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# Dietary index based on the Food Standards Agency nutrient profiling system and risk of Crohn's disease and ulcerative colitis

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## Summary

**Background:** Nutri-score is now widely available in food packages in Europe.

**Aim:** To study the overall nutritional quality of the diet in relation to risks of Crohn's disease (CD) and ulcerative colitis (UC), in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort

**Methods:** We collected dietary data at baseline from validated food frequency questionnaires. We used a dietary index based on the UK Food Standards Agency modified nutrient profiling system (FSAm-NPS-DI) underlying the Nutri-Score label, to measure the nutritional quality of the diet. We estimated the association between FSAm-NPS-DI score, and CD and UC risks using Cox models stratified by centre, sex and age; and adjusted for smoking status, BMI, physical activity, energy intake, educational level and alcohol intake.

**Results:** We included 394,255 participants (68.1% women; mean age at recruitment 52.1 years). After a mean follow-up of 13.6 years, there were 184 incident cases of CD and 459 incident cases of UC. Risk of CD was higher in those with a lower nutritional quality, that is higher FSAm-NPS-DI Score (fourth vs. first

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quartile: aHR: 2.04, 95% CI: 1.24–3.36; *p*-trend: <0.01). Among items of the FSAm-NPS-DI Score, low intakes of dietary fibre and fruits/vegetables/legumes/nuts were associated with higher risk of CD. Nutritional quality was not associated with risk of UC (fourth vs. first quartile of the FSAm-NPS-DI Score: aHR: 0.91, 95% CI: 0.69–1.21; *p*-trend: 0.76).

**Conclusions:** A diet with low nutritional quality as measured by the FSAm-NPS-DI Score is associated with a higher risk of CD but not UC.

## 1 | INTRODUCTION

Growing evidence supports the association between diet composition and the risk of developing inflammatory bowel disease (IBD). Several studies, based on large prospective cohorts of healthy participants have investigated the association between nutrients or foods, and the risk of IBD.<sup>1–5</sup> Investigation of food patterns rather than single nutrients or foods is a more holistic approach. Recent studies have found associations between adherence to a Mediterranean diet,<sup>6</sup> consumption of ultra-processed<sup>7</sup> or proinflammatory foods,<sup>8</sup> and the risk of Crohn's disease (CD). In contrast, consumption of unprocessed/minimally processed foods is associated with a lower risk of CD.<sup>7</sup> However, these food patterns do not measure the global nutritional quality of the diet. For instance, foods rich in saturated fat, sugars or sodium have low nutritional quality but can be included in any category of the NOVA classification of food processing.

The Nutri-Score is a front-of-pack label which provides user-friendly information on the nutritional quality of foods. It was developed as a complement to food-based dietary guidelines, to help people adhere to the recommendations aiming to promote limited intake of energy, saturated fats, added sugars and sodium, and high intakes of dietary fibre and protein, as well as consumption of vegetables, legumes, fruit and nuts. The Nutri-Score classifies the nutritional quality of food products into five categories (from category A, indicating higher nutritional quality, to category E, indicating lower nutritional quality) according to the UK Food Standards Agency modified nutrient profiling system (FSAm-NPS).<sup>9</sup> The FSAm-NPS Dietary Index (DI) summarises the mean food composition of an individual's diet. Diets with lower FSAm-NPS DI scores (representing higher nutritional quality) are associated with reduced risks of asthma, weight gain, metabolic

syndrome, cardiovascular disease, cancers, all-cause mortality and mortality from cancer, as well as from diseases of the circulatory, respiratory and digestive systems.<sup>10,11</sup>

In this study, we aimed to investigate the association between the FSAm-NPS DI Score and risks of CD and UC using data from the European Prospective Investigation into Cancer and Nutrition (EPIC), a large prospective cohort of healthy volunteers, which uses a validated assessment of food intake.

## 2 | METHODS

### 2.1 | 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, Greece, Italy, the Netherlands, Norway, Spain, Sweden and the United Kingdom).<sup>12</sup> 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 without IBD from eight European countries within the EPIC cohort (namely Denmark, France, Germany, Italy, the Netherlands, Spain, Sweden and the United Kingdom).

## 2.2 | 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.<sup>13</sup> Participants who did not complete 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.

## 2.3 | FSAm-NPS DI score computation

The FSAm-NPS score (food level score) was computed based on the nutrient content for 100 g of foods or beverages (with the exception of alcoholic beverages that are beyond the scope of the nutrient profile). Up to 10 points were allocated for each nutrient that should be eaten in limited quantities, that is sugars (g), saturated fatty acids (g), sodium (mg), and energy (kJ) and up to 5 points were allocated for each nutrient that is recommended, that is dietary fibre (g) and protein (g) and for the proportion of vegetables, legumes, fruit and nuts (%) in the food. To obtain the FSAm-NPS score, the sum of points for nutrients that are recommended is then subtracted from the sum of points for nutrients that should be eaten in limited quantities. Therefore, the FSAm-NPS score for each food or beverage is based on a continuous scale ranging from –15 points (highest nutritional quality) to 40 points (lowest nutritional quality). Cut-offs are then applied to the FSAm-NPS score to derive the Nutri-Score. It should be noted that sodium intake has an incomplete reliability as it has not been initially recorded. The FSAm-NPS is a modified version of the original FSA-NPS initially developed by the British Food Standards Agency, with slight adaptations to the allocation of points for specific foods (beverages, cheese and added fats) recommended by the French High Council for Public Health to ensure a proper discrimination of the nutritional quality of products within these groups and a high consistency of the FSAm-NPS score with dietary guidelines (see Appendix S1).

