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Association of ultra-processed food intake with risk of inflammatory bowel disease: prospective cohort study

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ABSTRACT

OBJECTIVE
To evaluate the relation between intake of ultra-processed food and risk of inflammatory bowel disease (IBD).

DESIGN
Prospective cohort study.

SETTING
21 low, middle, and high income countries across seven geographical regions (Europe and North America, South America, Africa, Middle East, south Asia, South East Asia, and China).

PARTICIPANTS
116 087 adults aged 35-70 years with at least one cycle of follow-up and complete baseline food frequency questionnaire (FFQ) data (country specific validated FFQs were used to document baseline dietary intake). Participants were followed prospectively at least every three years.

MAIN OUTCOME MEASURES
The main outcome was development of IBD, including Crohn's disease or ulcerative colitis. Associations between ultra-processed food intake and risk of IBD were assessed using Cox proportional hazard multivariable models. Results are presented as hazard ratios with 95% confidence intervals.

RESULTS
Participants were enrolled in the study between 2003 and 2016. During the median follow-up of 9.7 years (interquartile range 8.9-11.2 years), 467 participants developed incident IBD (90 with Crohn's disease and 377 with ulcerative colitis). After adjustment for potential confounding factors, higher intake of ultra-processed food was associated with a higher risk of incident IBD (hazard ratio 1.82, 95% confidence interval 1.22 to 2.72 for ≥5 servings/day and 1.67, 1.18 to 2.37 for 1-4 servings/day compared with <1 serving/day, P=0.006 for trend). Different subgroups of ultra-processed food, including soft drinks, refined sweetened foods, salty snacks, and processed meat, each were associated with higher hazard ratios for IBD. Results were consistent for Crohn's disease and ulcerative colitis with low heterogeneity. Intakes of white meat, red meat, dairy, starch, and fruit, vegetables, and legumes were not associated with incident IBD.

CONCLUSIONS
Higher intake of ultra-processed food was positively associated with risk of IBD. Further studies are needed to identify the contributory factors within ultra-processed foods.

STUDY REGISTRATION
ClinicalTrials.gov NCT03225586.

Introduction

Inflammatory bowel disease (IBD), comprised of Crohn's disease and ulcerative colitis, is a chronic inflammatory disorder of the gastrointestinal tract. The pathophysiology of IBD is thought to be related to activation of the intestinal mucosal immune system in response to dysbiosis of the gastrointestinal tract in genetically susceptible people.[1] Diet alters the microbiome[2] and modifies the intestinal immune response and so could play a role in the pathogenesis of IBD.[3] The incidence of IBD has increased in several countries where both diseases were previously uncommon.[4] This increase has paralleled the adoption of a western diet in these countries. Dietary changes in such countries, including increased intake of refined sugars and dietary fats such as n-6 polyunsaturated fatty acids and decreased intake of fibre, have been suggested as potential risk factors for the development of IBD.[5-7]

Specific data linking dietary factors with IBD in human populations have been limited and conflicting.[8-10] Most previous studies of diet and IBD

WHAT IS ALREADY KNOWN ON THIS TOPIC

Inflammatory bowel disease (IBD) is more common in industrialised nations

It is hypothesised that environmental factors such as diet might influence the risk of IBD

Many dietary risk factors have been investigated for an association with IBD, but data for an association between ultra-processed food (which contain additives and preservatives) intake and IBD are limited

WHAT THIS STUDY ADDS

A higher intake of ultra-processed food was associated with higher risk of IBD

Individual food categories (meats, dairy, starches, fruit, and vegetables) were not associated with risk of IBD, suggesting that risk might be related to the food itself rather than the way it is processed or ultra-processed

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have used retrospective or case-control designs.[9 10] The few prospective studies that have examined dietary risk factors have been limited by small numbers of participants, lack of adjustment for potential confounders, or use of homogenous populations confined to individual countries or specific regions of countries.[6 7 11-15]

A recent systematic review synthesised all studies that evaluated dietary intake and risk of IBD.[10] It was evident from the findings that many associations have been examined repeatedly, including the association of different dietary fats, carbohydrates, proteins, fruit, vegetables, fibre, and dairy with IBD.[10] Meats have been assessed as a whole, with some, but not all, studies suggesting an increased odds for the development of IBD with higher meat intake.[10 16] The systematic review also found high intake of total fats, polyunsaturated fatty acids, and omega-6 fatty acids to be associated with increased risk of IBD. High fibre and fruit intake might decrease the risk of Crohn's disease, and high vegetable intake was associated with a decreased risk of ulcerative colitis.[17 18]

Recent attention has focused on the non-nutritional components of diet and potential associated risks. Processed foods often include many non-natural ingredients and additives such as artificial flavours, sugars, stabilisers, emulsifiers, and preservatives. Detergents and emulsifiers that are added to foods might have a detrimental effect on the gut barrier. Carboxymethylcellulose has been shown to increase bacterial adherence to intestinal epithelium and might lead to bacterial overgrowth and infiltration of bacteria into the spaces between intestinal villi.[19] Polysorbate 80, an emulsifier commonly used in processed foods, increases translocation of bacteria such as *Escherichia coli* across M cells and Peyer's patches in people with Crohn's disease.[20] Associations have been reported between diets high in processed foods and development of diseases such as cancer and cardiovascular disease.[21 22] One recent study investigated whether ultra-processed foods were associated with risk of IBD and did not find any association, but this study was limited by few patients with IBD (75 among 105 832 participants).[15]

