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Dietary Inflammatory Potential and Risk of Crohn's Disease and Ulcerative Colitis

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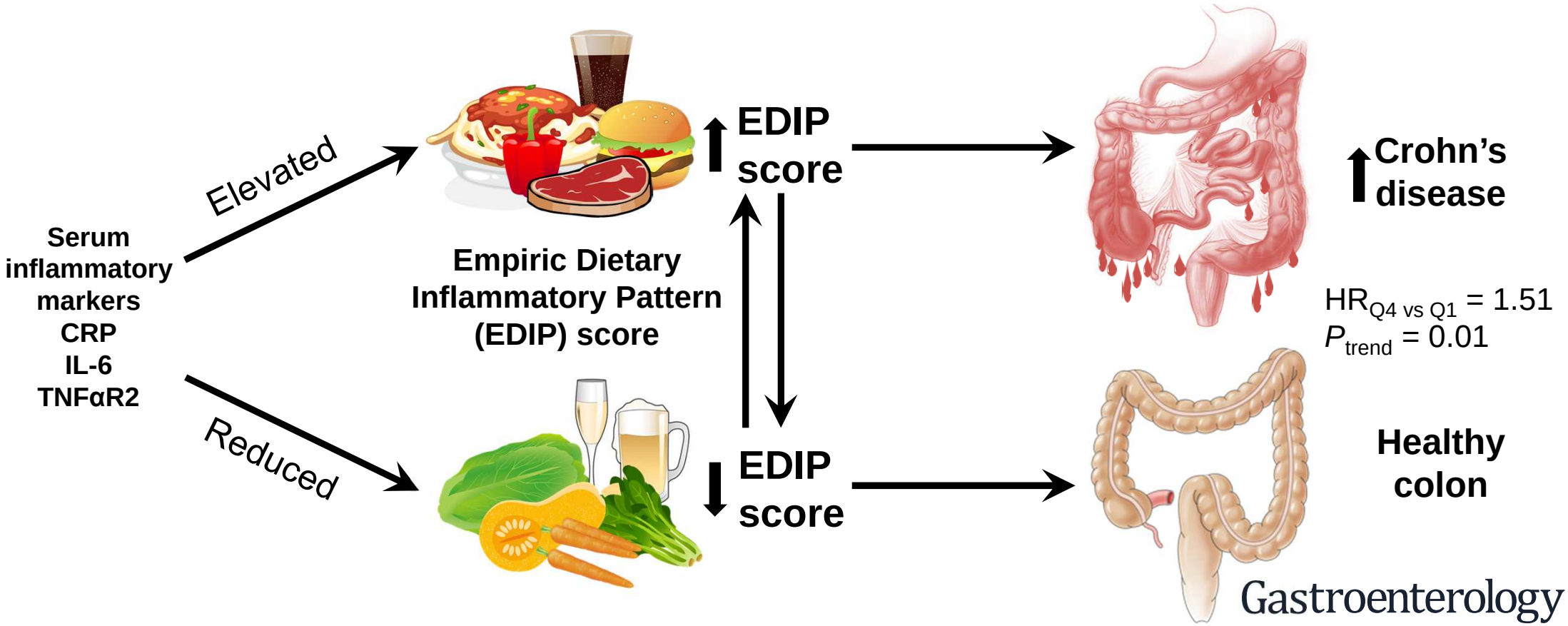
Serum inflammatory markers
CRP
IL-6
TNFαR2
Elevated
Reduced
Empiric Dietary Inflammatory Pattern (EDIP) score
EDIP score
EDIP score
Crohn's disease
HR Q4 vs Q1 = 1.51
P trend = 0.01
Healthy colon
Gastroenterology

Dietary Inflammatory Potential and Risk of Crohn's Disease and Ulcerative Colitis