In a second step, the FSAm-NPS DI score was computed to characterise the nutritional quality of an individual's diet (individual level score). The FSAm-NPS DI score was obtained as the sum of FSAm-NPS scores for each consumed food or beverage multiplied by the amount of energy provided by this product, and divided by the total energy intake with the exception of alcoholic beverages.<sup>14</sup> A higher FSAm-NPS DI score reflects an overall lower nutritional quality of the diet. Details on the FSAm-NPS DI score have been described elsewhere and are available in Appendix S1.

## 2.4 | 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 who developed indeterminate colitis or microscopic colitis were censored.

## 2.5 | Assessment of other variables

At baseline, standardised 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<sup>2</sup> from the participants' weights and heights 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 questionnaires were excluded.

## 2.6 | Statistical analysis

Associations between the FSAm-NPS DI Score and risks of CD/UC were estimated using Cox proportional hazards models to obtain Hazard Ratios (HR) and 95% confidence intervals (95% CI). Sex-specific quartiles of the FSAm-NPS DI Score were used, the lowest quartile (i.e. higher nutritional quality of the diet) serving as the reference category. Age was used as time scale, with 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 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/m<sup>2</sup>), physical activity (active, moderately active, moderately inactive, inactive), educational level (primary school, secondary school, university degree), energy intake except alcohol (quartiles) and alcohol intake at recruitment (quartiles). Linear trends were tested by using the median value for each category of the studied variables. The assumption of proportional hazards was assessed and confirmed using graphs based on the Schoenfeld residuals and Kolmogorov-type supremum tests. 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 FSAm-NPS DI 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 FSAm-NPS DI Score: total energy intake, sugars, saturated fatty acids, total protein intake, dietary fibre and fruits/vegetables/legumes/nuts. Sensitivity analyses were performed: to assess potential reverse causality due to delayed IBD diagnosis by excluding the first 2 years of follow-up, and to assess misreporting of energy intake by excluding participants with implausible energy intake based on their basal metabolic rate and physical activity level (Goldberg method).<sup>15,16</sup> We also conducted an additional analysis based on macronutrient categories (fat, protein, carbohydrates) to compare

it to the analysis based on the FSAm-NPS DI Score on the risk of CD and UC.

All tests were two-tailed with a limit of significance of  $p < 0.05$ . Analyses were performed with SAS<sup>®</sup> 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 8 European countries with different legal frameworks. Information on submitting applications to access the EPIC data can be made to <https://epic.iarc.fr/access>.

**TABLE 1** Baseline characteristics of participants according to sex-specific quartiles of FSAm-NPS DI Score.

	All	Sex-specific quartiles of FSAm-NPS DI score <sup>a</sup>			
		Quartile 1	Quartile 2	Quartile 3	Quartile 4
Number of participant, <i>n</i>	394,255	98,563	98,564	98,564	98,564
Person-years, <i>n</i>	4,889,910	1,181,244	1,223,999	1,242,074	1,242,592
FSAm-NPS DI Score <sup>a</sup> , mean (SD)	6.1 (2.1)	3.4 (1.1)	5.5 (0.4)	6.8 (0.4)	8.7 (1.1)
Male	6.2 (2.1)	3.5 (1.1)	5.6 (0.4)	6.9 (0.4)	8.9 (1.1)
Female	6.1 (2.1)	3.4 (1.1)	5.4 (0.4)	6.8 (0.4)	8.7 (1.1)
Female, <i>n</i> (%)	268,599 (68.1)	67,149 (68.1)	67,150 (68.1)	67,150 (68.1)	67,150 (68.1)
Age at recruitment (years), mean (SD)	52.1 (9.6)	52.3 (9.6)	52.0 (9.7)	52.0 (9.6)	52.2 (9.6)
Body mass index at inclusion (kg/m <sup>2</sup> ), mean (SD)	25.3 (4.2)	26.0 (4.3)	25.4 (4.1)	25.0 (4.1)	24.7 (4.1)
Smoking status <sup>b</sup> , <i>n</i> (%)					
Never	194,303 (50.2)	50,899 (52.2)	48,180 (49.6)	48,167 (49.8)	47,057 (49.0)
Former	109,097 (28.2)	28,061 (28.8)	28,472 (29.3)	27,015 (27.9)	25,549 (26.6)
Current	83,985 (21.7)	18,609 (19.1)	20,488 (21.1)	21,493 (22.2)	23,395 (24.4)
Educational level <sup>b</sup> , <i>n</i> (%)					
Primary school	109,413 (28.8)	35,561 (37.6)	26,834 (28.1)	23,294 (24.5)	23,724 (25.1)
Secondary school	170,473 (44.9)	36,668 (38.8)	43,476 (45.5)	45,256 (47.5)	45,073 (47.8)
Longer education	99,865 (26.3)	22,382 (23.7)	25,151 (26.4)	26,729 (28.1)	25,603 (27.1)
Physical activity <sup>b</sup> , <i>n</i> (%)					
Inactive	79,304 (20.5)	22,189 (22.8)	18,751 (19.4)	18,285 (19.0)	20,079 (20.8)
Moderately inactive	135,012 (34.9)	32,435 (33.3)	33,759 (35.0)	34,271 (35.5)	34,547 (35.7)
Moderately active	97,112 (25.1)	22,666 (23.3)	23,965 (24.8)	25,054 (26.0)	25,427 (26.3)
Active	75,745 (19.6)	20,062 (20.6)	20,085 (20.8)	18,899 (19.6)	16,699 (17.3)
Total energy (kcal/day), mean (SD)	2111 (620)	1908 (587)	2043 (583)	2160 (590)	2335 (639)
Total carbohydrates (g/day), mean (SD)	232.7 (75.2)	224.4 (74.3)	227.8 (72.2)	233.0 (72.8)	245.4 (79.6)
Sugars (g/day), mean (SD)	106.4 (44.5)	97.0 (39.7)	101.2 (39.5)	107.1 (42.1)	120.3 (52.2)
Dietary fibres (g/day), mean (SD)	22.9 (7.8)	25.7 (8.9)	23.2 (7.5)	22.2 (7.1)	20.8 (6.8)
Total fat (g/day), mean (SD)	82.1 (29.5)	65.1 (24.3)	77.2 (24.7)	86.5 (26.3)	99.6 (31.0)
Saturated fatty acids (g/day), mean (SD)	32.3 (13.2)	22.7 (8.7)	29.8 (9.8)	34.8 (11.2)	41.9 (14.3)
Total protein (g/day), mean (SD)	87.8 (27.8)	85.7 (28.6)	87.2 (27.4)	88.6 (26.8)	89.7 (28.0)
Fruits, vegetables, legumes, nuts (g/day), mean (SD)	444.4 (260.2)	563.7 (312.6)	443.0 (240.9)	405.3 (224.8)	365.9 (206.6)
Alcohol (g/day), median [IQR]	6.6 [1.4–17.1]	4.8 [0.5–14.6]	6.5 [1.4–16.5]	7.5 [1.9–18.1]	7.7 [1.8–18.8]

