Ultra-processed Foods and Risk of Crohn's Disease and Ulcerative Colitis: A Prospective Cohort Study

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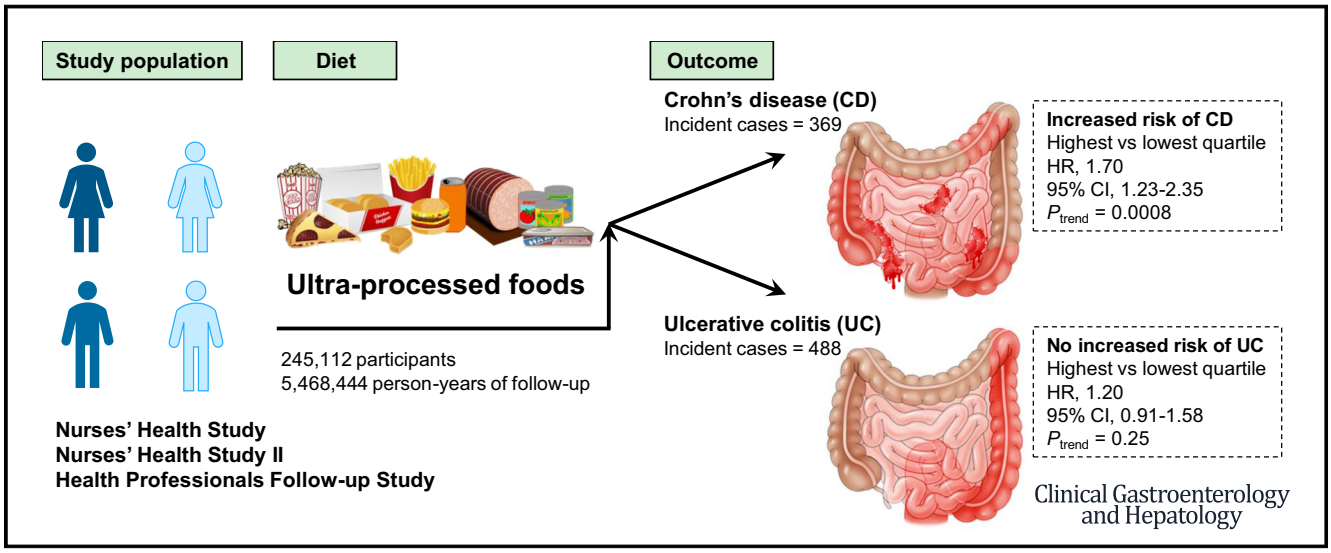
This article has an accompanying continuing medical education activity, also eligible for MOC credit on page e1502. Upon completion of this activity, successful learners will be able to understand the role of diet as a risk factor for IBD and define the role of diet for treatment of IBD.



BACKGROUND & AIMS: **The rising incidence of inflammatory bowel disease in regions undergoing Westernization has coincided with the increase in ultra-processed food (UPF) consumption over the past few decades. We aimed to examine the association between consumption of UPFs and the risk of Crohn's disease (CD) and ulcerative colitis (UC).**

METHODS: **We performed a prospective cohort study of 3 nationwide cohorts of health professionals in the United States—the Nurses' Health Study (1986–2014), the Nurses' Health Study II (1991–2017), and the Health Professionals Follow-up Study (1986–2012). We employed Cox proportional hazards models with adjustment for confounders to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for CD and UC according to self-reported consumption of UPFs.**

Abbreviations used in this paper: AHEI-2010, Alternate Healthy Eating Index-2010; BMI, body mass index; CD, Crohn's disease; CI, confidence interval; HPFS, Health Professionals Follow-up Study; HR, hazard ratio; IBD, inflammatory bowel disease; NHS, Nurses' Health Study; NSAID, nonsteroidal anti-inflammatory drug; PCI, processed culinary ingredient; SFFQ, semi-quantitative food frequency questionnaire; UC, ulcerative colitis; UMP, unprocessed or minimally processed food; UPF, ultra-processed food.

Most current article

1542-3565/$36.00
https://doi.org/10.1016/j.cgh.2021.08.031

RESULTS: **The study included 245,112 participants. Over 5,468,444 person-years of follow-up, we documented 369 incident cases of CD and 488 incident cases of UC. The median age at diagnosis was 56 years (range, 29–85 years). Compared with participants in the lowest quartile of simple updated UPF consumption, those in the highest quartile had a significantly increased risk of CD (HR, 1.70; 95% CI, 1.23–2.35; $P_{trend} = .0008$). Among different UPF subgroups, ultra-processed breads and breakfast foods; frozen or shelf-stable ready-to-eat/heat meals; and sauces, cheeses, spreads, and gravies showed the strongest positive associations with CD risk (HR per 1 standard deviation increase in intake, 1.18 [95% CI, 1.07–1.29], 1.11 [95% CI, 1.01–1.22], and 1.14 [95% CI, 1.02–1.27], respectively). There was no consistent association between UPF intake and UC risk.**

CONCLUSIONS: **Higher UPF intake was associated with an increased risk of incident CD. Further studies are needed to identify specific contributory dietary components.**

Keywords: Emulsifier; Epidemiology; Inflammation; Nutrition.

The incidence of inflammatory bowel disease (IBD; Crohn's disease [CD], ulcerative colitis [UC]) has been increasing worldwide,[1] in part due to changes in lifestyle, especially diet. Epidemiologic studies have provided rigorous evidence in support of an association between diet and the risk of IBD.[2] However, a limitation of prior studies has been the focus on individual nutrients rather than food items, and thus dietary recommendations are not directly inferable. Studies investigating dietary patterns examined established dietary indices such as the Western or Mediterranean diet based on the frequency of consumption of individual food items.[3,4] An important factor hitherto not robustly examined in the context of diet and IBD has been the role of food processing.

Ultra-processed foods (UPFs), defined within the NOVA classification system, consist of ready-to-consume formulations of ingredients, typically created by series of industrial techniques and processes.[5] They frequently involve the incorporation of additives, such as sweeteners, preservatives, emulsifiers, thickeners, and flavors, which aid in food preservation and produce hyperpalatable products. There has been a significant increase in UPF consumption in several regions of the world over the past few decades, including Asia where the steepest rise in IBD incidence has been observed.[6,7] The health impact of UPFs has been widely examined in the context of obesity and cardiometabolic outcomes.[8] Yet epidemiologic evidence for IBD has been lacking thus far. Although there are likely overlaps between UPFs and other dietary patterns, the purpose of studying UPFs is to investigate the role of food processing in IBD risk, especially given the strong biological plausibility. Experimental studies have linked constituents enriched in UPFs including sweeteners, sugars, and salt to intestinal inflammation.[9-12] Elegant experimental models have demonstrated that dietary emulsifiers may promote colonic inflammation through disrupting the intestinal mucous barrier and altering the microbiome.[13-17]

We herein utilized 3 large prospective cohorts of women and men to examine the association between overall UPF consumption as well as individual food group categories and the risk of incident CD and UC.