Short Title: Proinflammatory diet and IBD

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Abbreviations: AIEC, adherent-invasive *Escherichia coli*; BMI, body mass index; CEACAM, carcinoembryonic antigen-related cell adhesion molecule; CI, confidence interval; CD, Crohn's disease; CRP, C-reactive protein; EDIP, empirical dietary inflammatory pattern; EEN, exclusive enteral nutrition; FFQ, food frequency questionnaire; HR, hazard ratio; HPFS, Health Professionals Follow-up Study; IBD, inflammatory bowel disease; IL-6, interleukin-6; IQR, interquartile range; MET, metabolic equivalent task; NSAID, nonsteroidal anti-inflammatory drug; NHS, Nurses' Health Study; PUFA, polyunsaturated fatty acid; PG, prostaglandin; TNF-α, tumor necrosis factor-α; TNFαR2, tumor necrosis factor-α receptor 2; ; SCFA, short-chain fatty acids; UC, ulcerative colitis.

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ABSTRACT

Background & Aims: Inflammation is a potential mechanism through which diet modulates the onset of inflammatory bowel disease. We analyzed data from 3 large prospective cohorts to determine the effects of dietary inflammatory potential on the risk of developing Crohn's disease (CD) and ulcerative colitis (UC).

Methods: We collected data from 166,903 women and 41,931 men in the Nurses' Health Study (1984–2014), Nurses' Health Study II (1991–2015), and Health Professionals Follow-up Study (1986–2012). Empirical dietary inflammatory pattern (EDIP) scores were calculated based on the weighted sums of 18 food groups obtained via food frequency questionnaires. Self-reported CD and UC were confirmed by medical record review. Cox proportional hazards models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs).

Results: We documented 328 cases of CD and 428 cases of UC over 4,949,938 person-years of follow up. The median age at IBD diagnosis was 55 years (range 29–85 years). Compared with participants in the lowest quartile of cumulative average EDIP score, those in the highest quartile (highest dietary inflammatory potential) had a 51% higher risk of CD (HR, 1.51; 95% CI, 1.10–2.07; P_{trend}=.01). Compared to participants with persistently low EDIP scores (at 2 time points, separated by 8 years), those with a shift from a low to high inflammatory potential of diet or persistently consumed a proinflammatory diet had greater risk of CD (HR, 2.05; 95% CI, 1.10–3.79 and HR, 1.77; 95% CI, 1.10–2.84). In contrast, dietary inflammatory potential was not associated with the risk of developing UC (P_{trend}=0.62).

Conclusions: In an analysis of 3 large prospective cohorts, we found dietary patterns with high inflammatory potential to be associated with increased risk of CD but not UC.

Keywords: inflammatory bowel disease; food; nutrition; lifestyle factor.

INTRODUCTION

Inflammatory bowel disease (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), affects nearly 2 million individuals in the United States, over 3 million in Europe, and thousands more worldwide[1]. They are characterized by a dysregulated immune response to the gut microbiome on a background of genetic susceptibility[2]. It is increasingly recognized that environmental factors play an important role. In support of this is the rising incidence of IBD in most regions globally over the past 4 decades in parallel with changing diet and lifestyle, and its emergence in regions of the world that have seen a rapid westernization[3]. While a number of environmental factors have been proposed, considerable interest has centered on the role of diet, which is supported by the mechanistic plausibility of its involvement in intestinal inflammation. Dietary components have been linked to maintenance of gut epithelial barrier[4], modification of the intestinal immune response[5], and alteration of microbial composition[6], all of which are critical factors in the pathogenesis of IBD.

A number of prospective cohort studies have attempted to characterize the link between diet and risk of IBD by leveraging validated measures of diet at a single or multiple time points[7]. However, a limitation of many prior studies has been their focus on single macro- or micronutrients. As dietary intake involves complex interactions between different

foods and nutrients, analyses restricted to individual components may fail to capture the inter-relatedness of food groups and lead to residual confounding[8]. Although previous publications have examined whether specific dietary patterns may trigger or protect against the onset of CD or UC[9–11], these prior studies of dietary patterns have focused on the co-clustering of different food groups in diet rather than using a hypothesis-oriented dietary pattern, designed to optimize dietary determinants of inflammation.