Using information from the Prospective Urban Rural Epidemiology (PURE) cohort, we describe the association between ultra-processed food intake and risk of developing IBD.[24-26]

Methods
The design and methods of the PURE study have been described and published previously.[23-25] The first and second phases of the study took place between 1 January 2003 and 31 December 2016 and included 136 384 adults aged 35-70 years who had dietary information assessed. Participants were enrolled from 21 countries: Argentina, Bangladesh, Brazil, Canada, Chile, China, Colombia, India, Iran, Malaysia, Palestine, Pakistan, Philippines, Poland, South Africa, Saudi Arabia, Sweden, Tanzania, Turkey, United Arab Emirates, and Zimbabwe. The sampling and recruitment strategies from PURE have been published previously (see supplementary appendix 1).[26] Data were collected at the community, household, and individual level using standardised questionnaires. Standard case report forms were used to record new diagnoses of Crohn's disease and ulcerative colitis during the follow-up period. For the current analysis, the data include all outcome events up to 5 July 2019. The Population Health Research Institute and McMaster University and Hamilton Health Sciences in Hamilton, Ontario, Canada coordinated the study.

Procedures
For each participant in PURE, usual food intake was assessed at baseline using country specific validated food frequency questionnaires (FFQ). Validated FFQs were developed for countries where such questionnaires had not been available previously (supplementary table 1). Participants received a list of food items and were asked to input their frequency for intake of each item in the past year. To compute daily food and nutrient intakes, participant's answers were converted to daily intake and multiplied by United States Department of Agriculture (USDA) serving size. Ultra-processed food included all types of packaged and formulated foods and beverages that contain food additives, artificial flavourings, colours, or other chemical ingredients. Included in this group were processed meat, cold breakfast cereal, various types of sauce, soft drinks, refined sweetened foods (eg, candy, chocolate, jam, jelly, brownies, pudding), chips, ice cream, commercially prepared pastries, biscuits, and fruit drinks. To make the unit of consumption consistent between countries, we used daily serving intake.

Outcomes
The primary outcome was the development of IBD after completion of the baseline questionnaire. Other outcomes of interest were development of Crohn's disease and ulcerative colitis individually by dietary risk factors that had statistically significant associations with the development of IBD overall. Although data collection for PURE started in 2003, an amendment was implemented in 2014 to record diagnoses of Crohn's disease and ulcerative colitis. Participants were asked at every follow-up questionnaire whether they had a diagnosis of Crohn's disease or ulcerative colitis. They were asked when the condition was diagnosed and those with prevalent diagnoses of IBD (diagnosis before baseline questionnaire) were excluded. Participants were also excluded if their baseline FFQ was completed less than one year from the time of the reported IBD diagnosis. Participants self-reported the diagnosis. A validation exercise was conducted to validate 20% of the diagnoses using a sample of the population where medical records could be provided for review by the authors.

Statistical analysis
Continuous variables are expressed as means with standard deviation, and categorical variables are

expressed as percentages. Education was categorised as college, university, or trade (age >11 years), secondary or high school (age 7-11 years), or none or primary school (age <6 years). Alcohol was categorised as <1 serving/month (eg, per serving: beer 14 g, wine 16 g, vodka, rum, spirits 10 g, liqueur 27 g), 1 serving/month to 1/week, or >1 serving/week. Geographical region was treated as binary variable of North America and Europe or rest of the world because the prevalence of IBD is typically highest in North America and Europe and lower in other parts of the world. Other binary variables included smoking status (current versus no smoking) and location (rural versus urban). Other categorical variables included body mass index, classified as obese, overweight, or normal, and physical activity, classified as low (<600 metabolic equivalent of task (MET) min/week), moderate (600-3000 MET min/week), or high (>3000 MET min/week). Continuous variables included age, daily total energy (in kcal), and waist to hip ratio.

For the overall analysis of total ultra-processed food, participants were grouped into categories according to servings as <1 serving/day, 1-4 servings/day, or ≥5 servings/day. The lowest intake group was always used as the reference group. In a sensitivity analysis, we also grouped participants based on grams of intake of ultra-processed food into <50 g/day, 50-99 g/day, and ≥100 g/day. We also assessed the association using categories of ultra-processed foods individually. Processed meat was categorised into <1 serving/week, 1-6 servings/week, or ≥7 servings/week. Soft drink intake was categorised into <0.5 serving/week, 0.5 to <3 servings/week, or ≥3 servings/week. Refined sweetened foods—those high in refined sugars (eg, cake, cookies)—and intake was categorised as none, 1-99 g/day, or ≥100 g/day. Salty foods and snacks (eg, crackers, potato chips, nachos, popcorn) were categorised into <50 g/day, 50-99 g/day, and ≥100 g/day. An additional analysis of urinary sodium was conducted, as a surrogate of dietary sodium, to determine whether dietary sodium could potentially be implicated should ultra-processed foods be associated with risk of IBD. The Kawasaki formula was used to estimate urinary sodium excretion.[27] Based on a previous study assessing urinary sodium, categories chosen were <2.5 g/day, 2.5-3.4 g/day, and ≥3.5 g/day.[27] A sensitivity analysis was planned to exclude China because of its significantly higher observed sodium intake compared with the rest of the world and relatively low event rates for IBD.[27]

