were collected at baseline by using country-specific validated questionnaires [individual interviews or self-administered questionnaires].[12] Food frequency

questionnaires [FFQ] recorded average intakes of 170-260 food items over the past 12 months and enabled the computation of individual mean consumptions of foods or food groups in grams per day.

Total energy and macronutrient intakes were estimated by using the FFQs and the standardised EPIC Nutrient Database.[13] Participants 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.

Baseline standardised, self-administered questionnaires recorded information on smoking, physical activity, and educational level. Body mass index [BMI] was calculated in kg/m² from the participant's weight and height measured at baseline except in France, Norway, and Oxford [UK], where anthropometric data were self-reported at baseline.

2.3. Follow-up and case ascertainment

Participants who developed incident IBD during follow-up were identified either by self-administered questionnaires or by national registries of cancers and chronic diseases, depending on centres. For each case, local physicians ascertained the diagnoses of UC or CD by reviewing the medical, endoscopic, radiological, and histological reports. Participants with prevalent IBD at baseline, as well as participants who developed indeterminate colitis and microscopic colitis, were excluded.

2.4. Statistical analyses

The associations between dietary factors and IBD were estimated using Cox proportional hazard models to obtain hazard ratios [HRs] and 95% confidence intervals [CI]. Age was used as time scale, with exit time as age at diagnosis of IBD, at death, or at censoring date. Graphs based on Schœnfeld residuals were used to assess the assumption of proportional hazards. We considered total protein, animal protein, and vegetable protein intakes. Food sources of animal protein were meat [total meat, red meat, and processed meat], eggs, dairy products, and fish [fish and shellfish]. Model 1 was stratified by centre, age at baseline [1-year interval], and sex; it was adjusted for smoking status [never, former, or current smoker] and energy, without alcohol according to the partition method.[14] In the partition method, energy from carbohydrates, from lipids, and from proteins are considered as three separate mutually adjusted variables. When analysing total protein intake, adjustment was made with non-protein energy [addition of carbohydrates and lipids]. When analysing subtypes of proteins [animal or vegetable] or food sources of animal proteins, covariates were mutually adjusted, and non-protein energy was added as a covariate in the Cox model. Model 2 was further adjusted for educational level [primary school, secondary school, university degree, not specified/missing], physical activity [active, moderately active, moderately inactive, inactive, missing/unknown], and BMI [continuous variable].

For clarity, we display the results of Model 2 in the text, except when there were differences with Model 1. All results are available in the tables.

Daily dietary intakes of macronutrients were analysed as quartiles of consumption. The thresholds of quartiles were calculated separately for women and men. Linear trends were tested by building-up semi-continuous variables considering the median value for each category of the studied variables. Potential interactions with smoking status, physical activity, body mass index, and educational level were investigated.

Analyses were performed separately for CD and UC risks. To assess potential reverse causality due to delayed IBD diagnosis, a sensitivity analysis was performed by excluding the first 2 years of follow-up.

2.5. Calibration of dietary data

A calibration study was conducted within a sample of 36 034 men and women [about 8% of the cohort], using a computerised 24-h dietary recall method [EPIC-Soft]. Calibration corrected errors of measures related to each country-specific questionnaire, in order to reduce bias in

Table 1. Characteristics of the cohort.