To elucidate the role of dietary inflammatory potential in the development of IBD, we examined the association between an empirical dietary inflammatory pattern (EDIP) score, systematically derived by weighting food groups based on their relationship with circulating markers of inflammation, and the risk of incident CD and UC in 3 large prospective cohorts. We also aimed to examine change in dietary inflammatory potential and risk of IBD to establish diet as a crucial modifiable factor in IBD prevention.

METHODS

Study population

The study included data from 3 ongoing prospective cohorts in the United States. Briefly, the Nurses' Health Study (NHS) recruited 121,700 female registered nurses aged 30 to 55 years at baseline in 1976[12]. The NHS II, established in 1989, enrolled 116,429 female

nurses between the ages of 25 and 42 years. The Health Professionals Follow-up Study (HPFS) enrolled 51,529 male health professionals between the ages of 40 and 75 years in 1986[13]. In all 3 cohorts, questionnaires were mailed to participants at enrollment and every 2 years thereafter to obtain information on various lifestyle factors and medical history. Diet was assessed using validated semi-quantitative food frequency questionnaires (FFQs) beginning in 1980, 1991, and 1986 in the NHS, the NHS II, and the HPFS, respectively, and updated every 2 to 4 years. 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 empirical dietary inflammatory pattern score

The development of EDIP score has been described in detail previously[14]. Briefly, in the NHS, investigators applied reduced rank regression models and stepwise linear regression analysis and identified from 39 pre-defined food groups a dietary pattern most predictive of 3 plasma inflammatory biomarkers: interleukin-6 (IL-6), C-reactive protein (CRP), and tumor necrosis factor-α (TNF-α) receptor 2 (TNFαR2). The EDIP score is the weighted sum of 18 food groups, with higher scores indicating proinflammatory diets and lower scores indicating anti-inflammatory diets. The detailed composition of the food group components is presented in **Supplementary Table 1**. The score has been validated in the

NHS II, the HPFS[14,15], and the multi-ethnic Women's Health Initiative[16] in which it has shown consistent correlation with plasma levels of IL-6, CRP, TNFαR2, and adiponectin. We calculated the EDIP score for each participant based on FFQ data in each questionnaire cycle[17,18] and adjusted for total energy intake using the residual method[19]. The cumulative average EDIP score in each questionnaire cycle was computed by averaging EDIP scores in all prior cycles up to the latest to best represent habitual long-term dietary intake and reduce within-person variation.

Ascertainment of inflammatory bowel disease diagnosis

We have previously detailed our methods for defining cases of CD and UC[20]. In brief, participants self-reported a diagnosis of CD or UC in biennial questionnaires. We obtained permission for review of medical records from those who reported ever having been diagnosed with CD or UC. A detailed supplemental questionnaire was sent to these participants inquiring type of IBD, date of diagnosis, disease complications, and treatment. Two board-certified gastroenterologists (H.K., A.N.A., K.E.B., P.L., J.M.R.) blinded to exposure and outcome reviewed the records independently. A diagnosis of CD or UC was made based on accepted clinical criteria incorporating symptoms, endoscopic, histologic, radiographic, or operative findings[21,22]. Disagreements on case definition were infrequent and resolved through consensus.

Assessment of covariates

In the baseline and biennial follow-up questionnaires, we assessed IBD risk factors including race, smoking, body mass index (BMI), physical activity, and use of medication including nonsteroidal anti-inflammatory drug (NSAID), oral contraceptive pill, and hormone replacement therapy[23]. BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Physical activity was measured by multiplying the typical intensity expressed in metabolic equivalent of task (MET) by the reported hours spent per week. Intake of calorie, total fiber, fatty acids, and red meat was assessed using validated semi-quantitative FFQ every 2 to 4 years[17,18].