Methods

Study Population

The study included data from 3 ongoing prospective cohorts in the United States. The Nurses' Health Study (NHS) recruited 121,700 female registered nurses aged 30 to 55 years at baseline in 1976.[18] The NHS II, established in 1989, enrolled 116,429 female registered nurses between the ages of 25 and 42 years. The Health Professionals Follow-up Study (HPFS) enrolled 51,529 male health professionals aged 40 to 75 years in 1986.[19] In all 3 cohorts, questionnaires were mailed to participants at enrollment and every 2 years thereafter to ascertain information related to medical history and lifestyle factors. Diet was assessed using validated semi-quantitative food frequency questionnaires (SFFQs) beginning in 1980, 1991, and 1986 in the NHS, the NHS II, and the HPFS, respectively, and every 4 years thereafter (1986 for the NHS).[20,21]

The current study included participants who completed a detailed SFFQ in 1986 in the NHS and the HPFS and in 1991 in the NHS II. We excluded those who had been diagnosed with CD, UC, or cancer (except for non-melanoma skin cancer) at baseline, those who reported implausible energy intake (<600 or >3500 kcal/d for women; <800 or >4200 kcal/d for men), those who only returned baseline questionnaire, or HPFS participants who did not return questionnaires after 1994 (1996 was the first year when CD was assessed as a specific and not a write-in diagnosis). After these exclusions, the study included 203,516 women and 41,596 men. The study protocol was approved by the Institutional Review Boards of the Brigham and Women's Hospital and the Harvard T.H. Chan School of Public Health.

Assessment of UPF Consumption and the NOVA Classification System

We categorized food intake according to the NOVA classification system based on the extent and purpose of the processing they undergo.[5] Details about the assessment methods can be found in the Supplementary Methods. Briefly, a 4-step process was undertaken to identify the NOVA category for each food item available in the SFFQs in our cohorts. We first compiled a list of all food items in the SFFQs. Three researchers then independently assigned food items to 1 of 4 NOVA food groups—unprocessed or minimally processed foods (UMPs), processed culinary ingredients, processed foods, and UPFs. Categorization was guided by the definitions of NOVA food groups and the example food items they contain.[22] Food items with discordant categorization or those that could be categorized into more than 1 group were short-listed and subject to further scrutiny. Finally, collective resources were used to guide the final categorization of the short-listed items. A conservative approach to the classification of food items was adopted for UPFs such that only food items that could be justifiably considered ultra-processed were assigned to this NOVA food group. Consistent with many prior studies,[23-25] we used the percentage of total energy consumption from UPFs as the primary indicator for UPF intake. In a secondary analysis, we further classified UPFs into 9 subgroups (Supplementary Table 1).

Assessment of Covariates

Information on demographic and lifestyle characteristics, including race/ethnicity, family history of IBD, smoking status, body mass index (BMI), physical activity, and medication use (nonsteroidal anti-inflammatory drugs [NSAIDs], oral contraceptives, menopausal hormone therapy), was assessed using biennial questionnaires. Dietary factors, including total energy intake and the Alternate Healthy Eating Index-2010 (AHEI-2010), were assessed using SFFQs. More information can be found in the Supplementary Methods.

Ascertainment of IBD Diagnosis

We have previously detailed our methods for defining cases of CD and UC.[26] Briefly, with each biennial questionnaire, participants indicated whether they had been diagnosed with CD or UC. We obtained permission from those who self-reported a diagnosis for review of medical records and invited them to complete a detailed supplemental questionnaire detailing the type of IBD, date of diagnosis, disease complications, and treatment. After requesting permission, medical records were independently reviewed by 2 gastroenterologists blinded to exposure information (P.L., E.W.L., K.E.B., J.M.R., H.K., A.N.A.). A diagnosis of CD or UC was made based on accepted clinical criteria incorporating symptoms, endoscopic, histologic, radiographic, or operative findings.[27,28] Disagreements on case definition were infrequent and resolved through consensus.

What You Need to Know

Background

The global emergence of inflammatory bowel disease has coincided with the increase in consumption of ultra-processed foods (UPFs) over the past few decades. Despite the strong biological plausibility from experimental studies, epidemiologic evidence in support of an association between UPF intake and the risk of inflammatory bowel disease is lacking.

Findings

Higher consumption of UPFs was associated with a significantly increased risk of Crohn's disease (CD) but not ulcerative colitis. This finding was be driven by a few UPF subgroups that showed particularly strong associations with CD risk.

Implications for patient care

By avoiding UPF consumption, individuals might substantially lower their risk of developing CD in addition to gaining other health benefits.

Statistical Analysis

Person-years were accrued from the date of return of the baseline questionnaire to the date of diagnosis of CD or UC, last questionnaire response, death, or the end of the study (June 1, 2014 for the NHS; June 1, 2017 for the NHS II; June 1, 2012 for the HPFS), whichever occurred first. In our primary analysis, we adopted the simple updated intake model, which utilized the most recent SFFQ for each participant. We also examined the impact of long-term intake by modeling the average of all available SFFQs up to the start of each 2-year follow-up. We employed Cox proportional hazards models stratified by age, cohort, and questionnaire cycle with adjustment for confounders to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for CD and UC according to consumption of UPFs. Confounders selected a priori included race/ethnicity, family history of IBD, smoking status, BMI, physical activity, total energy intake, AHEI-2010, regular NSAID use, oral contraceptives (women only), and menopausal hormone therapy (women only). Tests for linear trend were performed using the median value of each quartile of UPF consumption as a continuous variable in the regression models. In a secondary analysis, we explored the associations across different CD locations according to the Montreal classification.[29] We then separately examined various UPF subgroups to identify foods with

the strongest association with CD and UC risk. In addition to UPF intake, we also explored the association between the other 3 NOVA food groups and the risk of CD and UC.

We performed various sensitivity analyses. First, we conducted a lag analysis by skipping the immediate prior questionnaire. This extended the interval between exposure and follow-up by an additional 4 years to further reduce the possibility of pre-diagnostic symptoms potentially modifying diet.[30] Second, to examine the generalizability to younger-onset IBD, we censored participants at the age of 60 years. Finally, we used the percentage of grams per day from UPFs in the total diet as an alternative indicator for UPF consumption and repeated the main analysis.

We conducted all analyses using SAS 9.4 (SAS Institute Inc, Cary, NC). All statistical tests were 2-sided, with a P value less than .05 indicating statistical significance.