Country	Cohort size [*n*]	CD cases [*n*]	UC cases [*n*]	Mean age at recruitment [years	Recruitment period range [year]	Mean follow-up [years	Male [%]	Total energy intake [kcal/day	Total protein intake [g/day	Animal protein [g/day	Vegetable protein [g/day
All	413 593	177	418	52.5 [8.6]	1991–2001	16.8 [3.7]	31.42	2103.1 [618.8]	87.2 [27.7]	52.2 [23.0]	26.9 [10.6]
France	72 987	29	39	52.9 [6.7]	1993–1997	18.8 [2.7]	0	2151.6 [576.2]	94.1 [27.2]	59.2 [22.1]	26.6 [10.1]
Italy	29 108	7	29	50.2 [7.8]	1992–1998	15.7 [2.8]	40.84	2331.8 [688.6]	97.1 [29.2]	58.4 [21.6]	31.2 [12.3]
Spain	32 247	20	30	49.5 [8.0]	1992–1996	17.8 [2.6]	38.14	2163.8 [680.0]	102.9 [31.5]	66.4 [23.9]	30.7 [12.4]
UK	80 493	22	61	49.8 [14.4]	1993–2001	16.0 [3.4]	29.83	1985.0 [557.3]	80.5 [24.3]	40.2 [21.7]	30.7 [12.4]
The Netherlands	38 195	18	43	49.3 [11.9]	1993–1997	16.2 [2.9]	25.58	2047.9 [590.8]	86.7 [23.9]	52.8 [17.9]	26.2 [8.7]
Germany	52 011	20	42	50.4 [8.6]	1994–1998	13.6 [3.5]	43.02	2050.2 [643.8]	76.1 [24.9]	39.6 [17.0]	22.1 [7.4]
Sweden	52 736	31	63	52.4 [10.8]	1991-1996–	17.9 [4.2]	43.65	2039.4 [642.1]	76.6 [24.8]	48.3 [19.3]	21.6 [8.1]
Denmark	55 816	30	111	56.7 [4.4]	1993–1997	16.1 [3.3]	47.61	2202.4 [596.2]	94.6 [26.9]	63.9 [22.2]	27.0 [7.6]

All values are means ± SDs [standard deviations] unless otherwise indicated.
CD, Crohn's disease; UC, ulcerative colitis.

Table 2. Baseline characteristics of participants according to their total protein intake [sex-specific quartiles].

Characteristics	Total protein intake			
	Q1	Q2	Q3	Q4
Total protein intake [g/day]				
Men	<75.7	75.7-93.8	93.8-114.3	>114.3
Women	<64.3	64.3-80.2	80.2-97.7	>97.7
CD cases [*n*]	31	46	47	53
UC cases [*n*]	81	111	108	118
Age at inclusion [years]	52.0 [9.2]	53.0 [8.8]	52.9 [8.4]	51.1 [7.9]
Sex [%]				
Men	31.42	31.42	31.42	31.42
Women	68.58	68.58	68.58	68.58
Weight at inclusion [kg]	69.1 [13.4]	70.0 [13.6]	70.3 [13.8]	71.0 [14.4]
BMI at inclusion [kg/m²]	24.9 [4.1]	25.2 [4.1]	25.3 [4.2]	25.6 [4.4]
Smoking status [%]				
Never	50.35	49.24	49.14	49.82
Former	27.99	28.64	27.85	26.17
Current smoker	20.29	20.60	21.27	21.88
Unknown	1.38	1.52	1.74	2.13
Educational level [%]				
Primary school	24.95	25.64	26.68	28.65
Secondary school	42.73	43.30	43.66	42.51
Longer education	27.79	26.60	25.29	24.56
Unknown	4.53	4.46	4.38	4.27
Alcohol intake [g/day] [%]				
Non-consumer	10.59	10.94	11.12	10.97
–2.09	26.38	20.51	18.82	16.84
2.10–7.14	23.64	22.28	21.03	19.29
7.15–17.29	21.36	24.03	24.53	23.78
17.30	18.03	22.25	24.50	29.12
Physical activity [%]				
Inactive	17.89	17.60	16.86	15.84
Moderately inactive	29.98	32.40	33.49	35.26
Moderately active	30.22	35.03	35.91	35.89
Active	6.23	7.73	8.74	9.74
Missing	15.69	7.24	5.01	3.28
Total energy intake [kcal/day]	1544.2 [352.0]	1921.9 [381.0]	2211.9 [428.4]	2734.3 [568.8]
Animal protein intake [g/day]	28.8 [10.7]	44.0 [10.7]	56.8 [11.7]	79.0 [20.1]
Vegetable protein intake [g/day]	20.8 [8.1]	24.7 [8.5]	27.9 [9.0]	34.3 [11.5]
Total meat intake [g/day]	53.1 [36.3]	84.3 [43.3]	110.6 [48.4]	154.8 [67.8]
Red meat intake [g/day]	19.9 [19.7]	36.1 [27.3]	50.0 [32.7]	68.5 [44.5]
Processed meat intake [g/day]	21.5 [21.0]	29.2 [26.3]	34.7 [29.9]	46.6 [40.1]
Poultry intake [g/day]	8.5 [10.4]	15.0 [15.1]	20.9 [18.4]	30.4 [25.9]
Fish and shellfish intake [g/day]	18.1 [17.3]	28.2 [22.8]	36.0 [27.7]	49.9 [39.7]
Eggs intake [g/day]	10.6 [11.4]	15.8 [14.3]	19.8 [17.0]	26.9 [22.6]
Milk and dairy products intake [g/day]	235.0 [164.4]	316.2 [197.4]	374.8 [228.7]	459.6 [303.7]