Exploratory analyses were planned with other dietary variables to confirm or refute risk factors that had been reported in the literature as showing associations. Participants were categorised by white meat intake into <1 serving/week, 1-2 servings/week, or ≥3 servings/week. Red meat (unprocessed) was categorised into <3 servings/week, 3-6 servings/week, or ≥7 servings/week. Dairy intake was categorised into <1 serving/day, 1 to <2 servings/day, or ≥2 servings/day. Starch intake was categorised into <200 g/day, 200-399 g/day, and ≥400 g/day. Fruit, vegetables, and legumes were analysed together and classified as <2

servings/day, 2-5 servings/day, and ≥6 servings/day and were also analysed separately. Lastly, fried foods were categorised into none, 1 serving/week to <1 serving/day, or ≥1 servings/day.

We calculated hazard ratios using multivariable Cox proportional hazard models. Estimates of hazard ratios and 95% confidence intervals are presented for each dietary risk factor of interest. Results are presented as unadjusted hazard ratios, minimally adjusted hazard ratios for age, sex, and geographical region, and fully adjusted hazard ratios. Covariates included in the fully adjusted model were those known from previous literature to have an association with the development of IBD (eg, smoking) or those found to have an association on univariable analyses (P<0.15). Covariates for consideration in the fully adjusted multivariable model included age, sex, geographical region, education, alcohol intake, smoking status, physical activity, energy intake, BMI, waist to hip ratio, and urban versus rural location. An additional model was run including adjustment for diet quality as measured by the Alternate Health Eating Index (AHEI).[28] The Kolmogorov-type Supremum test was used to test the proportional hazards assumptions.[29] The χ^2 test of linear trend was used to compare across categories of food intake. A two sided P<0.05 was considered to be statistically significant. Sensitivity analysis were conducted by using multiple imputation for participants with missing FFQ data to determine whether this had any impact on the results. For separate analyses of Crohn's disease and ulcerative colitis conducted when a dietary risk factor had statistically significant association with development of IBD, we anticipated lower power to achieve statistical significance separately within each subgroup. For comparison of subgroup effects, we assessed heterogeneity by calculating the χ^2 and I^2 statistics. For the χ^2 test, we considered a P value of <0.10 to be statistically significant. I^2 values greater than 50% were considered to indicate substantial heterogeneity. We used heterogeneity of the subgroup analyses to determine whether the association was predominantly due to effect from one subgroup. Data were analysed using Stata/IC 15.

Patient and public involvement
No patients were involved in setting the research question or outcome measures, or in the design and implementation of this study.

Results
Between 1 January 2003 and 31 December 2016, a total of 153 220 participants completed the FFQ. Of these participants, 126 662 had a plausible energy intake (500-5000 kcal/day; 1 kcal=4.18 kJ or 0.00418 MJ) and had at least one cycle of follow-up. Overall, 10 625 (8.3%) were excluded owing to incomplete FFQ data, leaving a total of 116 037 participants included in this study.

During a median follow-up of 9.7 years (interquartile range 8.9-11.2 years), 467 participants (0.4%) had a

Table 1 | Characteristics of study population at enrolment and diagnosis of inflammatory bowel disease (IBD) during follow-up by region. Values are numbers (percentages) unless stated otherwise