Abbreviations: IQR, interquartile range; SD, standard deviation.

<sup>a</sup>FSAm-NPS DI Score: Food Standards Agency modified nutrient profiling system dietary index score. A higher score indicates a lower nutritional quality of foods consumed.

<sup>b</sup>Missing values: smoking status: 1.7%, educational level: 3.7%, physical activity: 1.8%.

### 3 | RESULTS

#### 3.1 | Study population

Among 521,323 participants of the EPIC cohort, 394,255 were included in this study (Figure S1). 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. FSAM-NPS DI Score ranged from -6.5 to 18.9 (1st percentile: 1.0 and 99th percentile: 11.0). A higher FSAM-NPS DI score reflects an overall lower nutritional quality of the diet. Mean FSAM-NPS DI Scores were 3.4 (SD: 1.1) in the first quartile, and 8.7 (1.1) in the fourth quartile. Mean sugars, saturated fatty acids and total energy intakes were 97.0g/day, 22.7g/day and 1908kcal/day in the first quartile; and 120.3g/day, 41.9g/day; and 2335 kcal/day in the fourth quartile, respectively. Among nutrients that are recommended, mean dietary fibre, vegetables/legumes/fruits/nuts and total protein intake were 25.7, 563.7 and 85.7g/day in the first quartile; and 20.8, 365.9; and

89.7g/day in the fourth quartile, respectively. 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 diagnosis of CD and UC occurred after a median of 6.0 years (IQR: 3.0–9.6) and 6.2 years (IQR: 3.3–9.8) of follow-up, respectively. Characteristics of participants per country are shown in Table S1. The highest mean FSAM-NPS DI Score was seen in France (7.1) and the lowest one in Spain (4.1). Characteristics of cases and non-cases are shown on Table S2.

#### 3.2 | FSAM-NPS DI score and risk of IBD

High FSAM-NPS DI scores (lower nutritional quality of foods consumed) were associated with an increased risk of CD but not of UC (Table 2). Compared with the first quartile, the adjusted HRs for CD were 1.55 (95% CI: 0.95–2.53) for the second, 1.66 (95% CI: 1.01–2.74) for the

TABLE 2 Association between sex-specific quartiles of FSAM-NPS DI Score and Crohn's disease or ulcerative colitis (N=394,255).

	Sex-specific quartiles of FSAM-NPS DI score <sup>a</sup>				p-trend <sup>b</sup>
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
Number of participants	98,563	98,564	98,564	98,564	
Female	67,149	67,150	67,150	67,150	
Male	31,414	31,414	31,414	31,414	
Crohn's disease					
Cases, n	29	44	48	63	
Female	20	32	33	43	
Male	9	12	15	20	
Sex, age and centre stratified Cox models, aHR (95% CI)					
Overall	1 (Ref)	1.62 (0.99–2.63)	1.79 (1.09–2.92)	2.32 (1.43–3.77)	<0.01
Multi-adjusted Cox models, aHR (95% CI) <sup>c</sup>					
Overall	1 (Ref)	1.55 (0.95–2.53)	1.66 (1.01–2.74)	2.04 (1.24–3.36)	<0.01
Female	1 (Ref)	1.54 (0.86–2.73)	1.57 (0.87–2.83)	2.01 (1.11–3.62)	0.03
Male	1 (Ref)	1.64 (0.65–4.13)	1.98 (0.78–5.01)	2.21 (0.87–5.60)	0.10
Ulcerative colitis					
Cases, n	118	96	117	128	
Female	71	59	59	60	
Male	47	37	58	68	
Sex, age and centre stratified Cox models, aHR (95% CI)					
Overall	1 (Ref)	0.80 (0.61–1.05)	0.96 (0.73–1.26)	1.03 (0.78–1.35)	0.58
Multi-adjusted Cox models, aHR (95% CI) <sup>c</sup>					
Overall	1 (Ref)	0.78 (0.59–1.03)	0.91 (0.69–1.20)	0.91 (0.69–1.21)	0.76
Female	1 (Ref)	0.82 (0.57–1.16)	0.81 (0.56–1.17)	0.76 (0.52–1.12)	0.18
Male	1 (Ref)	0.73 (0.47–1.14)	1.06 (0.69–1.61)	1.12 (0.73–1.72)	0.30