All values are means ± standard deviations [SDs] unless otherwise indicated.
CD, Crohn's disease; UC, ulcerative colitis; BMI, body mass index.

the estimation of relative risks.[15,16] For each macronutrient, the 24-h recall data were regressed on the questionnaire data, controlling for age at recruitment, centre, sex, smoking status, and total energy intake without alcohol. Data were weighted by the day of the week and the season of the year in which the 24-h dietary recall was collected. Zero consumption values in the main dietary questionnaires were excluded in the calibration models

Table 3. Baseline characteristics of cases and non-cases.

	UC [*n* = 418]	CD [*n* = 177]	Non-cases [*n* = 412 998]
Age at inclusion [years]	53.1 [8.3]	51.8 [8.3]	52.5 [8.6]
Gender [%]			
Men	45.69	28.81	31.40
Women	54.31	71.19	68.60
Weight at inclusion [kg]	72.9 [13.7]	70.9 [13.8]	70.1 [13.8]
BMI at inclusion [kg/m²]	25.7 [4.1]	25.4 [4.3]	25.2 [4.2]
Smoking status [%]			
Never	28.47	40.68	49.66
Former	36.36	21.47	27.66
Current smoker	33.97	36.72	20.99
Unknown	1.20	1.13	1.69
Educational level [%]			
Primary school	34.93	27.68	26.47
Secondary school	44.02	49.72	43.05
Longer education	18.90	20.90	26.07
Unknown	2.15	1.69	4.41
Alcohol intake [g/day] [%]			
Non-consumer	9.81	12.99	10.91
–2.09	19.62	22.60	20.64
2.10–7.14	17.94	24.86	21.56
7.15–17.30	27.75	20.90	23.42
17.31	24.88	18.64	23.47
Physical activity [%]			
Inactive	20.33	19.77	17.04
Moderately inactive	29.43	30.51	32.78
Moderately active	36.36	32.20	34.26
Active	7.42	10.17	8.11
Missing	6.46	7.34	7.81
Total energy intake [kcal/day]	2234.6 [663.1]	2173.1 [609.9]	2102.9 [618.7]
Total protein intake [g/day]	92.2 [28.8]	91.4 [29.6]	87.2 [27.7]
Animal protein intake [g/day]	56.9 [23.5]	57.3 [25.9]	52.2 [23.0]
Vegetable protein intake [g/day]	27.7 [10.3]	26.1 [8.8]	26.9 [10.6]
Total meat intake [g/day]	120.3 [65.7]	116.6 [65.0]	100.7 [62.6]
Red meat [g/day]	55.7 [39.6]	49.5 [38.0]	43.9 [37.1]
Processed meat intake [g/day]	39.5 [37.8]	38.7 [33.3]	33.0 [31.5]
Poultry intake [g/day]	20.0 [18.9]	21.9 [23.2]	18.7 [20.0]
Fish and shellfish intake [g/day]	34.6 [27.3]	35.9 [35.2]	33.1 [30.4]
Eggs intake [g/day]	20.4 [20.6]	19.0 [16.7]	18.3 [17.9]
Milk and dairy products intake [g/day]	337.8 [239.3]	357.3 [262.8]	346.4 [243.7]

All values are means ± standard deviations [SDs] unless otherwise indicated.
CD, Crohn's disease; UC, ulcerative colitis; BMI, body mass index.

and a zero was directly imputed as a corrected value. Calibrated dietary data were obtained from country and sex-specific calibration models for all participants. The associations between calibrated dietary data [continuous scale] and IBD were then estimated using Cox proportional hazard models. The standard error of the calibrated coefficient was estimated using bootstrap sampling [10 loops].

Statistical analyses were conducted using SAS, version 9.4, software [SAS Institute, Cary, NC]; p-values <0.05 were considered statistically significant.