Characteristics	Overall (n=116 037)	Europe and North America (n=17 232)	South America (n=18 611)	Africa (n=3871)	Middle East (n=9399)	South Asia (n=21 834)	South East Asia (n=8998)	China (n=36 092)	Participants who developed IBD (n=467)
Diagnosis of IBD	467 (0.4)	192 (1.1)	33 (0.2)	25 (0.6)	103 (1.1)	94 (0.4)	1 (0.01)	19 (0.1)	
Crohn's disease	90 (0.1)	51 (0.3)	5 (0)	4 (0.1)	5 (0.1)	24 (0.1)	0	1 (0)	90 (0.1)
Ulcerative colitis	377 (0.3)	141 (0.8)	28 (0.2)	21 (0.5)	98 (1.0)	70 (0.3)	1 (0)	18 (0.1)	377
Mean (SD) age (years)	50.2 (9.7)	52.7 (9.2)	51.0 (9.5)	50.0 (10.1)	47.8 (9.2)	47.3 (9.8)	51.4 (9.7)	50.8 (9.7)	50.5 (9.3)
Women	68 732 (59.2)	9766 (56.7)	11 655 (62.6)	2897 (74.9)	4951 (52.7)	12 879 (59.0)	5503 (61.2)	21 081 (58.4)	273 (58.5)
Urban setting	60 412 (52.1)	11 925 (69.2)	10 489 (56.4)	1772 (45.8)	5298 (56.4)	9110 (41.7)	4472 (49.7)	17 346 (48.1)	276 (59.1)
Current smoker	22 563 (19.6)	2820 (16.4)	3673 (19.8)	807 (21.4)	1323 (14.1)	4847 (22.3)	1320 (14.8)	7773 (21.9)	75 (16.1)
Mean (SD) energy intake (kcal)	2161 (812)	2277 (832)	2198 (794)	2084 (965)	2322 (827)	2115 (829)	2552 (987)	1984 (664)	2105 (775)
Mean (SD) ultra-processed food (servings/day)	1.8 (3.9)	6.0 (7.3)	2.9 (3.7)	0.7 (1.0)	1.2 (1.4)	0.3 (1.2)	2.0 (2.1)	0.3 (1.0)	4.0 (6.8)
Mean (SD) ultra-processed food (g/day)	94.2 (228.3)	220.9 (255.1)	238.4 (416.8)	83.4 (184.3)	88.7 (159.3)	14.5 (56.1)	73.7 (95.7)	15.0 (58.4)	145.4 (223.2)
Mean (SD) processed meat (servings/week)	1.2 (2.8)	2.8 (3.7)	2.2 (4.0)	1.8 (2.5)	0.6 (1.3)	0.01 (0.1)	0.3 (0.5)	0.2 (0.6)	2.2 (3.3)
Mean (SD) soft drinks (servings/week)	1.2 (4.0)	2.0 (4.3)	3.8 (7.8)	1.7 (3.8)	0.8 (1.6)	0.2 (0.9)	1.5 (3.2)	0.1 (0.3)	1.5 (3.4)
Mean (SD) refined sweetened foods (g/day)	92.0 (216.3)	99.9 (138.1)	306.1 (418.2)	61.6 (139.7)	103.0 (180.1)	25.8 (44.3)	100.5 (122.5)	17.2 (34.1)	100.4 (180.6)
Mean (SD) salty foods or snacks (g/day)	28.4 (37.6)	57.9 (50.0)	35.7 (35.5)	38.5 (52.0)	29.8 (29.2)	6.5 (16.4)	55.6 (46.7)	16.0 (20.3)	39.9 (47.2)
Mean (SD) sodium (g/day)*	4.1 (1.6)	3.6 (1.6)	4.7 (1.4)	4.2 (1.5)	4.6 (1.7)	3.4 (1.7)	3.8 (1.2)	5.7 (1.9)	4.2 (1.5)

1 kcal=4.18 kJ or 0.00418 MJ.

*Urinary sodium was used as a surrogate for sodium intake.

diagnosis of incident IBD (supplementary figure 1): 90 participants with Crohn's disease and 377 with ulcerative colitis. Supplementary appendix 2 provides the results of the validation exercise.

Ultra-processed food intake was higher in North America, Europe, and South America than in other regions (table 1), both in servings and grams of intake daily. Similarly, processed meat and soft drink intakes were highest in these three regions. Consumption of refined sweetened foods was highest in South America, followed by the Middle East and South East Asia. Salty and snack food intake was highest in North America and South East Asia. Sodium intake was highest in China.

Table 2 summarises the results of the univariable associations. Those dietary variables that were nominally significant were included in the multivariable Cox proportional hazard regression models. In addition to age, sex, and geographical region used in the minimally adjusted model, education, alcohol intake, smoking status, BMI, total energy intake, and location were all found to be significantly associated with the development of IBD and were included within the multivariable model. None of the variables in the model violated the proportional hazards assumption (P>0.05) when tested using the Supremum test for total ultra-processed food intake, individual categories of ultra-processed food intake, urinary sodium, and other food categories, and the outcome of IBD development.

Ultra-processed food intake and risk of IBD

Table 3 shows the graded association between intake of total ultra-processed foods and risk of IBD. Higher intake of ultra-processed food was associated with a higher risk of incident IBD (hazard ratio 1.82, 95% confidence interval 1.22 to 2.72 for ≥5 servings/day and 1.67, 1.18 to 2.37 for 1-4 servings/day compared with <1 serving/day, P=0.006 for trend). When further adjusted using the AHEI, findings were similar, as higher risk of IBD was observed for ≥5 servings/day (1.92, 1.28 to 2.90) and 1-4 servings/day (1.75, 1.23 to 2.50) compared with <1 serving/day (P=0.004 for trend). The results were directionally consistent for Crohn's disease and ulcerative colitis, with no statistical evidence of heterogeneity (χ^2 P=0.60; I^2=0%). In sensitivity analysis (supplementary table 2), the risk of IBD development in participants with ultra-processed food intake (g/day) was also found to be significantly increased. Higher intake (g/day) of ultra-processed food was associated with higher risk of incident IBD (1.73, 1.23 to 2.45 for ≥100 g/day and 1.33, 0.88 to 2.01 for 50-100 g/day compared with <50 g/day, P=0.007 for trend). Sensitivity analysis with multiple imputation for missing FFQ data also showed a higher risk of IBD with increased ultra-processed food intake, suggesting that the missing data did not alter the findings (table 3). Subgroup analyses were performed to determine whether participant age was an effect modifier, but similar patterns of increased hazard ratios at higher levels of ultra-processed food intake were observed in participants younger than

Table 2 | Results from univariable and multivariable analyses of baseline covariates and risk of inflammatory bowel disease