Results

Study Population

Our study included 203,516 women and 41,596 men contributing to 5,468,444 person-years of follow-up. There were 369 incident cases of CD and 488 incident cases of UC, yielding incidence rates of 6.7 and 8.9 per 100,000 person-years, respectively. The median age of diagnosis was 56 years (range, 29-85 years). A higher percentage of energy intake from UPFs was associated with higher BMI, higher total energy intake, lower physical activity, and lower AHEI-2010 (Table 1). Throughout follow-up, participants in the highest

Table 1. Characteristics of study participants according to consumption of ultra-processed foods over the study period

	UPFs (% energy intake)			
Variables	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Person-years	1,369,955	1,367,466	1,356,769	1,374,253
Energy intake from UPFs, %, median (IQR)	21.0 (17.1–23.8)	29.9 (28.1–31.9)	36.4 (34.6–38.4)	46.4 (43.1–51.4)
Age at baseline, y	45.7 (10.2)	45.0 (10.2)	44.7 (10.1)	44.5 (10.3)
Female	83.5	83.5	83.5	83.5
Race/ethnicity				
Southern European/Mediterranean	20.0	20.0	19.8	19.2
Scandinavian	8.1	7.8	7.7	6.8
Other Caucasians	62.7	65.0	65.6	67.1
Asian, Hispanic, African, or others	9.2	7.2	6.9	6.9
Family history of IBD	4.1	4.1	4.1	4.1
Smoking status				
Never smokers	55.6	56.2	56.6	56.7
Former smokers	38.0	36.8	35.7	33.8
Current smokers	6.4	7.0	7.7	9.5
Body mass index, kg/m^2	25.8 (5.1)	26.4 (5.3)	26.8 (5.6)	27.2 (6.0)
Physical activity, MET-hrs/wk	24.7 (23.5)	21.5 (20.8)	19.7 (19.7)	17.5 (18.5)
Total energy intake, kcal/d	1727 (467)	1789 (476)	1821 (491)	1844 (513)
Alternate Healthy Eating Index-2010	57.6 (9.9)	53.3 (9.3)	50.5 (9.1)	46.6 (9.1)
Regular NSAID use	34.3	36.8	38.2	39.1
Oral contraceptives,[a]				
Never users	32.5	32.5	32.2	32.0
Ever users	67.5	67.5	67.8	68.0
Menopausal hormone therapy,[a]				
Premenopausal	36.1	36.4	36.5	36.1
Postmenopausal never users	23.3	23.8	24.3	24.6
Postmenopausal former users	21.5	21.7	21.7	21.7
Postmenopausal current users	19.1	18.1	17.5	17.6

Note: Characteristics of study participants are presented by quartiles of UPF consumption. UPF consumption was quantified using the percentage of total energy intake from UPFs. All variables are standardized to the age and cohort distribution of the study population except for age and sex. Mean (SD) is presented for continuous variables and percentage of participants for categorical variables. Updated information over the study period was used for all variables except for age.
Abbreviations: IBD, Inflammatory bowel disease; IQR, interquartile range; MET, metabolic equivalent of task; NSAID, nonsteroidal anti-inflammatory drug; SD, standard deviation; UPF, ultra-processed food.
[a]Among women.

quartile of UPF intake consumed a median of 46.4% of their total energy from UPFs, compared with 21.0% for those in the lowest quartile. Among the UPF subgroups, ultra-processed breads and breakfast foods contributed the largest share, followed by frozen or shelf-stable ready-to-eat/heat meals and packaged sweet snacks and desserts, accounting for 29.1%, 21.0%, and 20.4% of all UPF intake, respectively (Supplementary Table 1).

Ultra-processed Foods

Compared with participants in the lowest quartile of simple updated UPF consumption, those in the highest quartile had a significantly increased risk of CD (HR, 1.70; 95% CI, 1.23–2.35; $P_{trend} = .0008$) (Table 2). Similarly, participants in the highest quartile of cumulative average UPF intake were at increased risk of CD compared with those in the lowest quartile (HR, 1.40; 95% CI, 1.00–1.96; $P_{trend} = .05$). A secondary analysis across different CD locations demonstrated that participants in the highest quartile of simple updated UPF intake had the highest risk of ileal, colonic, and ileocolonic CD (Supplementary Table 2). In contrast, we observed no increase in the risk of UC among participants in the highest quartile of UPF intake compared with those in the lowest quartile, either using simple updated (HR, 1.20; 95% CI, 0.91–1.58; $P_{trend} = .25$) or cumulative average UPF intake (HR, 1.23; 95% CI, 0.92–1.65; $P_{trend} = .25$) (Table 2).

Certain food groups were more strongly associated with CD risk (Figure 1). These included ultra-processed breads and breakfast foods; frozen or shelf-stable ready-to-eat/heat meals; and sauces, cheeses, spreads, and gravies (HR per 1 standard deviation increase in intake, 1.18 [95% CI, 1.07–1.29], 1.11 [95% CI, 1.01–1.22], and 1.14 [95% CI, 1.02–1.27], respectively). As with overall intake, we did not find an association between individual UPF subgroups and UC risk.

Unprocessed or Minimally Processed Foods, Processed Culinary Ingredients, and Processed Foods

The percentage of total energy intake from UMP consumption was inversely associated with the risk of

Table 2. Risk of CD and UC According to Consumption of UPFs

	UPFs (% energy intake)				
Simple updated	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P_{trend}[c]
Person-years	1,369,955	1,367,466	1,356,769	1,374,253	
CD					
No. of cases	69	83	95	122	
Age-adjusted HR (95% CI)[a]	1 (reference)	1.24 (0.90–1.71)	1.42 (1.04–1.94)	1.75 (1.29–2.35)	.0001
Multivariable-adjusted HR (95% CI)[b]	1 (reference)	1.22 (0.88–1.69)	1.37 (0.99–1.89)	1.70 (1.23–2.35)	.0008
UC					
No. of cases	108	123	121	136	
Age-adjusted HR (95% CI)[a]	1 (reference)	1.18 (0.91–1.52)	1.14 (0.88–1.48)	1.25 (0.97–1.62)	.11
Multivariable-adjusted HR (95% CI)[b]	1 (reference)	1.15 (0.88–1.49)	1.10 (0.84–1.45)	1.20 (0.91–1.58)	.25
Cumulative average	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P_{trend}[c]
Person-years	1,368,223	1,365,047	1,362,821	1,372,353	
CD					
No. of cases	70	91	102	106	
Age-adjusted HR (95% CI)[a]	1 (reference)	1.32 (0.96–1.80)	1.48 (1.09–2.01)	1.49 (1.10–2.02)	.01
Multivariable-adjusted HR (95% CI)[b]	1 (reference)	1.25 (0.90–1.71)	1.38 (1.00–1.90)	1.40 (1.00–1.96)	.05
UC					
No. of cases	98	130	132	128	
Age-adjusted HR (95% CI)[a]	1 (reference)	1.37 (1.05–1.78)	1.38 (1.06–1.79)	1.30 (1.00–1.70)	.08
Multivariable-adjusted HR (95% CI)[b]	1 (reference)	1.32 (1.01–1.73)	1.31 (0.99–1.73)	1.23 (0.92–1.65)	.25

Abbreviations: CD, Crohn's disease; CI, confidence interval; HPFS, Health Professionals Follow-up Study; HR, hazard ratio; IBD, inflammatory bowel disease; MET, metabolic equivalent of task; NHS, Nurses' Health Study; NSAID, nonsteroidal anti-inflammatory drug; UC, ulcerative colitis; UPF, ultra-processed food.