Abbreviation: aHR (95% CI), adjusted hazard ratio (95% confidence interval).

<sup>a</sup>FSAM-NPS DI Score: Food Standards Agency modified nutrient profiling system dietary index score. A higher score indicates a lower nutritional quality of foods consumed.

<sup>b</sup>p-trend was computed by modelling the median value for each quartile as a continuous variable.

<sup>c</sup>Cox models with age used as time scale, stratified for centre and sex, and adjusted for smoking status, body mass index, physical activity, educational level, total energy and alcohol.



**TABLE 3** Association between sex-specific deciles of FSAm-NPS DI Score and Crohn's disease or ulcerative colitis (N=394,255).

	Sex-specific deciles of FSAm-NPS DI score <sup>a</sup>										Continuous FSAm-NPS DI score	p-value
	Decile 1	Decile 2	Decile 3	Decile 4	Decile 5	Decile 6	Decile 7	Decile 8	Decile 9	Decile 10		
<b>Crohn's disease</b>												
Cases, n	8	12	15	13	25	13	18	28	26	26	184	
Multi-adjusted Cox model, aHR (95% CI) <sup>b</sup>	1 (Ref)	1.63 (0.66–4.03)	2.11 (0.87–5.11)	1.84 (0.74–4.58)	3.53 (1.53–8.14)	1.84 (0.73–4.63)	2.53 (1.05–6.11)	3.92 (1.69–9.11)	3.61 (1.54–8.49)	3.24 (1.37–7.67)	1.13 (1.05–1.22)	<0.01
<b>Ulcerative colitis</b>												
Cases, n	42	47	47	41	37	47	49	43	50	56	459	
Multi-adjusted Cox model, aHR (95% CI) <sup>b</sup>	1 (Ref)	1.06 (0.69–1.61)	1.06 (0.69–1.62)	0.91 (0.59–1.42)	0.82 (0.52–1.29)	1.02 (0.66–1.57)	1.04 (0.67–1.62)	0.90 (0.57–1.41)	1.01 (0.65–1.57)	1.04 (0.67–1.61)	1.00 (0.95–1.05)	0.96

Abbreviation: aHR (95% CI), adjusted hazard ratio (95% confidence interval).

<sup>a</sup>FSAm-NPS DI Score: Food Standards Agency modified nutrient profiling system dietary index score. A higher score indicates a lower nutritional quality of foods consumed.

<sup>b</sup>Cox models with age used as time scale, stratified for centre and sex, and adjusted for smoking status, body mass index, physical activity, educational level, total energy and alcohol.

third and 2.04 for the fourth quartile (95% CI: 1.24–3.36; *p*-trend: <0.01). Compared with the first quartile, the adjusted HRs for UC were 0.78 (95% CI: 0.59–1.03) for the second, 0.91 (95% CI: 0.69–1.20) for the third and 0.91 for the fourth quartile (95% CI: 0.69–1.21; *p*-trend: 0.76), respectively. Results were consistent in both sexes (Table 2).

We also divided the FSAm-NPS DI Score into sex-specific deciles. Compared with the first decile, the adjusted HRs for CD were 3.61 (95% CI: 1.54–8.49) for the ninth decile and 3.24 (95% CI: 1.37–7.67) for the tenth decile (*p*-value <0.01). Compared with the first decile, the adjusted HRs for UC were 1.01 (95% CI: 0.65–1.61) for the ninth decile, and 1.04 (95% CI: 0.67–1.61) for the tenth decile (*p*-value 0.96) (Table 3). A one-unit increase in the FSAm-NPS DI Score is associated with a 13% increase in the risk of CD (aHR: 1.13; 95% CI: 1.05–1.22) without association with the risk of UC (aHR: 1.00; 95% CI: 0.95–1.05). Analyses with FSAm-NPS DI Score modelled using cubic natural splines showed consistent results (Figure 1). There was an association between FSAm-NPS DI Score and the risk of CD, whereas we found no association with macronutrient categories (Figure S2).

Among foods items included in the FSAm-NPS DI Score computation, dietary fibre and fruit/vegetables/legumes/nuts were inversely associated with the risk of CD (adjusted HRs for fourth vs. first quartile: 0.49, 95% CI: 0.28–0.85, and 0.50, 95% CI: 0.30–0.83, respectively) (Figure 2). There was a trend towards a positive association between consumption of saturated fatty acids and the risk of CD (adjusted HRs for fourth vs. first quartile: 1.78, 95% CI: 0.94–3.37).