2.6. Ethics

This study was approved by IARC ethics committee [IEC] under IEC project number 18-08.

3. Results

3.1. Description of the cohort

Characteristics of participants are shown in Tables 1–3. In total, 413 593 participants were included, with a mean follow-up duration of 16.8 years and a total follow-up of 6 961 118.6 person-years. Women accounted for 69% of the

Table 4. Association between protein intakes and risks of CD and UC in the EPIC-IBD cohort [*n* = 413 593]: hazard ratios and 95% confidence intervals.

	UC					
	Case	Model 1	Model 2	Case	Model 1	Model 2
Total protein intake [g/day]						
Q1 [M: 0-76, F: 0-65]	31	1	1	81	1	1
Q2 [M: 76-94, F: 65-80]	46	1.38 [0.84-2.23]	1.37 [0.83-2.25]	111	1.20 [0.87-1.64]	1.20 [0.87-1.65]
Q3 [M:94-114, F: 80-98]	47	1.34 [0.77-2.33]	1.31 [0.75-2.29]	108	1.08 [0.75-1.54]	1.08 [0.76-1.55]
Q4 [M >114, F >98]	53	1.48 [0.79-2.78]	1.43 [0.76-2.70]	118	1.18 [0.78-1.77]	1.18 [0.78-1.78]
p-trend		0.32	0.38		0.58	0.57
Observed continuous [10 g/day]		1.03 [0.94-1.13]	1.03 [0.94-1.13]		1.00 [0.95-1.07]	1.00 [0.95-1.07]
Calibrated continuous [10 g/day]		1.13 [0.92-1.39]	1.11 [0.91-1.35]		1.02 [0.89-1.16]	1.05 [0.93-1.19]
Animal protein intake[g/day]						
Q1 [M: 0-41, F: 0-34]	33	1	1	79	1	1
Q2 [M: 41-56, F: 34-48]	42	0.97 [0.59-1.58]	0.96 [0.59-1.56]	107	1.03 [0.75-1.41]	1.03 [0.75-1.41]
Q3 [M: 56-73, F: 48-62]	48	1.02 [0.61-1.70]	1.00 [0.60-1.67]	115	1.01 [0.73-1.42]	1.01 [0.72-1.40]
Q4 [M >73, F 62]	54	1.08 [0.62-1.88]	1.05 [0.60-1.83]	117	0.97 [0.67-1.39]	0.96 [0.67-1.39]
p-trend		0.61	0.70		0.72	0.69
Observed continuous [10 g/day]		1.04 [0.95-1.14]	1.04 [0.95-1.14]		1.01 [0.95-1.07]	1.01 [0.95-1.07]
Calibrated continuous [10 g/day]		1.14 [0.93-1.40]	1.12 [0.92-1.36]		1.06 [0.93-1.21]	1.08 [0.96-1.23]
Vegetable protein intake[g/day]						
Q1 [M: 0-22, F: 0-19]	43	1	1	98	1	1
Q2 [M: 22-28, F: 19-24]	39	0.89 [0.56-1.41]	0.89 [0.56-1.41]	111	1.05 [0.78-1.40]	1.06 [0.79-1.42]
Q3 [M: 28-36, F: 24-30]	59	1.28 [0.80-2.07]	1.29 [0.80-2.07]	98	0.90 [0.64-1.26]	0.92 [0.66-1.28]
Q4 [M >36, F >30]	36	0.81 [0.45-1.45]	0.81 [0.45-1.47]	111	1.14 [0.78-1.66]	1.18 [0.80-1.72]
p-trend		0.64	0.67		0.61	0.49
Observed continuous [10 g/day]		0.95 [0.74-1.21]	0.95 [0.74-1.21]		0.97 [0.83-1.13]	0.98 [0.84-1.14]
Calibrated continuous [10 g/day]		1.00 [0.59-1.71]	0.97 [0.58-1.62]		0.87 [0.63-1.18]	0.88 [0.66-1.18]

Model 1: stratification by centre, age at baseline and sex, and adjustment for smoking status and energy without alcohol [according to the partition method]. Model 2: additional adjustment for educational level, physical activity and body mass index [BMI].
M, male; F, female; CD, Crohn's disease; UC, ulcerative colitis.

studied population. The mean age at recruitment was 52.5 years. Mean protein intake was 87.2 g/day. The highest mean protein intake was seen in Spain and the lowest in Germany. Mean [SD] total meat intakes within the first and the fourth quartile of total protein intake were of 53.1 [36.3] g/day and 154.8 [67.8] g/day, respectively. These values were 19.9 [19.7] and 68.5 [44.5] for red meat intake. Participants in the highest quartile of protein intake were younger and reported higher physical exercise, energy intake, animal and vegetable protein intakes, and higher consumption of food sources of animal proteins.