Predictors	Univariable		Multivariable*	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Age	1.00 (0.99 to 1.01)	0.51	1.01 (0.99 to 1.02)	0.16
Sex (men)	1.03 (0.86 to 1.24)	0.73	0.93 (0.72 to 1.20)	0.59
North America and Europe	4.04 (3.36 to 4.86)	‹0.001	5.57 (3.97 to 7.81)	‹0.001
Education:		‹0.001		0.02
None	1.00 (ref)		1.00 (ref)	
Secondary or high school	1.26 (1.01 to 1.58)		1.60 (1.13 to 2.26)	
College, university, or trade	2.24 (1.78 to 2.81)		1.57 (1.07 to 2.26)	
Alcohol†:		‹0.001		0.34
‹1 serving/month	1.00 (ref)		1.00 (ref)	
1 serving/ month to ‹1 serving/week	3.52 (2.46 to 5.04)		1.21 (0.82 to 1.80)	
≥1 serving/week	2.93 (2.28 to 3.77)		0.92 (0.67 to 1.26)	
Current smoking	0.78 (0.61 to 1.00)	0.05	0.73 (0.51 to 1.06)	0.10
Physical activity (MET score):		0.16		
Low (‹600)	1.00 (ref)			
Moderate (600 to ‹3000)	1.28 (0.95 to 1.71)			
High (≥3000)	1.30 (0.98 to 1.74)			
Energy (kcal)	1.00 (0.99 to 1.00)	0.13	1.00 (0.99 to 1.00)	0.08
Body mass index:		0.03		0.78
Normal (‹25)	1.00 (ref)		1.00 (ref)	
Overweight (25 to ‹30)	1.09 (0.88 to 1.34)		0.91 (0.69 to 1.19)	
Obese (≥30)	1.38 (1.09 to 1.75)		0.96 (0.70 to 1.32)	
Waist to hip ratio	1.80 (0.61 to 5.28)	0.28		
Location:		0.002		0.91
Urban	1.00 (ref)		1.00 (ref)	
Rural	0.75 (0.62 to 0.90)		0.99 (0.76 to 1.28)	

MET=metabolic equivalent of task.
*Ultra-processed food intake in servings per day was used as main predictor.
†For example, per serving: beer 14 g, wine 16 g, vodka, rum, spirits 10 g, liqueur 27 g.

50 and 50 or older (supplementary tables 3 and 4). Region specific analyses (supplementary figure 2) were also performed to determine whether the pattern of increased ultra-processed food intake and higher risk of IBD persisted within each of the regions examined, and effect estimates were generally similar, with overlapping confidence intervals and no significant heterogeneity (χ^2 P=0.69; I^2=0%).

Supplementary table 5 shows that higher processed meat intake was associated with higher risk of IBD (2.07, 1.14 to 3.76 for ≥1 serving/day and 1.92, 1.24-2.98 for 1 serving/week to <1 serving/day compared with <1 serving/week, P=0.01 for trend; supplementary tables 5-8). Increased risk was observed for both Crohn's disease and ulcerative colitis (tests of heterogeneity: χ^2 P=0.93; I^2=0%). A graded risk was also found for soft drinks intake and risk of IBD (supplementary table 6). The highest intake of soft drinks (≥3 servings/week) compared with lowest intake (<0.5 serving/week) was associated with a higher risk of IBD (1.94, 1.42 to 2.66, P<0.001 for trend), with directionally consistent results observed for Crohn's disease and ulcerative colitis and no statistical evidence of heterogeneity (χ^2 P=0.72; I^2=0%).

Consumption of refined sweetened foods was associated with higher risk of IBD (supplementary table 7). The highest risk of IBD was observed in participants with ≥100 g/day intake (2.58, 1.44 to 4.62, P=0.003 for trend) compared with zero intake. Results were consistent for Crohn's disease and ulcerative colitis (tests of heterogeneity: χ^2 P=0.17; I^2=41%). A similar

pattern was observed for salty foods and snacks, where an increased risk of IBD was observed in participants with ≥100 g/day intake compared with <50 g/day (2.06, 1.41 to 3.00, P<0.001 for trend; supplementary table 8). Associations with similar direction were observed for the risk of Crohn's disease and ulcerative colitis, without significant heterogeneity (χ^2 P=0.25; I^2=27.8%).

Urinary sodium and risk of IBD
Urinary sodium was used as a surrogate of dietary sodium intake. The risk of IBD in participants with higher levels of urinary sodium (≥3.5 g/day) was found not to be higher than in those patients with the lowest levels of urinary sodium (<2.5 g/day, P=0.61 for trend; table 4). As a large number of participants with IBD was found among the highest urinary sodium cohort, a sensitivity analysis was performed to further subdivide this cohort (supplementary table 9), but again no difference in risk of IBD was observed in those with the highest levels of urinary sodium (≥5 g/day) compared with those with lower levels (P=0.45 for trend). Although urinary sodium was found to be highest among participants from China (table 1) with only 19 incident cases of IBD, the results did not differ after exclusion of participants from China (P=0.68 for trend).