These results were unchanged in the sensitivity analyses excluding the first 2 years of follow-up to avoid reverse causality bias or excluding participants with implausible energy intake (Tables S3 and S4).

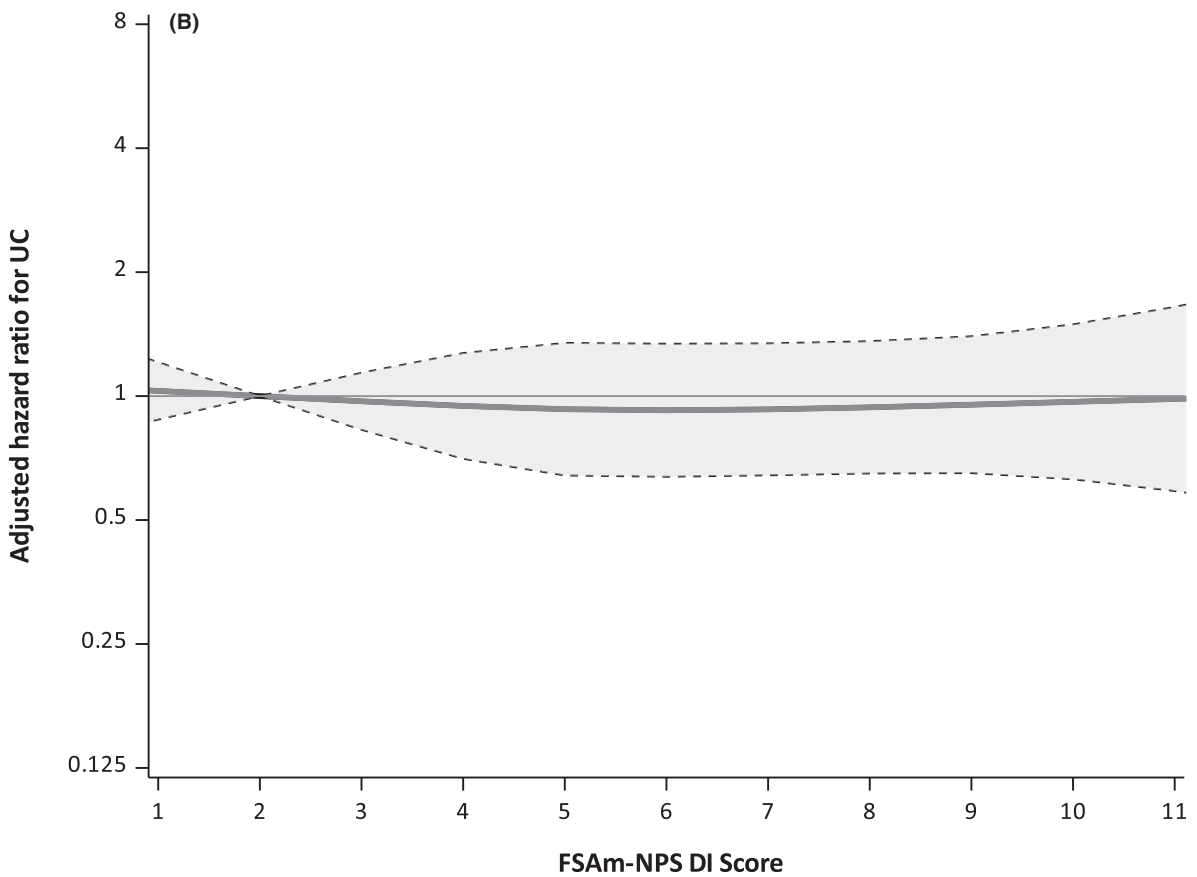
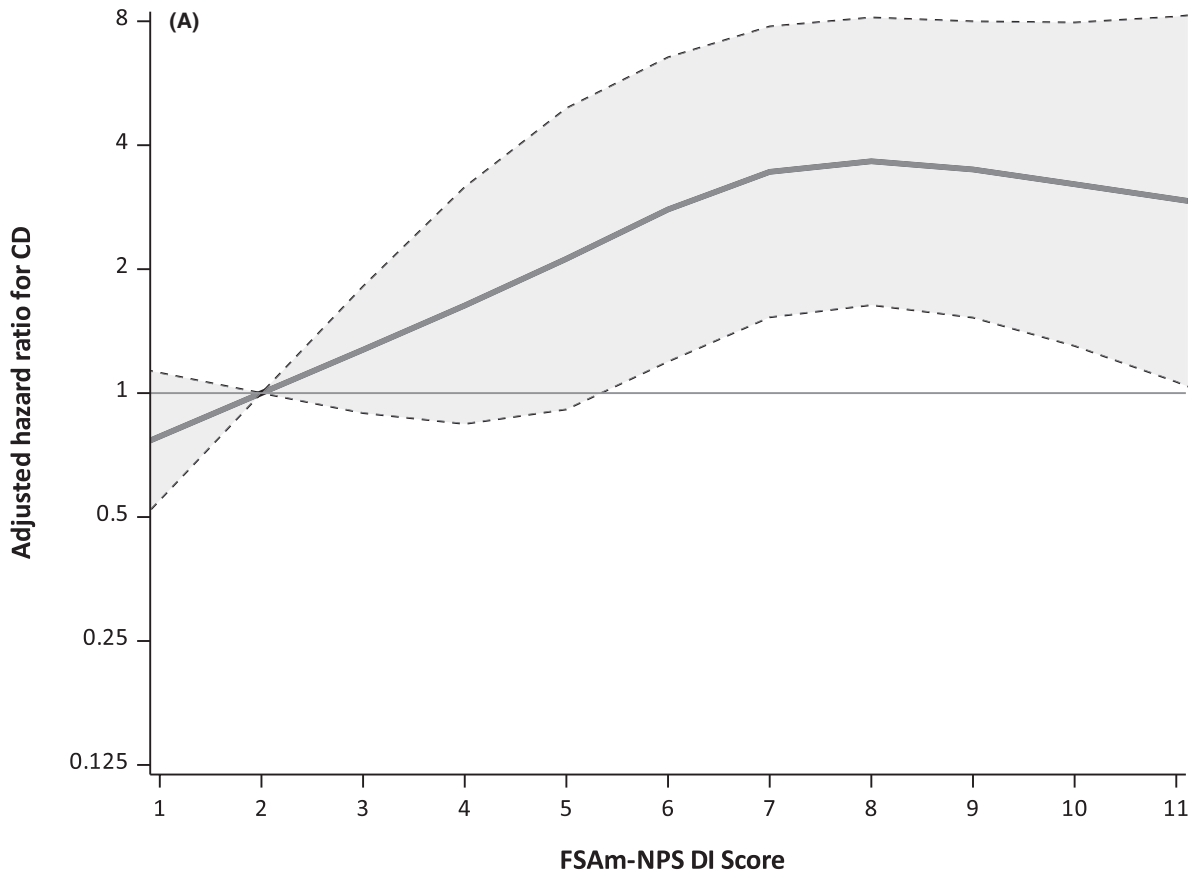
## 4 | DISCUSSION