In total, 177 incident CD cases and 418 incident UC cases were identified. The estimated annual incidence rates for CD and UC were 2.5 and 6.0 per 100 000 person-years, respectively. Participants with CD were more often active smokers [37%] than non-cases [21%], and UC patients were more often former or current smokers than non-cases.

3.2. Protein intake

There was no association between total protein, animal, or vegetable protein intakes and CD or UC risks [Table 4].

There was no evidence of interaction of the following factors with the association between protein intake and CD or UC risk: BMI [*p*-interaction = 0.15 and 0.53, respectively], smoking status [*p*-interaction = 0.48 and 0.30, respectively], physical activity [*p*-interaction = 0.94 and 0.25, respectively], and educational level [*p*-interaction = 0.90 and 0.45, respectively].

3.3. Sources of protein

UC risk was associated with total meat consumption for the calibrated variable [HR per 10-g/day increment: 1.05, 95% CI 1.006-1.09] with a significant trend [*p*-trend = 0.01] and an association for extreme quartiles [HR for the 4th vs 1st quartile: 1.40, 95% CI 0.99-1.98; Table 5] that reached statistical significance in model 1 [HR for the 4th vs 1st quartile: 1.45, 95% CI 1.03-2.04, *p*-trend = 0.007].

Consumption of red meat was associated with UC risk for the extreme quartiles [HR for the 4th vs 1st quartile: 1.61, 95% CI 1.10-2.36, *p*-trend = 0.007] and numerically associated for the calibrated variable [HR per 10-g/day increment: 1.04, 95% CI 0.99-1.10]. There was no association between other food sources of animal protein [processed meat, fish, shellfish, eggs, poultry] and UC.

No association with any food source of animal proteins or any type of meat was detected with CD, although associations were of the same order of magnitude as for UC for several foods.

3.4. Sensitivity analysis

In the sensitivity analysis in which participants who developed UC or CD within 2 years of follow-up were excluded,

Table 5. Association between sources of animal proteins and risk of CD and UC in the EPIC-IBD cohort [*n* = 413 593]: hazard ratios and 95% confidence intervals.