[a]Cox proportional hazards model stratified by age (months), cohort (NHS, NHS II, HPFS), and questionnaire cycle (in 2-year intervals).

[b]Additionally adjusted for race/ethnicity (Southern European/Mediterranean, Scandinavian, other Caucasians, other racial/ethnic groups), family history of IBD (no, yes), smoking status (never smokers, former smokers, current smokers), body mass index (<18.5, 18.5–24.9, 25–29.9, ≥30 kg/m^2), physical activity (in quintiles, MET-hrs/wk), total energy intake (in quintiles, kcal/d), Alternate Healthy Eating Index-2010 (in quintiles), regular NSAID use (no, yes), oral contraceptives (never users, ever users; women only), and menopausal hormone therapy (premenopausal, postmenopausal never users, postmenopausal former users, postmenopausal current users; women only).

[c]Test for trend was conducted by modeling the median value of each quartile of UPF consumption as a continuous variable.

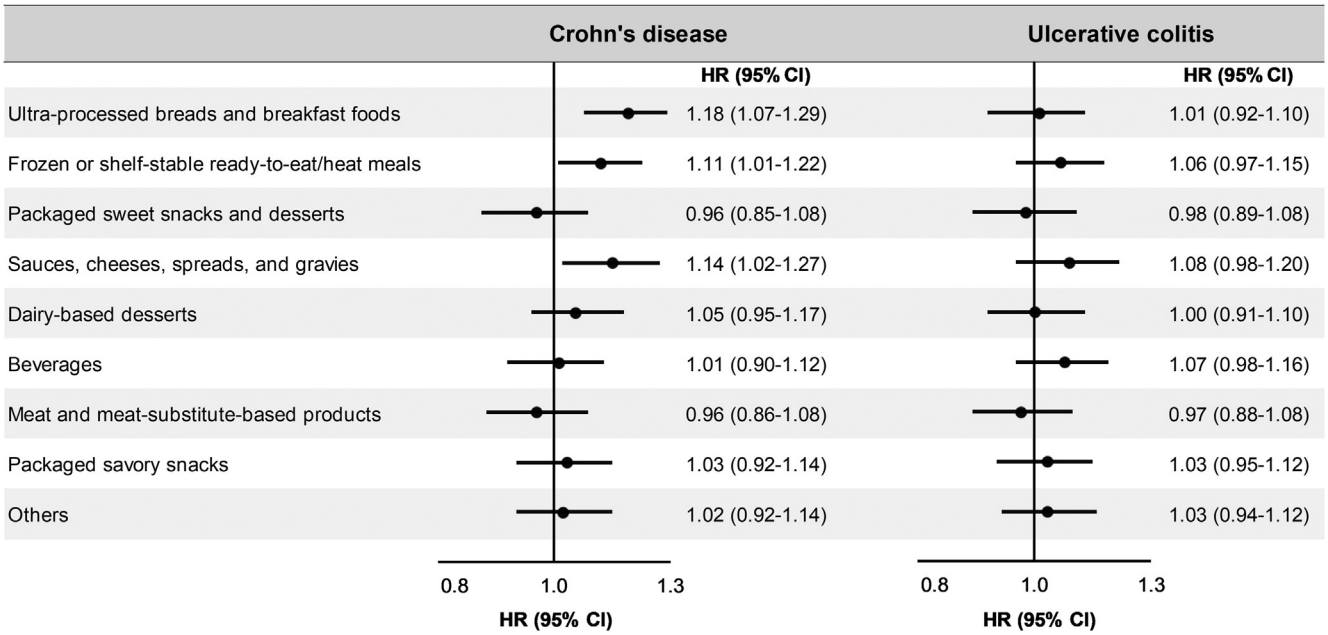


Figure 1. Risk of CD and UC according to consumption of various subgroups of UPFs. Food intake was modeled as 1 standard deviation increase in the percentage of total energy intake from that subgroup. Multivariable Cox proportional hazards models were stratified by and adjusted for the same variables as the multivariable models in Table 2. We mutually adjusted for the individual subgroups to evaluate whether the associations observed for each subgroup were independent of each other.

CD (HR, 0.70; 95% CI, 0.52–0.94; $P_{trend} = .02$) and UC (HR, 0.74; 95% CI, 0.57–0.95; $P_{trend} = .01$) in the age-adjusted but not the multivariable model (Supplementary Table 3). Consumption of PCIs and PFs was not associated with CD or UC risk.

Sensitivity Analysis

In a sensitivity analysis, we observed similar associations by extending the interval between diet assessment and follow-up (Supplementary Table 4). Censoring participants at age 60 years also yielded consistent results as in the overall cohort (Supplementary Table 5). Finally, by replacing the percentage of total energy intake with the percentage of grams per day from UPFs in the total diet, we saw a similar positive association between UPF consumption and the risk of CD (HR comparing Q4 and Q1, 1.40; 95% CI, 1.03–1.89; $P_{trend} = .05$), supporting the robustness of our results across various methods of quantifying UPF consumption.

Discussion

The global emergence of IBD has coincided with key changes in diet over the past few decades, including the increase in consumption of UPFs. Using 3 large prospective cohorts of women and men, we demonstrate that higher UPF consumption was associated with an increased risk of CD. Our findings lend robust epidemiologic support to the role of UPFs in the development of CD.