In this study based on a prospective cohort of 394,255 healthy participants, low nutritional quality, as characterised by FSAm-NPS DI score, was associated with an increased risk of CD but not UC. Consistently, low intakes of dietary fibre and fruit/vegetables/legumes/nuts were associated with a higher risk of CD.

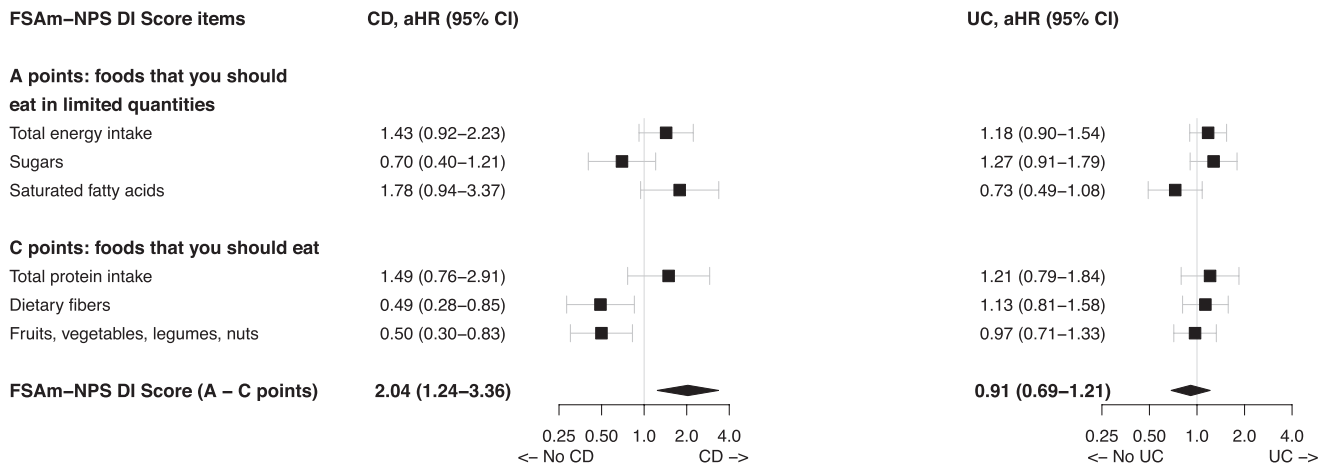
One recent study based on two Swedish cohorts and 83,147 participants (mean age: 67.7 years), investigated the association between four predefined diet quality scores and the risk of IBD.<sup>17</sup> It found a decreased risk of older-onset CD with greater adherence to two of them (the Healthful Plant-based Diet Index and the Modified Mediterranean Diet Score); no association was found with UC. Another recent, similar study was based on 125,445 Dutch participants (mean age: 44.8 years), and three predefined diet quality scores, including the healthy eating index, also studied in the Swedish cohorts.<sup>18</sup> It found a decreased risk of CD with greater adherence to one of them, the Lifeline Diet Score; no association was found with UC. Our study is based on a large number of participants and a wide range of food habits reflecting the recruitment of patients across Europe. To further investigate the diversity of diet nutritional quality, we used the FSAm-NPS DI score underlying the Nutri-Score label used in many European countries. We found that compared with the lowest decile, highest FSAm-NPS DI scores were associated with more than threefold higher risk of CD.