Other food categories and risk of IBD
Several other food categories were evaluated in exploratory analyses (table 5 and table 6, also see

Table 3 | Association between total ultra-processed food intake and risk of inflammatory bowel disease. Values are hazard ratios (95% confidence intervals) unless stated otherwise

| | Ultra-processed food intake | | | |
	<1 serving/day	1-4 servings/day	≥5 servings/day	P trend
Inflammatory bowel disease				
No of participants	76 415	25 453	11 742	
No (%) of events	199 (0.26)	134 (0.53)	95 (0.81)	
Unadjusted model	1 (ref)	2.20 (1.77 to 2.74)	3.18 (2.49 to 4.07)	<0.001
Minimally adjusted model*	1 (ref)	1.41 (1.11 to 1.79)	1.42 (1.07 to 1.90)	0.01
Fully adjusted model†	1 (ref)	1.67 (1.18 to 2.37)	1.82 (1.22 to 2.72)	0.006
Fully adjusted plus AHEI score model	1 (ref)	1.75 (1.23 to 2.50)	1.92 (1.28 to 2.90)	0.004
Sensitivity analysis using multiple imputation‡	1 (ref)	1.54 (1.21 to 1.84)	1.71 (1.22 to 2.37)	<0.001
Crohn's disease				
No of participants	76 415	25 453	11 742	
No (%) of events	34 (0.04)	23 (0.09)	30 (0.26)	
Unadjusted model	1 (ref)	2.19 (1.29 to 3.72)	5.84 (3.57 to 9.54)	<0.001
Minimally adjusted model*	1 (ref)	1.15 (0.64 to 2.06)	1.92 (1.05 to 3.49)	0.07
Fully adjusted model†	1 (ref)	2.72 (1.06 to 6.97)	4.50 (1.67 to 12.13)	0.01
Fully adjusted plus AHEI score model	1 (ref)	2.93 (1.13 to 7.60)	4.90 (1.78 to 13.45)	0.008
Sensitivity analysis using multiple imputation‡	1 (ref)	1.30 (0.71 to 2.37)	2.83 (1.45 to 4.65)	0.40
Ulcerative colitis				
No of participants	76 415	25 453	11 742	
No (%) of events	165 (0.22)	111 (0.44)	65 (0.55)	
Unadjusted model	1 (ref)	2.20 (1.73 to 2.80)	2.63 (1.97 to 3.51)	<0.001
Minimally adjusted model*	1 (ref)	1.48 (1.13 to 1.93)	1.27 (0.91 to 1.77)	0.02
Fully adjusted model†	1 (ref)	1.55 (1.06 to 2.28)	1.46 (0.93 to 2.28)	0.08
Fully adjusted plus AHEI score model	1 (ref)	1.61 (1.09 to 2.38)	1.52 (0.96 to 2.41)	0.06
Sensitivity analysis using multiple imputation‡	1 (ref)	1.59 (1.23 to 1.98)	1.45 (0.96 to 2.12)	<0.001

AHEI=Alternate Healthy Eating Index.
Heterogeneity of results from Crohn's disease and ulcerative colitis: x^2 P=0.595; I^2=0%.
*Adjusted for age, sex, and geographical region.
†Adjusted for age, sex, geographical region, education, alcohol intake, smoking status, body mass index, total energy intake, and location.
‡To account for participants with missing data on food frequency questionnaire.

supplementary tables 10-18 for detailed analyses). Intake of white meat, unprocessed red meat, dairy, starchy foods, and fruit, vegetables, and legumes was not associated with risk of IBD (supplementary tables 10-17). Intake of fried foods was associated with higher risk of IBD (supplementary table 18). Those with a fried food intake of ≥1 servings/day showed the highest risk of IBD (3.02, 1.51 to 6.03, P=0.006 for trend) compared with those with zero intake. No significant difference in risk was observed between Crohn's disease and ulcerative colitis (tests of heterogeneity: χ^2 P=0.19; I^2=37.6%).

Discussion

In this large, multinational, prospective cohort study involving 116 087 participants from 21 low, middle, and high income countries, we found that higher intake of ultra-processed foods was associated with an increased risk of IBD. This was seen for all ultra-

processed foods, as well as individual types, including processed meats, soft drinks, refined sweetened foods, and salty foods and snacks. No significant heterogeneity was observed when the results for Crohn's disease were compared with the results for ulcerative colitis within each of these types of ultra-processed foods. These results remained consistent in sensitivity analyses using alternative classifications for ultra-processed food intake and using multiple imputation to account for missing FFQ data. The results were still consistent after adjustment for a western diet using the AHEI. Our findings support the hypothesis that intake of ultra-processed foods could be an environmental factor that increases the risk of IBD.