There are several mechanisms through which UPF consumption may influence the development of IBD. First, higher UPF consumption may be associated with the replacement of UMPs, such as those rich in fiber. Second, UPFs contain additives that may promote intestinal inflammation, such as salt. In experimental models, a higher concentration of sodium chloride increased inflammatory cytokine production and exacerbated chemically-induced colitis.[9] Dietary salt also increased intestinal permeability and induced intestinal inflammation through a reduction in fecal short-chain fatty acid production and depletion of *Lactobacillus*.[10] Third, artificial sweeteners in UPFs may predispose the gut to inflammation, as supported by sucralose/maltodextrins supplementation in mice models of spontaneous ileitis.[11] Such supplementation has been shown to induce the expansion of proinflammatory phyla belonging to Proteobacteria, promote intra-cellular persistence of enteric pathogens such as *Salmonella*,[12] and affect gut epithelial cells with the downstream effect of reducing mucus production and enhancing colitis susceptibility.[31,32] Finally, UPFs contain nanoparticles such as titanium oxide (present in icing) and aluminum which also have experimental evidence supporting an increase in susceptibility to colitis.[33,34]

In addition, the high contents of emulsifiers, thickeners, and other additives in many UPFs may directly contribute to intestinal inflammation. In an elegant experiment, administration of synthetic emulsifiers—carboxymethylcellulose and polysorbate-80—disrupted the mucous barrier and induced proinflammatory alterations in the gut microbiome,

resulting in colitis.[13] Other studies also demonstrated altered human microbiota composition and gene expression ex vivo with the administration of these commonly used additives.[15] Furthermore, carrageenan, a gelling and thickening agent derived from seaweed, has been shown in experimental studies to be associated with microbial dysbiosis and depletion of species with anti-inflammatory activity such as *Akkermansia muciniphila.*[17] In small human pilot studies, emulsifier restriction in diets was associated with improvement in CD-related symptoms.[16] Notably, we found stronger associations between intake of certain UPF subgroups and the risk of CD, namely, ultra-processed breads and breakfast foods; packaged sweet snacks; and desserts, sauces, cheeses, spreads, and gravies. This may partly be explained by the fact that many food items included in these subgroups, for example, white bread, cake, margarine, and mayonnaise, are rich in emulsifying and thickening agents.

A few hypotheses may explain the exclusive association of UPF consumption with CD. First, diet may be more relevant and have a stronger effect biologically in CD compared with UC. Most prior epidemiologic studies on overall dietary patterns have identified associations with CD but not UC.[3,4,30] Our previous work showed that consuming a proinflammatory diet was associated with an increased risk of incident CD but not UC.[30] In addition, dietary intervention studies such as exclusive enteral nutrition have demonstrated efficacy in CD with no rigorous studies in UC.[35,36] Second, exposure to luminal content (microbiome or metabolites) may be more pertinent in CD. This is supported by the effective resolution of inflammation in CD patients through fecal diversion.[37] Finally, the difference in findings may reflect the greater specificity of dietary ligands and metabolites on the small intestine compared with the colon.

Few epidemiologic studies have examined the association between UPF intake and IBD. In the French NutriNet-Santé cohort, Vasseur et al found no association between UPF intake and IBD risk. However, this study had a median follow-up of only 2.3 years and included very few cases (75 IBD cases [27 CD and 48 UC]), which likely limited the statistical power.[38] A recent publication used data from the multinational Prospective Urban Rural Epidemiology (PURE) cohort and demonstrated a positive association between UPF intake and incident IBD.[39] However, that study was limited by important factors including lack of validation for all diagnoses, assessment of diet at baseline only, varying dietary assessment instruments across geographic regions, unclear definition of UPFs, and inability to separate UPF intake from other factors associated with Westernization, given the geographical heterogeneity of included participants. Our study was strengthened by the large sample size, long-term follow-up, validated IBD diagnoses, time-varying dietary data, careful adjustment for confounders, high degree of internal validity, and robust sensitivity analyses, including a latency analysis that minimized concern for reverse causation.

We readily acknowledge several limitations to our study. First, the cohort overall skewed older compared with other population-based cohorts due to our long-term follow-up. Although extrapolating our findings to those with younger-onset diseases should be done with caution, thus far there has not been any convincing demonstration of a differential impact of environmental factors on younger- and older-onset IBD. In addition, we observed similar findings in a sensitivity analysis restricting to participants under 60 years of age. Second, there may be measurement error in UPF consumption due to potential secular changes in the degree of processing of foods, variation across brands, and incomplete labeling over the study period. Such changes in additive content may explain the more modest effect of cumulative average UPF intake when compared with simple updated intake. We acknowledge that the lack of a comprehensive nutritional database to capture such trends limited the ability to incorporate these important factors into the analysis. Third, we observed a lower percentage of total energy intake from UPFs among our study participants. This could be due to participants being health professionals and consuming an overall healthier diet, our relatively conservative approach for classifying UPFs, or the limited resolution in assessing the degree of food processing through SFFQs. Fourth, as in any observational study, the potential for unmeasured confounders must be acknowledged despite robust adjustment for established environmental risk factors. We lacked information on certain risk factors such as history of antibiotic use and exposure to air pollution. However, we did not expect these to be differential between strata of UPF intake. We also did not have information on socioeconomic status. Nonetheless, the cohorts consisted mostly of white health professionals. Although this and the use of common instruments established the high degree of internal validity within the study, with the emergence of IBD globally, it is important to replicate our findings in racially and ethnically diverse cohorts.

In conclusion, we demonstrate that higher consumption of UPFs was associated with an increased risk of CD. Further studies are needed to identify specific contributory dietary components among UPFs that might be responsible for increasing the risk of developing CD. Whether the risk of incident CD differs by the duration of UPF exposure and if avoiding UPFs is beneficial to those with an established disease would also require further research.

Supplementary Material

Note: To access the supplementary material accompanying this article, please click here.

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Acknowledgments
The authors would like to thank the participants and staff of the Nurses' Health Study, the Nurses' Health Study II, and the Health Professionals Follow-up Study for their valuable contributions. The authors assume full responsibility for analyses and interpretation of these data.

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Conflicts of interest
These authors disclose the following: James M. Richter is a consultant for Policy Analysis Inc and Takeda Pharmaceuticals. Andrew T. Chan serves as a consultant for Janssen Pharmaceuticals, Pfizer Inc, and Bayer Pharma AG, and Boehringer Ingelheim for work unrelated to the topic of this manuscript. Ashwin N. Ananthakrishnan has served as a Scientific Advisory Board member for Abbvie, Gilead, and Kyn Therapeutics, and received research grants from Pfizer and Merck. The remaining authors disclose no conflicts.

Funding
This work was supported by the National Institutes of Health (UM1 CA186107 [NHS cohort infrastructure grant], U01 CA176726 [NHS II cohort infrastructure grant], U01 CA167552 [HPFS cohort infrastructure grant]; K24 DK098311 to ATC), the Beker Foundation (to HK), the Chleck Family Foundation (to ANA), and the Crohn's and Colitis Foundation (to PL, HK, ATC, ANA). ATC is a Stuart and Suzanne Steele MGH Research Scholar. The funders had no role in the design and conduct of the study. The content is solely the responsibility of the authors and does not necessarily represent the official views of the funders.