This is the first study to investigate the association between the FSAm-NPS DI score and the risk of IBD. However, other studies have investigated the association between individual nutrients that are

**FIGURE 1** Association between FSAm-NPS DI Score and Crohn's disease or ulcerative colitis using a Cox model with FSAm-NPS DI Score modelled as cubic natural splines with four knots. (A) CD, Crohn's disease; (B) UC, ulcerative colitis. Knots were placed at the 5th, 35th, 65th and 95th percentiles of the FSAm-NPS DI Score. FSAm-NPS DI Score ranged from –6.5 to 18.9 (1st percentile: 1.0 and 99th percentile: 11.0). FSAm-NPS DI score, Food Standards Agency modified nutrient profiling system dietary index score.







**FIGURE 2** Risk of Crohn's disease and ulcerative colitis according to FSAm-NPS DI Score items: quartile 4 versus quartile 1 in g/day except for total energy intake in kcal/day. Adjusted hazard ratios were computed using Cox models with age used as time scale, stratified for centre and sex, and adjusted for smoking status, body mass index, physical activity, educational level, total energy and alcohol. aHR, adjusted hazard ratio; CI, confidence interval; CD, Crohn's disease; UC, ulcerative colitis; FSAm-NPS DI score, Food Standards Agency modified nutrient profiling system dietary index score.

incorporated as components of the FSAm-NPS DI Score and the risk of IBD. Consistent with our results, recent meta-analysis found that a high intake of dietary fibre was associated with a lower risk of CD but not UC.<sup>19</sup> Another study found that high fibre and fruit intakes were associated with lower CD risk, and high vegetable intake was associated with lower UC risk.<sup>20</sup> However, prior studies did not find any association between saturated fat and CD risk.<sup>21,22</sup> High adherence to several food patterns have been associated with a lower risk of CD; the Mediterranean diet (high intakes of fruit, vegetables, legumes, nuts, dietary fibre, polyunsaturated fat and proteins from fish),<sup>6</sup> the prudent diet score (high intakes of dietary fibre, fruit, vegetables and fish) during adolescence,<sup>23</sup> and consumption of unprocessed/minimally processed food.<sup>7</sup>

The present study found a differential association of the nutritional quality of the diet on the risk of CD and UC. Most studies have found that dietary risk factors of CD differed from those of UC. Low fibre,<sup>2</sup> zinc<sup>3</sup> and potassium<sup>4</sup> intakes are associated with an increased risk of CD. Non-Mediterranean diet,<sup>6</sup> a diet with high inflammatory potential<sup>8</sup> and ultra-processed foods<sup>7</sup> are associated with higher risk of CD whereas unprocessed/minimally processed food<sup>7</sup> is associated with lower risk of CD. High intakes of linoleic acid<sup>1</sup> and red meat,<sup>5</sup> as well as a low intake of docosahexaenoic acid<sup>1,21</sup> have been reported to be associated with higher risk of UC. Overall, aetiopathogenesis of CD not only differs from that of UC in several respects, among which genetic factors and smoking but also in dietary factors. Studies dedicated to pre-illness dietary factors somehow mirror the established efficacy of enteral nutrition and exclusion diets in CD,<sup>24</sup> whereas for UC, evidence is more limited.

A survey based on annual food balance sheets from the Food and Agricultural Organisation database has studied nutritional quality measured by adherence to Mediterranean diet in 50 countries, in three periods, 1961–65, 2000–03 and 2004–2011.<sup>25</sup> Overall, nutritional quality deteriorated between the first and second period and stabilised

between the last two observation periods. For the three study periods, nutritional quality ranked descending in Southern Mediterranean, Mediterranean Europe, Central Europe and Northern Europe. Nutritional quality was low and relatively stable in Central and Northern Europe as well as Argentina, Canada, Australia and USA. Nutritional quality moved from high to low, in Southern and Mediterranean Europe as well as Brazil and Japan. These data coincide with the geographic distribution and time trends of CD<sup>26</sup> and add further evidence for the role of nutritional quality in the risk of acquiring CD.

Our study has several strengths. First, its prospective design lowered the risk of recall bias. Second, lifestyle, socio-demographic 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. Fourth, the Nutri-score is a very easy to use front-of-pack label and is available in many European countries.

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 24h dietary data and these questionnaires varied depending on the centre. This may have limited our ability to fully grasp the variability in the dietary choices of the individuals (and variability within the food supply). Since it is a prospective study, any measurement error would be non-differential, and thus underestimate potential associations.<sup>27</sup> Secondly, the EPIC study population included mainly middle-aged participants and it is therefore unclear if our findings may be generalizable to younger individuals at risk of IBD. While it is true that the peak incidence of IBD is as a young adult (18–29 years), there is a large proportion of people who develop IBD from age 50 onwards.<sup>28</sup> However, environmental factors may play a greater role in development of later-onset IBD, emphasising the importance of identifying modifiable risk factors in older-onset disease.<sup>29</sup> A few studies found different risk factors for later-onset IBD compared to early-onset IBD.

There were more former smokers<sup>30,31</sup> and less family history of IBD<sup>30</sup> in patients with late-onset IBD. However, to our knowledge, no study compared dietary factors of later- versus early-onset IBD. Thirdly, as in all observational studies, we cannot rule out residual confounding from unmeasured factors. Yet, the effect estimate for CD was strong and exceeded 3 (highest vs. lowest decile), the upper limit of “zone of potential bias”,<sup>32</sup> thus suggesting that the association was unlikely to be a chance finding. Additionally, we computed the E-value, which is the minimum strength of association that an unmeasured confounder would need to have with both the exposure and the outcome, to explain away the exposure–outcome association. A confounder with a hazard ratio as high as 1.79 or more would be required to explain the observed adjusted HR of 2.04 for the risk of CD with FSAm-NPS DI Score fourth versus first quartile.<sup>33</sup>

In conclusion, we found that low nutritional quality of the diet as measured by the FSAm-NPS DI Score was associated with a higher risk of CD but not UC. This study has practical implications; in Europe, the Nutri-Score is a front-of-pack label available for many foods. Individuals at high risk of CD, such as first-degree relatives of IBD patients could use the Nutri-Score as a tool towards healthier dietary alternatives.