	CD			UC		
	Case	**Model 1**	**Model 2**	**Case**	**Model 1**	**Model 2**
Total meat intake [g/day]						
Q1 [M: 0-79, F: 0-52]	31	1	1	72	1	1
Q2 [M: 79-120, F: 52-86]	30	0.80 [0.47-1.36]	0.79 [0.47-1.35]	87	0.97 [0.70-1.36]	0.96 [0.68-1.34]
Q3 [M: 120-166, F: 86-121]	59	1.49 [0.91-2.41]	1.47 [0.90-2.39]	120	1.27 [0.91-1.76]	1.23 [0.88-1.72]
Q4 [M >166, F >121]	57	1.31 [0.78-2.19]	1.28 [0.76-2.16]	139	1.45 [1.03-2.04]	1.40 [0.99-1.98]
p-trend		0.10	0.11		0.007	0.01
Observed continuous [10 g/day]		1.02 [0.99-1.05]	1.02 [0.995-1.05]		1.02 [1.003-1.04]	1.02 [1.001-1.04]
Calibrated continuous [10 g/day]		1.05 [0.996-1.12]	1.05 [0.99-1.11]		1.05 [1.01-1.09]	1.05 [1.006-1.09]
Red meat intake [g/day]						
Q1 [M: 0-21, F: 0-12]	38	1	1	67	1	1
Q2 [M: 21-46, F: 12-33]	34	0.70 [0.42-1.16]	0.69 [0.42-1.15]	89	1.14 [0.80-1.62]	1.13 [0.80-1.61]
Q3 [M: 46-80, F: 33-59]	47	0.92 [0.55-1.52]	0.91 [0.55-1.51]	112	1.30 [0.90-1.87]	1.28 [0.89-1.85]
Q4 [M >80, F >59]	58	1.08 [0.64-1.85]	1.08 [0.63-1.84]	150	1.63 [1.12-2.39]	1.61 [1.10-2.36]
p-trend		0.36	0.37		0.006	0.007
Observed continuous [10 g/day]		1.02 [0.97-1.06]	1.02 [0.97-1.06]		1.03 [0.999-1.06]	1.03 [0.997-1.06]
Calibrated continuous [10 g/day]		1.04 [0.95-1.14]	1.04 [0.96-1.13]		1.05 [0.98-1.12]	1.04 [0.99-1.10]
Processed meat intake [g/d]ay						
Q1 [M: 0-19, F: 0-10]	32	1	1	83	1	1
Q2 [M: 19-36, F: 10-21]	43	1.06 [0.65-1.72]	1.05 [0.65-1.71]	112	1.11 [0.82-1.51]	1.10 [0.81-1.49]
Q3 [M: 36-61, F: 21-38]	46	1.08 [0.66-1.77]	1.08 [0.66-1.76]	102	1.00 [0.73-1.37]	0.97 [0.71-1.34]
Q4 [M >61, F >38]	56	1.19 [0.72-1.99]	1.19 [0.71-1.98]	121	1.22 [0.88-1.71]	1.18 [0.84-1.65]
p-trend		0.38	0.39		0.19	0.29
Observed continuous [10 g/day]		1.02 [0.97-1.07]	1.02 [0.97-1.07]		1.03 [0.99-1.06]	1.02 [0.99-1.06]
Calibrated continuous [10 g/day]		1.04 [0.91-1.18]	1.03 [0.91-1.17]		1.06 [0.99-1.14]	1.04 [0.97-1.12]
Fish/shellfish intake [g/day]						
Q1 [M: 0-14, F: 0-12]	48	1	1	96	1	1
Q2 [M: 14-28, F: 12-25]	41	0.78 [0.51-1.21]	0.78 [0.50-1.21]	89	0.86 [0.64-1.17]	0.87 [0.64-1.18]
Q3 [M: 28-49, F: 25-43]	31	0.53 [0.32-0.87]	*0.52 [0.31-0.87]*	120	1.05 [0.77-1.44]	1.07 [0.79-1.46]
Q4 [M >49, F >43]	56	0.89 [0.55-1.42]	0.87 [0.54-1.40]	113	0.92 [0.67-1.29]	0.95 [0.68-1.32]
p-trend		0.96	0.90		0.77	0.88
Observed continuous [10 g/day]		1.01 [0.95-1.06]	1.01 [0.95-1.06]		0.99 [0.95-1.02]	0.99 [0.95-1.03]
Calibrated continuous [10 g/day]		1.06 [0.94-1.19]	1.03 [0.93-1.15]		0.93 [0.86-1.02]	0.96 [0.89-1.02]
Egg intake[g/day]						
Q1 [M: 0-6, F: 0-7]	37	1	1	85	1	1
Q2 [M: 6-14, F: 7-14]	43	1.10 [0.68-1.78]	1.10 [0.68-1.78]	94	0.90 [0.65-1.24]	0.90 [0.65-1.24]
Q3 [M: 14-24, F: 14-24]	45	1.13 [0.70-1.85]	1.13 [0.70-1.85]	124	1.14 [0.84-1.56]	1.14 [0.84-1.56]
Q4 [M >24, F >24]	50	1.08 [0.65-1.79]	1.07 [0.65-1.78]	113	0.94 [0.67-1.31]	0.93 [0.67-1.30]
p-trend		0.96	0.99		0.95	0.98
Observed continuous [10 g/day]		0.96 [0.87-1.06]	0.96 [0.87-1.06]		1.02 [0.97-1.08]	1.02 [0.97-1.08]
Calibrated continuous[10 g/day]		0.95 [0.75-1.20]	0.93 [0.75-1.16]		1.04 [0.90-1.19]	1.05 [0.91-1.22]
Dairy products intake [g/day]						
Q1 [M: 0-150, F: 0-184]	52	1	1	106	1	1
Q2 [M: 150-290, F: 184-305]	39	0.75 [0.49-1.14]	0.75 [0.49-1.14]	98	0.94 [0.71-1.24]	0.95 [0.71-1.25]
Q3 [M: 290-492, F: 305-462]	34	0.63 [0.40-1.00]	0.63 [0.40-1.00]	115	1.12 [0.85-1.49]	1.13 [0.86-1.51]
Q4 [M >492, F >462]	52	0.85 [0.55-1.31]	0.84 [0.54-1.30]	99	0.87 [0.64-1.18]	0.88 [0.65-1.19]
p-trend		0.54	0.53		0.43	0.46
Observed continuous [10 g/day]		1.00 [0.99-1.01]	1.00 [0.99-1.01]		1.00 [0.99-1.00]	1.00 [0.99-1.00]
Calibrated continuous [10 g/day]		1.00 [0.99-1.01]	1.00 [0.99-1.01]		0.99 [0.99-1.00]	0.99 [0.99-1.001]
Poultry intake [g/d]						
Q1 [M: 0-7, F: 0-4]	33	1	1	97	1	1
Q2 [M: 7-15, F: 4-13]	50	1.39 [0.86-2.26]	1.69 [0.86-2.26]	96	0.81 [0.59-1.10]	0.82 [0.60-1.12]