Comparison with other studies

Processed foods are a diverse food group that include meats, dairy, starchy foods, fruit, vegetables, and legumes. None of these categories on its own was found to be implicated as a risk factor for IBD in our study. Recent attention has focused on diet as an environmental factor that might be implicated in the development of IBD, and studies have suggested that western-type diets that are typically high in protein, fat, salt, and sugar but low in fruit, vegetables, and fibre, are associated with increased risk of IBD.[30-32] A recent meta-analysis suggested western-type diets were associated with a relative risk for IBD of 1.92 (95% confidence interval 1.37 to 2.68).[33] Western-type diets, however, also contain higher levels of additives and preservatives, which could explain the association

Table 4 | Association between urinary sodium intake and risk of inflammatory bowel disease. Values are hazard ratios (95% confidence intervals) unless stated otherwise

| | Sodium intake (g/day) | | | |
	<2.5	2.5 to <3.5	≥3.5	P trend
No of participants	8444	11 555	61 033	
No (%) of events	42 (0.50)	73 (0.62)	269 (0.44)	
Unadjusted	1 (ref)	1.33 (0.91 to 1.95)	0.89 (0.64 to 1.23)	0.008
Minimally adjusted*	1 (ref)	1.88 (1.28 to 2.76)	1.66 (1.18 to 2.34)	0.004
Fully adjusted†	1 (ref)	1.26 (0.80 to 1.97)	1.17 (0.79 to 1.74)	0.61

*Adjusted for age, sex, and geographical region.
†Adjusted for age, sex, geographical region, education, alcohol intake, smoking status, body mass index, total energy intake, and location.

Table 5 | Summary of associations between meat and dairy intake and risk of inflammatory bowel disease. Values are hazard ratios (95% confidence intervals) unless stated otherwise

Model	White meat (servings/week)				Red meat (servings/week)				Dairy (servings/day)			
	<1	1 to <3	≥3	P trend	<3	3 to <7	≥7	P trend	<1	1 to <2	≥2	P trend
Minimally adjusted*	1 (ref)	1.16 (0.92 to 1.45)	1.06 (0.82 to 1.36)	0.46	1 (ref)	0.83 (0.65 to 1.05)	1.03 (0.82 to 1.30)	0.18	1 (ref)	1.06 (0.80 to 1.41)	1.50 (1.15 to 1.96)	0.006
Fully adjusted†	1 (ref)	1.31 (0.99 to 1.74)	1.38 (0.97 to 1.95)	0.10	1 (ref)	1.00 (0.74 to 1.35)	1.12 (0.81 to 1.53)	0.72	1 (ref)	1.14 (0.78 to 1.68)	1.26 (0.86 to 1.83)	0.49

*Adjusted for age, sex, and geographical region.
†Adjusted for age, sex, geographical region, education, alcohol intake, smoking status, body mass index, total energy intake, and location.

Table 6 | Summary of associations between starch; fruit, vegetables, and legumes; and fried foods intake and risk of inflammatory bowel disease. Values are hazard ratios (95% confidence intervals) unless stated otherwise

Model	Starch (g/day)				Fruit, vegetables, and legumes (servings/day)				Fried foods (servings/day)			
	<200	200 to <400	≥400	P trend	<2	2 to <6	≥6	P trend	0	<1	≥1	P trend
Minimally adjusted*	1 (ref)	1.22 (0.89 to 1.67)	1.23 (0.89 to 1.71)	0.43	1 (ref)	1.02 (0.72 to 1.43)	1.23 (0.86 to 1.77)	0.21	1 (ref)	1.00 (0.72 to 1.41)	1.26 (0.88 to 1.79)	0.12
Fully adjusted†	1 (ref)	1.41 (0.98 to 2.04)	1.50 (0.95 to 2.38)	0.16	1 (ref)	0.97 (0.59 to 1.60)	1.31 (0.77 to 2.22)	0.11	1 (ref)	2.35 (1.21 to 4.55)	3.02 (1.51 to 6.03)	0.006

*Adjusted for age, sex, and geographical region.
†Adjusted for age, sex, geographical region, education, alcohol intake, smoking status, body mass index, total energy intake, and location.

with higher risk of IBD. We hypothesised that increased sodium intake could be implicated, as various animal models have shown increased dietary sodium to be associated with exacerbation of autoimmune conditions, including collagen induced rheumatoid arthritis[34] and 2,4,6-trinitrobenzenesulfonic acid induced colitis for IBD.[35] In our study, however, we found no relation between urinary sodium, a surrogate for dietary sodium intake, and development of IBD. This suggests that components other than sodium in ultra-processed foods might be responsible for the higher risk of IBD observed with higher consumption of salty snacks.

Further studies are required to identify potential contributory factors in ultra-processed foods. Preclinical studies in mice models found that emulsifiers, which are widely used in western diets and include carboxymethylcellulose and polysorbate 80, induce thinning of the mucosal layer and dysbiosis and promote development of colitis and colitis associated colon cancer.[36-38] In preclinical studies other additives that have been implicated include maltodextrin[39 40] and titanium dioxide.[41] Intake of foods containing these types of additives could be a plausible pathway for disruption of gut microbiota and propagation of the subsequent immune activation that occurs in IBD.