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#### AUTHOR CONTRIBUTIONS

**Antoine Meyer:** Conceptualization; data curation; formal analysis; methodology; validation; writing – original draft; writing – review and editing. **Catherine Dong:** Conceptualization; data curation; writing – review and editing. **Simon S. M. Chan:** Supervision; validation; writing – review and editing. **Mathilde Touvier:** Writing – review and editing. **Chantal Julia:** Writing – review and editing. **Inge Huybrechts:** Writing – review and editing. **Geneviève Nicolas:** Writing – review and editing. **Bas Oldenburg:** Writing – review and editing. **Alicia K. Heath:** Writing – review and editing. **Tammy Y. N. Tong:** Writing – review and editing. **Timothy K. Key:** Writing – review and editing. **Anne Tjønneland:** Writing – review and editing. **Cecilie Kyrø:** Writing – review and editing. **Rudolf Kaaks:** Writing – review and editing. **Verena A. Katzke:** Writing – review and editing. **Manuela Bergmann:** Writing – review and editing. **Domenico Palli:** Writing – review and editing. **Giovanna Masala:** Writing – review and editing. **Rosario Tumino:** Writing – review and editing. **Carlotta Sacerdote:** Writing – review and editing. **Sandra M. Colorado-Yohar:** Writing – review and editing. **Maria José Sanchez Perez:** Writing – review and editing. **Marcela Guevara:** Writing – review and editing. **Olof Grip:** Writing – review and editing. **Johanna Holmgren:** Writing – review and editing. **Amanda J. Cross:** Writing – review and editing. **Pontus Karling:** Writing – review and editing. **Johan Hultdin:** Writing – review and editing. **Neil Murphy:** Writing – review and editing. **Mélanie Deschasaux:** Methodology; writing – review and editing. **Serge Herberg:** Writing – review and editing. **Pilar Galan:** Writing – review and editing. **Yahya Mahamat-Saleh:** Writing – review and editing. **Aurélien AMIOT:** Writing – review and editing. **Marc J. Gunter:** Writing – review and editing. **marie-christine boutron:** Conceptualization; methodology; supervision; validation; writing – review and editing. **Franck Carbonnel:** Conceptualization; methodology; supervision; validation; writing – review and editing.

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### CONFLICT OF INTEREST STATEMENT

Antoine Meyer: no competing interest. Catherine Dong: no competing interest. Simon Chan: he benefited from travel grants from Abbvie and Takeda. Mathilde Touvier: no competing interest. Chantal Julia: no competing interest. Inge Huybrechts: no competing interest. Geneviève Nicolas: no competing interest. Bas Oldenburg: he benefited from grants from Takeda, Pfizer, Ferring and Celltrion; he participated to advisory boards of Takeda, BMS, Galapagos, Janssen and Cosmofer. Alicia K Heath: no competing interest. Tammy YN Tong: no competing interest. Timothy J Key: no competing interest. Anne Tjønneland: no competing interest. Cecilie Kyrø: no competing interest. Rudolf Kaaks: no competing interest. Verena A Katzke: no competing interest. Manuela M Bergman: no competing interest. Domenico Palli: no competing interest. Giovanna Masala: no competing interest. Rosario Tumino: no competing interest. Carlotta Sacerdote: no competing interest. Sandra M. Colorado-Yohar: no competing interest. Maria-Jose Sánchez: no competing interest. Marcela Guevara: no competing interest. Olof Grip: he served as a speaker, a consultant and an

advisory board member for Ferring, Janssen, Pfizer and Takeda. Johanna Holmgren: no competing interest. Amanda Cross: no competing interest. Pontus Karling: no competing interest. Johan Hultdin: no competing interest. Neil Murphy: no competing interest. Mélanie Deschasaux-Tanguy: no competing interest. Serge Herberg: no competing interest. Pilar Galan: no competing interest. Yahya Mahamat-Saleh: no competing interest. Aurélien Amiot: he received consulting fees from Abbvie, Hospira, Janssen, Tillotts, Pfizer, Takeda, Gilead and Biocodex as well as lecture fees and travel accommodations from Abbvie, Janssen, Biocodex, Hospira, Ferring, Pfizer, Biogen, Amgen, Fresenius Kabi, Ferring, Tillotts, Takeda and MSD. He also received advisory board fees from Gilead, Tillotts, Takeda and Abbvie. Marc J Gunter: no competing interest. Marie-Christine Boutron-Ruault: no competing interest. Franck Carbonnel: he received speaker fees for Abbvie, Biogen, Ferring, Janssen, MSD, Pfizer, Pileje and Takeda; he participated to advisory boards of Amgen, Arena, Celltrion, Enterome, Ferring, Janssen, Medtronic, Pfizer, Pharmacosmos, Roche and Tillotts.

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## SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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