Statistical analysis

Person-years were calculated from the date of return of the baseline questionnaire (1984 in the NHS; 1991 in the NHS II; 1986 in the HPFS) to the date of diagnosis of CD or UC, death, or the end of follow-up (June 1, 2014 for the NHS; June 1, 2015 for the NHS II; June 1, 2012 for the HPFS), whichever occurred first. We excluded participants who had been diagnosed with CD, UC, or cancer (except for non-melanoma skin cancer) or reported implausible energy intake (< 600 or > 3,500 kcal/d for women; < 800 or > 4,200 kcal/d for men) at the start of follow-up. Given that CD was not inquired before the 1996

questionnaire in the HPFS, we also excluded HPFS participants who did not return questionnaires after 1994. Cox proportional hazards models stratified by age (continuous, month), cohort (NHS, NHS II, HPFS), and time period (in 2-year intervals) were used to estimate the age-adjusted and multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs).

All multivariable models were adjusted for race (Southern European/Mediterranean, Scandinavian, other Caucasian, other races), smoking (never smoker, past smoker, current smoker), BMI (< 18.5, 18.5-24.9, 25-29.9, ≥ 30 kg/m^2), physical activity (in quintiles, MET-hr/wk), regular NSAID use (no, yes), oral contraceptive pill (never user/men, ever user), and hormonal replacement therapy (premenopausal, postmenopausal never user/men, postmenopausal past user, postmenopausal current user).

For our primary analysis examining proinflammatory diet and risk of CD and UC, we modeled our main exposure–EDIP score–as quartiles of cumulative average score since baseline. Separately, we also examined the association with recent (within 4 years prior to the current follow-up cycle) and baseline (at study entry) EDIP scores by using dietary data from the respective questionnaire cycles. Tests for linear trend were conducted by modeling EDIP score as a continuous variable in the regression models. In a subgroup analysis, we examined the risk of CD by location according to the Montréal classification[24]. CD was

grouped into ileal CD, colonic CD, and ileocolonic CD.

We then examined the impact of dynamic variation in dietary inflammatory potential. As there were fewer cases within each combination of quartiles for robust statistical power, we categorized participants according to tertiles of their EDIP scores at baseline and from the FFQ 8 years later. Classifying participants into low (first tertile), moderate (second tertile) or high EDIP score (third tertile) at each of these 2 time points yielded 9 distinct patterns of dietary inflammatory potential (low-low, low-moderate, low-high, moderate-low, moderate-moderate, moderate-high, high-low, high-moderate, high-high). We then examined the association of these patterns with the risk of CD and UC by using participants who persistently consumed a diet with low inflammatory potential (low-low) as the reference group. In this analysis, we excluded cases who were diagnosed in the intervening 8-year period.

In a sensitivity analysis, we considered the potential modification of diet by development of symptoms prior to the formal diagnosis of disease and conducted a lag analysis in which we used exposure information derived at least 2 questionnaire cycles before a follow-up interval[25,26]. To ensure the independence of our associations from the cohort of derivation of the EDIP score (the NHS), we repeated the analysis separately for

the NHS II and the HPFS. We also excluded cases diagnosed over the age of 60 to identify whether the associations were age-specific. We conducted all analyses using the SAS software (SAS Institute, Inc., Version 9.4, Cary, NC). All statistical analyses were two-sided with a *P*-value less than 0.05 indicating statistical significance.

RESULTS

Our study included 166,903 women and 41,931 men contributing to 4,949,938 person-years of follow-up. Among these participants, there were 328 cases of CD and 428 cases of UC, yielding crude incidence rate of 6.6 and 8.6/100,000 person-years, respectively. The median age of diagnosis was 55 years (range 29-85 years). The age- and cohort-standardized basic characteristics according to quartiles of cumulative average EDIP score are summarized in **Table 1**. Those with higher EDIP score were more likely to have higher BMI and lower physical activity. For dietary factors, a proinflammatory diet was associated with higher intakes of calories and red meat, and lower total fiber intake.