Supplementary Methods

The NOVA Food Classification System and Its 4 Food Groups

NOVA is a food classification system used to classify foods into 1 of the 4 food groups, based on the physical, biological, and chemical processing methods used during their manufacture, including the use of additives.[1] The 4 NOVA food groups include unprocessed or minimally processed foods (UMPs), processed culinary ingredients (PCIs), processed foods, and ultra-processed foods (UPFs).

UMPs are natural foods altered by methods that include removal of inedible or unwanted parts, and processes that include drying, crushing, grinding, powdering, fractioning, filtering, roasting, boiling, non-alcoholic fermentation, pasteurization, chilling, freezing, placing in containers, and vacuum packaging. PCIs are substances derived from UMPs or else from nature by processes such as pressing, refining, grinding, milling, and drying. Some methods used to make PCIs are industrial products, designed to make durable products suitable for use in home, restaurant, and canteen kitchens to prepare, season, and cook freshly prepared dishes and meals. Processed foods are made by adding salt, oil, sugar, or other substances from PCIs to UMPs and include various preservation or cooking methods, and with breads, cheeses, and non-alcoholic fermentation. UPFs are formulations of ingredients, mostly of exclusive industrial use, typically created by series of industrial techniques and processes such as hydrolysis, hydrogenation, extrusion, moulding, and pre-frying.

Classification of Food Items Into the NOVA Food Groups

The approach to categorization of food items in our cohorts was comprised of 4 stages. The full explanation of the approach was explained in great detail in a preprint (unpublished data)[2] at the time of writing. The full-length article is expected to complete peer review and be published soon.

1. Validated semi-quantitative food frequency questionnaires (SFFQs) administered every 4 years in the Nurses' Health Study (1986–2010), the Nurses' Health Study II (1991–2015), and the Health Professionals Follow-up Study (1986–2014) were used.[3,4] All food items for which information was collected across different waves of data collection were complied. The compiled list of food items was then subject to categorization.
2. Three researchers worked independently to assign food items in the 3 cohorts to 1 of the 4 NOVA food groups. Categorization was guided by the definitions of NOVA food groups and the example food items they contain.[5] This was an iterative process requiring the review of the original SFFQs used to gather dietary information at each wave of data collection to contextualize food items within the larger food lists.
3. Categorization between researchers was triangulated. Food items for which there was consensus on the categorization among all researchers were assigned to their NOVA food groups. A food item was flagged and short-listed for further scrutiny in case of disagreement between any 2 researchers.
4. An expert panel, comprised of 3 senior researchers with substantial experience working with the dietary intake in these cohorts, was convened to review and discuss the categorization of the short-listed food items. All discussions were additionally informed by the additional resources including input from research dieticians, cohort-specific documents, and online grocery store scans.

A conservative approach to the classification of food items was adopted for UPFs. This meant that only food items that could be justifiably considered ultra-processed were assigned to this NOVA food group. For the current study, we used the percentage of total energy consumption from UPFs as the primary indicator for UPF intake. This method is consistent with many prior studies on UPF intake.[6-9] In addition, dietary components that have been previously shown to be associated with inflammatory bowel disease or colitis, such as sodium,[10-12] sugar,[13-15] fats,[16,17] fiber,[18,19] red meat,[20] and emulsifying and thickening agents,[21-25] are largely contained in energy-dense food products. Therefore, the potential associations of these components with inflammatory bowel disease would arguably be better captured through the percentage of total energy intake.

In a secondary analysis, to identify which group of UPFs contributed more strongly to disease risk, we classified UPFs into subgroups that comprised ultra-processed breads and breakfast foods; frozen or shelf-stable ready-to-eat/heat meals; packaged sweet snacks and desserts; sauces, cheeses, spreads, and gravies; dairy-based desserts; beverages; meat and meat-substitute-based products; packaged savory snacks; and others (Supplementary Table 1).

Nonsteroidal Anti-inflammatory Drug (NSAID)

Information on NSAID use was collected starting from 1990, 1989, and 1986 in the NHS, the NHS II, and the HPFS, respectively, using biennial questionnaires. Regular NSAID users were defined as participants who used NSAID at least twice per week in the past 2 years.

Alternate Healthy Eating Index-2010 (AHEI-2010)

Development of the AHEI-2010 has been described in detail previously.[26] Briefly, it consists of 11 components: 6 components for which higher intakes are better (vegetables, fruit, whole grains, nuts and legumes, long-chain ω-3 fatty acids, and polyunsaturated fatty acids); 1 component for which moderate intake is better (alcohol: 2.5 or more drinks/day is assigned 0 points, nondrinkers are assigned 2.5 points, and 0.5-1.5 drinks/day is assigned 10 points); and 4 components for which lower intake is better (sugar-sweetened beverages and fruit juice, red and processed meats, trans fats, and sodium). Each component is given a minimal score of 0 to indicate the "worst" level of intake and a maximum score of 10 to indicate the "best" level of intake, with intermediate values scored proportionally. The best levels of intake were determined a priori and based on a combination of the current dietary guidelines and the scientific literature regarding the dietary factor and chronic disease risk. All of the component scores are summed to obtain the total AHEI-2010 score, with a range from 0 (nonadherence) to 110 (perfect adherence).

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Supplementary Table 1. UPF Subgroups, Examples of Food Items for Each Subgroup, and the Share of the Percentage of Total Energy Intake Among UPFs Over the Study Period

UPF subgroups	Examples of food items	Contribution to % energy intake among UPFs
Ultra-processed breads and breakfast foods	Cold breakfast cereal; English muffins, bagels, and rolls; white bread	29.1
Frozen or shelf-stable ready-to-eat/heat meals	Beef, pork hot dogs; chowder or cream soup; pizza; ready-made pie	21.0
Packaged sweet snacks and desserts	Brownies; chocolate bars; ready-made cake; ready-made sweet rolls, coffee cakes	20.4
Sauces, cheeses, spreads, and gravies	Cream cheese; margarine; mayonnaise	13.3
Dairy-based desserts	Ice cream; frozen yogurt, ice cream; artificially sweetened yogurt	5.9
Beverages	Coke or Pepsi; Hawaiian punch; caffeine-free Coke or Pepsi	4.9
Meat and meat-substitute-based products	Bacon; processed meats, and sausages; breaded fish cakes	3.3
Packaged savory snacks	Regular crackers; fat-free popcorn; fat-free, crackers	1.8
Others	Liquor; non-dairy whiteners; other artificial sweeteners	0.3

Abbreviation: UPF, Ultra-processed food.