Recent studies have assessed the association between processed food intake and IBD. One study from Romania and Belgium reported that participants with IBD were more likely to report higher intake of refined sweetened foods, processed and high fat meats, fried food, salt, ice cream, mayonnaise, margarine, and chips or other snacks compared with healthy controls. A US study using data from the National Health Interview Study in 2015 reported higher intake of cheese, cookies, French fries, sports drinks, and soda among participants with IBD compared with no IBD. These studies, however, had design limitations, including using a case-control or retrospective design, which are vulnerable to recall bias. A nested matched case-control study conducted using the large European Prospective Investigation into Cancer and Nutrition (EPIC) prospective database found that diets of high sugar and soft drink intake and low vegetable intake were associated with an increased risk of ulcerative colitis.[5] A prospective study using data from the Nurses Health Study II cohort found that participants with a "prudent" dietary pattern in high school (higher intake of vegetables, fibre, and fish) showed a lower risk of subsequent Crohn's disease.[42] A French study using the NutriNet-Sante prospective cohort did not find higher intake of ultra-processed foods among participants who subsequently developed IBD compared with those who did not, after adjustment for confounders, but this study might have been underpowered because of too few participants (n=75) with IBD.[15]

We also found higher intake of fried food to be associated with higher risk of IBD. This association might exist because many fried foods are also processed (eg, chicken nuggets, French fries). It could be that the action of frying and the processing of oil leads to

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modification of nutrients within the food.[43 44] The type and quality of oil used might also be relevant.[45]

In our study, intake of white meat, unprocessed red meat, dairy, starch, and fruit, vegetables, and legumes were not found to be associated with risk of IBD. Recent meta-analyses that included high quality studies found no associations between pre-illness intake of carbohydrates, sugar, protein, or fat for either Crohn's disease or ulcerative colitis.[46-48] Although some studies have suggested increased meat intake could increase the risk of IBD,[10 16] and higher fruit and vegetable intake might be protective,[17 18] these findings have not been found consistently in all studies that have examined this potential association.[10 49 50] This finding could be partly due to study design limitations, particularly in case-control studies where the selection of controls might have an impact on associations being evaluated.

For positive associations found in our study, similar directional effects were observed for Crohn's disease and ulcerative colitis. Overall, a lower number of participants with Crohn's disease were observed in our study (n=90) compared with ulcerative colitis (n=377). Reasons for the higher incidence of ulcerative colitis compared with Crohn's disease in our study probably reflects participants being from developing nations, where ulcerative colitis is known to be relatively more prevalent.[51] Furthermore, the age of participants in the PURE study was 35-70 years, and the risk of Crohn's disease is lower at older ages, whereas ulcerative colitis has a bimodal peak, with many patients receiving a diagnosis in their 50s and 60s.[1 52]

Strengths and limitations of this study

We investigated dietary risk factors for IBD in a large prospective multinational cohort study. The study design overcomes the limitations of many of the existing studies in this specialty, which are retrospective or case-control in design and restricted to homogenous populations with limited external validity.[10] The longitudinal design of our study allowed us to focus on people with incident IBD and to use medical record review and central adjudication to validate a sample of the diagnoses. Information on diet was collected at baseline before diagnosis to minimise risk of bias from reverse causation or recall bias. We excluded participants who received a diagnosis within one year of the baseline FFQ assessment to account for the possibility of dietary changes related to gastrointestinal symptoms that would later lead to a diagnosis of IBD. Validated, standardised, and country specific questionnaires were used for collection of dietary information. Because other baseline covariates on univariable analysis were found to be associated with risk of IBD, including smoking status and location, the validity of our study findings was increased.[53 54] We also identified other factors on univariable analysis, such as alcohol intake and BMI, that were significant but possibly correlated with other confounding factors and when put into a multivariable model were no longer associated with risk of IBD (analyses not shown).

Nonetheless, our study also has some potential limitations. Owing to the age of participants in the PURE study (35-70 years), incident Crohn's disease was observed in a relatively small number of participants, which might have resulted in our study being underpowered to determine risk factors for Crohn's disease. Furthermore, the generalisability of these findings to patients who develop IBD at an earlier age (children or young adulthood) is unclear. We did, however, run subgroup analyses to determine whether age was an effect modifier and found similar increased hazard ratios for risk of IBD in those younger than or older than 50 years. Only a sample of participants with IBD were selected for validation, which increases the risk of misclassification for cases that did not undergo verification processes, but misclassification of participants with IBD would tend to bias associations to the null and this should not affect our findings. We did not account for dietary changes over time, but dietary intake as measured by the FFQ has been shown to be relatively stable over time.[55] During follow-up, however, some of the diets in included countries might have become partly westernised, which could lead to inaccuracy in capturing the degree of processed foods and their influence in these participants. FFQs are not an ideal instrument for measuring absolute intake—however, FFQs might still be useful to assess relative intake, so our results should be taken in the context of higher versus lower levels of ultra-processed food intake.[56] Multiple comparisons were made and a possibility remains of positive results being found owing to chance alone. Our findings did, however, show a high level of statistical significance, thereby providing some reassurance that our observations are probably real. Lastly, although we were able to adjust for many variables through our multivariable models, owing to the observational nature of our study the possibility of residual bias from unmeasured (eg, antibiotic use in early childhood), imprecisely measured, or unknown confounders remains.

Conclusions

In this study, higher ultra-processed food intake was associated with higher risk of IBD. As white meat, unprocessed red meat, dairy, starch, and fruit, vegetables, and legumes were not found to be associated with development of IBD, this study suggests that it might not be the food itself that confers this risk but rather the way the food is processed or ultra-processed. A possibility also remains of residual confounding owing to unmeasured or unknown confounders. Further studies are needed to identify specific potential contributory factors among processed foods that might be responsible for the observed associations in our study.

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Supplementary information: appendices 1 and 2, tables 1-18, and figures 1 and 2