Table 5. Continued

	CD			UC		
	Case	Model 1	Model 2	Case	Model 1	Model 2
Q3 [M: 15-28, F: 13-25]	39	1.07 [0.64-1.79]	1.06 [0.64-1.78]	114	0.91 [0.67-1.23]	0.92 [0.68-1.25]
Q4 [M >28, F >25]	55	1.44 [0.88-2.37]	1.42 [0.87-2.34]	111	0.91 [0.67-1.25]	0.92 [0.67-1.26]
p-trend		0.30	0.33		0.98	0.99
Observed continuous [10 g/day]		1.05 [0.98-1.11]	1.05 [0.98-1.12]		1.01 [0.96-1.05]	1.01 [0.96-1.06]
Calibrated continuous [10 g/day]		1.05 [0.90-1.22]	1.02 [0.89-1.18]		1.00 [0.91-1.10]	1.01 [0.92-1.11]

Model 1: stratification by centre, age at baseline and sex, and adjustment for smoking status and energy without alcohol [according to the partition method]. Model 2: additional adjustment for educational level, physical activity and body mass index [BMI].
M, male; F, female; CD, Crohn's disease; UC, ulcerative colitis.

associations between protein intakes and UC or CD risks were similar to those in the entire cohort [Supplementary Tables 1 and 2].

4. Discussion

In this prospective European study based upon 595 incident cases of IBD, we found that consumptions of meat and red meat were associated with the risk of UC, but not CD. Other sources of dietary proteins such as fish, eggs, and dairy products were associated with neither UC nor CD risks. Results were consistent between quartiles of intake and calibrated data. Cases of UC and CD emerged among 413 593 participants included in eight European countries, during a mean follow-up of 16.8 years. Each country used its own validated FFQ. We used calibration to correct for discrepancies and potential errors of measures due to country-specific questionnaires.

This study adds further evidence for the association between Western diet and UC risk. Two studies have previously investigated the association between protein intake and risk of UC. The Nurses' Health Study has found that higher dietary intakes of red meat were associated with a higher risk of UC which did not reach statistical significance.[8] The French E3N prospective study, which is part of the EPIC cohort, found a positive association between animal protein intake and the risk of UC in 77 incident cases within a cohort of 67581 women.[9]

Several hypotheses might explain the association between red meat consumption and the higher risk of UC. Previous investigations based on the EPIC and the Nurses' Health Study have found that high intakes of n-6 polyunsaturated fatty acids and low intakes of n-3 polyunsaturated fatty acids were associated with an higher risk of UC.[2,17,18] High meat consumption might also increase UC risk through accrued formation of end products by the colonic microbiota. A fraction of haem and amino acids, contained in meat, reach the colonic lumen, where they are metabolised by the microbiota into end products that are potentially toxic to the colon, such as hydrogen sulphide, phenolic compounds, amines, ammonia, phenols, and cresols. Additionally, the role of the gut microbiome in diet-associated IBD risk is under investigation. Recent studies have shown that animal protein intake was associated with bacteria that are dominant in the upper gastrointestinal [GI] tract and oral cavity[19] and reduced α-diversity,[20] both of which have been reported in UC,[21,22] although reduced α-diversity is more common in CD than in UC.[22] Further studies are needed to understand the mechanisms of the association between IBD risk and meat consumption.