Supplementary Table 2. Risk of Crohn's Disease According to Consumption of UPFs by Location

	UPFs (% energy intake)				
Simple updated	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P_{trend}[c]
Person-years	1,370,056	1,367,593	1,356,890	1,374,389	
Ileal Crohn's disease					
No. of cases	19	33	23	37	
Age-adjusted HR (95% CI)[a]	1 (reference)	1.88 (1.07–3.32)	1.29 (0.70–2.37)	1.98 (1.13–3.46)	.05
Multivariable-adjusted HR (95% CI)[b]	1 (reference)	1.82 (1.02–3.24)	1.20 (0.64–2.25)	1.83 (1.00–3.32)	.13
Colonic Crohn's disease					
No. of cases	33	32	49	53	
Age-adjusted HR (95% CI)[a]	1 (reference)	0.99 (0.61–1.61)	1.53 (0.98–2.39)	1.60 (1.03–2.48)	.01
Multivariable-adjusted HR (95% CI)[b]	1 (reference)	0.98 (0.60–1.60)	1.48 (0.93–2.34)	1.60 (1.00–2.57)	.02
Ileocolonic Crohn's disease					
No. of cases	16	17	22	30	
Age-adjusted HR (95% CI)[a]	1 (reference)	1.04 (0.52–2.06)	1.37 (0.71–2.61)	1.78 (0.96–3.28)	.04
Multivariable-adjusted HR (95% CI)[b]	1 (reference)	1.04 (0.52–2.09)	1.33 (0.68–2.62)	1.73 (0.88–3.39)	.07

Abbreviations: CI, Confidence interval; HPFS, Health Professionals Follow-up Study; HR, hazard ratio; IBD, inflammatory bowel disease; MET, metabolic equivalent of task; NHS, Nurses' Health Study; NSAID, nonsteroidal anti-inflammatory drug; UPF, ultra-processed food.

[a]Cox proportional hazards model stratified by age (months), cohort (NHS, NHS II, HPFS), and questionnaire cycle (in 2-year intervals).

[b]Additionally adjusted for race/ethnicity (Southern European/Mediterranean, Scandinavian, other Caucasians, other racial/ethnic groups), family history of IBD (no, yes), smoking status (never smokers, former smokers, current smokers), body mass index ($<$18.5, 18.5–24.9, 25–29.9, $\geq$30 kg/m^2), physical activity (in quintiles, MET-hrs/wk), total energy intake (in quintiles, kcal/d), Alternate Healthy Eating Index-2010 (in quintiles), regular NSAID use (no, yes), oral contraceptives (never users, ever users; women only), and menopausal hormone therapy (premenopausal, postmenopausal never users, postmenopausal former users, postmenopausal current users; women only).

[c]Test for trend was conducted by modeling the median value of each quartile of UPF consumption as a continuous variable.

Supplementary Table 3. Risk of Crohn's Disease and Ulcerative Colitis According to Consumption of Unprocessed or Minimally Processed Foods, Processed Culinary Ingredients, and Processed Foods

	Unprocessed or minimally processed foods (% energy intake)				
Simple updated	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P_{trend}[c]
Person-years	1,373,390	1,381,177	1,342,368	1,371,509	
Crohn's disease					
No. of cases	110	91	91	77	
Age-adjusted HR (95% CI)[a]	1 (reference)	0.86 (0.65–1.14)	0.87 (0.65–1.15)	0.70 (0.52–0.94)	.02
Multivariable-adjusted HR (95% CI)[b]	1 (reference)	0.89 (0.67–1.17)	0.91 (0.68–1.22)	0.78 (0.57–1.06)	.14
Ulcerative colitis					
No. of cases	144	124	113	107	
Age-adjusted HR (95% CI)[a]	1 (reference)	0.88 (0.69–1.12)	0.80 (0.62–1.03)	0.74 (0.57–0.95)	.01
Multivariable-adjusted HR (95% CI)[b]	1 (reference)	0.90 (0.71–1.15)	0.83 (0.64–1.07)	0.80 (0.61–1.04)	.08

	Processed culinary ingredients (% energy intake)				
Simple updated	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P_{trend}[c]
Person-years	1,379,757	1,369,016	1,355,076	1,364,595	
Crohn's disease					
No. of cases	107	88	80	94	
Age-adjusted HR (95% CI)[a]	1 (reference)	0.84 (0.63–1.12)	0.83 (0.62–1.11)	0.94 (0.70–1.24)	.94
Multivariable-adjusted HR (95% CI)[b]	1 (reference)	0.85 (0.63–1.13)	0.83 (0.62–1.12)	0.91 (0.68–1.22)	.81
Ulcerative colitis					
No. of cases	134	114	117	123	
Age-adjusted HR (95% CI)[a]	1 (reference)	0.89 (0.69–1.14)	0.97 (0.75–1.24)	1.00 (0.77–1.28)	.73
Multivariable-adjusted HR (95% CI)[b]	1 (reference)	0.88 (0.68–1.13)	0.97 (0.75–1.25)	0.99 (0.77–1.27)	.74

	Processed foods (% energy intake)				
Simple updated	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P_{trend}[c]
Person-years	1,376,175	1,369,762	1,353,250	1,369,257	
Crohn's disease					
No. of cases	101	85	104	79	
Age-adjusted HR (95% CI)[a]	1 (reference)	0.84 (0.63–1.12)	1.08 (0.82–1.43)	0.78 (0.58–1.06)	.22
Multivariable-adjusted HR (95% CI)[b]	1 (reference)	0.83 (0.62–1.11)	1.07 (0.80–1.41)	0.76 (0.56–1.03)	.15
Ulcerative colitis					
No. of cases	117	121	119	131	
Age-adjusted HR (95% CI)[a]	1 (reference)	1.05 (0.81–1.35)	1.07 (0.83–1.39)	1.16 (0.90–1.50)	.25
Multivariable-adjusted HR (95% CI)[b]	1 (reference)	1.05 (0.81–1.35)	1.05 (0.81–1.36)	1.12 (0.86–1.45)	.42

Abbreviations: CI, Confidence interval; HPFS, Health Professionals Follow-up Study; HR, hazard ratio; IBD, inflammatory bowel disease; MET, metabolic equivalent of task; NHS, Nurses' Health Study; NSAID, nonsteroidal anti-inflammatory drug.

[a]Cox proportional hazards model stratified by age (months), cohort (NHS, NHS II, HPFS), and questionnaire cycle (in 2-year intervals).

[b]Additionally adjusted for race/ethnicity (Southern European/Mediterranean, Scandinavian, other Caucasians, other racial/ethnic groups), family history of IBD (no, yes), smoking status (never smokers, former smokers, current smokers), body mass index (<18.5, 18.5–24.9, 25–29.9, ≥30 kg/m2), physical activity (in quintiles, MET-hrs/wk), total energy intake (in quintiles, kcal/d), Alternate Healthy Eating Index-2010 (in quintiles), regular NSAID use (no, yes), oral contraceptives (never users, ever users; women only), and menopausal hormone therapy (premenopausal, postmenopausal never users, postmenopausal former users, postmenopausal current users; women only).

[c]Test for trend was conducted by modeling the median value of each quartile of food consumption as a continuous variable.

Supplementary Table 4. Risk of Crohn's Disease and Ulcerative Colitis According to Consumption of UPFs in a Lag Analysis

	UPFs (% energy intake)				
Simple updated	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P_{trend}[c]
Person-years	1,130,332	1,137,147	1,122,278	1,133,191	
Crohn's disease					
No. of cases	62	73	76	104	
Age-adjusted HR (95% CI)[a]	1 (reference)	1.17 (0.83–1.64)	1.23 (0.88–1.73)	1.66 (1.21–2.28)	.001
Multivariable-adjusted HR (95% CI)[b]	1 (reference)	1.12 (0.80–1.59)	1.15 (0.81–1.63)	1.54 (1.09–2.17)	.01
Ulcerative colitis					
No. of cases	91	102	103	97	
Age-adjusted HR (95% CI)[a]	1 (reference)	1.13 (0.85–1.50)	1.14 (0.86–1.52)	1.06 (0.79–1.41)	.74
Multivariable-adjusted HR (95% CI)[b]	1 (reference)	1.10 (0.82–1.46)	1.09 (0.81–1.47)	0.99 (0.73–1.35)	.91
Cumulative average	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P_{trend}[c]
Person-years	1,131,541	1,129,547	1,129,240	1,132,619	
Crohn's disease					
No. of cases	57	81	80	97	
Age-adjusted HR (95% CI)[a]	1 (reference)	1.43 (1.02–2.02)	1.44 (1.02–2.02)	1.70 (1.22–2.37)	.003
Multivariable-adjusted HR (95% CI)[b]	1 (reference)	1.35 (0.95–1.91)	1.33 (0.93–1.91)	1.56 (1.08–2.24)	.03
Ulcerative colitis					
No. of cases	85	103	108	97	
Age-adjusted HR (95% CI)[a]	1 (reference)	1.24 (0.93–1.66)	1.29 (0.97–1.71)	1.13 (0.84–1.52)	.43
Multivariable-adjusted HR (95% CI)[b]	1 (reference)	1.20 (0.89–1.61)	1.21 (0.90–1.64)	1.06 (0.77–1.47)	.79

Abbreviations: CI, Confidence interval; HPFS, Health Professionals Follow-up Study; HR, hazard ratio; IBD, inflammatory bowel disease; MET, metabolic equivalent of task; NHS, Nurses' Health Study; NSAID, nonsteroidal anti-inflammatory drug; UPF, ultra-processed food.

[a]Cox proportional hazards model stratified by age (months), cohort (NHS, NHS II, HPFS), and questionnaire cycle (in 2-year intervals).

[b]Additionally adjusted for race/ethnicity (Southern European/Mediterranean, Scandinavian, other Caucasians, other racial/ethnic groups), family history of IBD (no, yes), smoking status (never smokers, former smokers, current smokers), body mass index ($<$18.5, 18.5–24.9, 25–29.9, $\geq$30 kg/m2), physical activity (in quintiles, MET-hrs/wk), total energy intake (in quintiles, kcal/d), Alternate Healthy Eating Index-2010 (in quintiles), regular NSAID use (no, yes), oral contraceptives (never users, ever users; women only), and menopausal hormone therapy (premenopausal, postmenopausal never users, postmenopausal former users, postmenopausal current users; women only).

[c]Test for trend was conducted by modeling the median value of each quartile of UPF consumption as a continuous variable.

Supplementary Table 5. Risk of Crohn's Disease and Ulcerative Colitis According to Consumption of UPFs Among Participants Under age 60 Years

	UPFs (% energy intake)				
Simple updated	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P_{trend}[c]
Person-years	794,663	793,666	795,240	798,298	
Crohn's disease					
No. of cases	39	60	54	76	
Age-adjusted HR (95% CI)[a]	1 (reference)	1.53 (1.02–2.29)	1.34 (0.88–2.02)	1.83 (1.23–2.70)	.006
Multivariable-adjusted HR (95% CI)[b]	1 (reference)	1.45 (0.96–2.19)	1.24 (0.81–1.90)	1.68 (1.10–2.56)	.03
Ulcerative colitis					
No. of cases	58	80	84	90	
Age-adjusted HR (95% CI)[a]	1 (reference)	1.39 (0.99–1.96)	1.41 (1.01–1.98)	1.47 (1.05–2.05)	.04
Multivariable-adjusted HR (95% CI)[b]	1 (reference)	1.38 (0.98–1.96)	1.41 (0.99–2.01)	1.46 (1.01–2.10)	.06
Cumulative average	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P_{trend}[c]
Person-years	794,376	794,335	795,494	797,661	
Crohn's disease					
No. of cases	48	55	65	61	
Age-adjusted HR (95% CI)[a]	1 (reference)	1.10 (0.75–1.63)	1.28 (0.88–1.87)	1.17 (0.80–1.72)	.35
Multivariable-adjusted HR (95% CI)[b]	1 (reference)	1.01 (0.68–1.49)	1.11 (0.74–1.65)	0.99 (0.65–1.52)	.97
Ulcerative colitis					
No. of cases	58	83	88	83	
Age-adjusted HR (95% CI)[a]	1 (reference)	1.44 (1.02–2.01)	1.49 (1.06–2.08)	1.34 (0.95–1.89)	.13
Multivariable-adjusted HR (95% CI)[b]	1 (reference)	1.41 (1.00–1.99)	1.46 (1.02–2.08)	1.30 (0.89–1.90)	.26

Abbreviations: CI, Confidence interval; HPFS, Health Professionals Follow-up Study; HR, hazard ratio; IBD, inflammatory bowel disease; MET, metabolic equivalent of task; NHS, Nurses' Health Study; NSAID, nonsteroidal anti-inflammatory drug; UPF, ultra-processed food.

[a]Cox proportional hazards model stratified by age (months), cohort (NHS, NHS II, HPFS), and questionnaire cycle (in 2-year intervals).

[b]Additionally adjusted for race/ethnicity (Southern European/Mediterranean, Scandinavian, other Caucasians, other racial/ethnic groups), family history of IBD (no, yes), smoking status (never smokers, former smokers, current smokers), body mass index ($<$18.5, 18.5–24.9, 25–29.9, $\geq$30 kg/m^2), physical activity (in quintiles, MET-hrs/wk), total energy intake (in quintiles, kcal/d), Alternate Healthy Eating Index-2010 (in quintiles), regular NSAID use (no, yes), oral contraceptives (never users, ever users; women only), and menopausal hormone therapy (premenopausal, postmenopausal never users, postmenopausal former users, postmenopausal current users; women only).

[c]Test for trend was conducted by modeling the median value of each quartile of UPF consumption as a continuous variable.