The association between red meat and UC is in line with temporal trends of IBD incidence. During the past 50 years, meat consumption has increased dramatically in China and Brazil in parallel with the rising incidence of IBD. By contrast, meat consumption is relatively stable in Western Europe and North America, geographical areas in which UC incidence has stabilised [https://ourworldindata.org/meat-production#which-countries-eat-the-most-meat].

Our study supports dietary counselling toward a low intake of red meat in persons at risk for IBD, such as first-degree relatives of IBD patients. This study also supports the setting of a randomised trial of low vs high or standard meat intake in patients with UC.

Our study has several strengths. First, its prospective design avoided recall bias. Second, dietary questionnaires were validated and allowed the assessment of a large range of macronutrient intakes between subjects. Indeed, when comparing the levels of macronutrients in the EPIC country-specific cohorts, we noticed that the level of some nutrients was nearly one-third higher in some countries [France, Italy] as compared with others [UK, Germany]. Third, the cohort design minimised selection biases. We were able to adjust for important confounders such as smoking, country of residence, and educational level [a proxy for socioeconomic status]. Fourth, we used calibrated data. Fifth, IBD cases only included physician-confirmed CD or UC cases. The associations were also found in participants diagnosed more than 24 months after the dietary questionnaire; this does not support reverse causation.

Our study has also some limitations. First, diet was measured once at baseline, although it might change over time. There is an updating process at present in EPIC. However, it has been demonstrated that, by and large, the dietary habits are stable over time, especially in middle-aged populations with strong dietary habits, like most European populations. Furthermore, considering changes in dietary habits also have limitations since changes may be dictated by first symptoms of a disease and, when changes are independent of the disease, they are non-differential and only reduce the study power but cannot bring forth significant associations.[23] Our study is restricted to relatively late-onset IBD, and our results may thus not apply to early-onset disease. Participants included in the EPIC study [volunteers, among whom about 65% were women of middle age] might not be representative of

dietary habits of the overall European populations. Finally, as in all observational studies, we cannot rule out residual confounding from unmeasured factors.

In conclusion, this study substantiates the association between meat and red meat consumption and risk of UC. These results support dietary counselling toward low meat intake in people at high risk of UC.

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Conflict of Interest

AR has received grants from Abbvie, Biogen, Ferring, MSD, Pfizer, Takeda, and Tillots. BO has benefited from grants from Takeda, Pfizer, Ferring, and Celltrion and participated in the advisory boards of Takeda, BMS, Galapagos, Janssen, and Cosmofer. OG has served as a speaker, a consultant and an advisory board member for Ferring, Janssen, Pfizer, and Takeda. SMC has benefited from travel grants from Abbvie and Takeda. FC received speaker fees from Abbvie, Biogen, Ferring, Janssen, MSD, Pfizer, Pileje, and Takeda and participated in the advisory boards of Amgen, Arena, Celltrion, Enterome, Ferring, Janssen, Medtronic, Pfizer, Pharmacosmos, Roche, and Tillotts. M-CB-R received a speaker fee from Mayoli-Spindler and from Gilead. Other authors declare no competing interest. Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy, or views of the International Agency for Research on Cancer/World Health Organization.

Author Contributions

CD: formal analysis, writing original draft, writing review and editing. SSMC: data curation, writing review and editing. PJ: concept, formal analysis, writing original draft. AR: concept, formal analysis, writing original draft. BO, EW, AKH, TYT, AT, CK, BBM, RK, VAK, MMB, HB, DP, GM, RT, CS, SMC-Y, M-JS, OG, SL, RL, IH, MJG: data curation, resources, writing review and editing. YM-S: formal analysis, data curation, writing review and editing. FC: concept, writing original draft, writing review and editing. M-CB-R: concept, writing original draft, writing review and editing.

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Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

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