Table 2 presents the association between cumulative average EDIP score and risk of CD and UC. Compared to participants in the lowest quartile of cumulative average EDIP score (CD incidence 5.8/100,000 person-years), those in the highest quartile had 51% higher risk of CD (HR 1.51; 95% CI 1.10-2.07; P_{trend} 0.01) (incidence 8.7/100,000

person-years). A similar increase in risk of CD was observed in those in the highest quartile of recent (HR 1.49; 95% CI 1.07-2.06; P_{trend} 0.03) (**Table 3**) or baseline EDIP scores (HR 1.45; 95% CI 1.06-2.00; P_{trend} 0.004) (**Table 4**) when compared to the respective lowest quartiles. To examine if these associations were mediated solely by dietary fiber, we additionally adjusted for fiber intake and found no material difference in our risk estimates, suggesting that differential fiber intake is unlikely to be the explanation for these associations. In a subgroup analysis by location of CD according to the Montréal classification (**Figure 1** & **Supplementary Table 2**), we observed a stronger association between proinflammatory diet and ileal CD ($HR_{Q4\ vs\ Q1}$ 1.85; 95% CI 1.01-3.37; P_{trend} 0.03) compared to colonic CD ($HR_{Q4\ vs\ Q1}$ 1.27; 95% CI 0.80-2.00; P_{trend} 0.54) and ileocolonic CD ($HR_{Q4\ vs\ Q1}$ 1.28; 95% CI 0.71-2.29; P_{trend} 0.18).

In contrast to the findings in CD, no association was observed for UC (all $P > 0.05$) (**Tables 2-4**). Compared to participants in the lowest quartile of cumulative average EDIP score (incidence 8.3/100,000 person-years), those in the highest quartile had a similar risk of incident UC ($HR_{Q4\ vs\ Q1}$ 1.10; 95% CI 0.83-1.46; P_{trend} 0.44) (incidence 9.3/100,000 person-years).

We then examined the change in EDIP score from baseline to 8 years into the study

(**Figure 2**). Compared to participants with persistently low EDIP score at both time points, those who changed to a proinflammatory diet 8 years after baseline had a 2-fold increase in the risk of incident CD (HR 2.05; 95% CI 1.10-3.79). Despite numerically similar estimates, participants who changed from a high to a low dietary inflammatory potential (high-low) had a risk of CD statistically similar to the low-low group (HR 1.51; 95% CI 0.76-3.00), while those with persistently high EDIP scores (high-high) had a significantly elevated risk (HR 1.77; 95% CI 1.10-2.84). No association with change in EDIP score was found for risk of UC (all $P > 0.05$).

We also considered the possibility that symptoms of CD and UC may precede a formal diagnosis by several months, thereby influencing dietary intake. Using dietary assessment derived at least 4 years prior to the 2-year follow-up intervals in a lag analysis, we observed similar positive association between cumulative average EDIP score and CD ($HR_{Q4\ vs\ Q1}$ 1.51; 95% CI 1.08-2.12; P_{trend} 0.005). In a sensitivity analysis, we found similar directions and magnitude of effect in the NHS II ($HR_{Q4\ vs\ Q1}$ 1.40; 95% CI 0.86-2.29) and the HPFS ($HR_{Q4\ vs\ Q1}$ 3.19; 95% CI 1.08-9.41), demonstrating the independence of findings from the cohort of derivation of the EDIP. Excluding cases diagnosed over the age of 60 years revealed a similar association between cumulative average EDIP score and risk of CD ($HR_{Q4\ vs\ Q1}$ 1.44; 95% CI 1.01-2.07; P_{trend} 0.04).

DISCUSSION

The global emergence of CD and UC has highlighted the role of changing environmental factors, in particular diet, on disease development. Using 3 large prospective cohorts of women and men and an intentionally-derived dietary pattern based on association with circulating inflammatory markers, we found that women and men who consumed diets with high inflammatory potential had increased risk of developing CD but not UC. Shift from a low to high inflammatory potential of diet and a persistently proinflammatory diet were both associated with greater risk of CD when compared to a diet with constantly low inflammatory potential. These findings suggest a dynamic and cumulative effect of inflammatory potential of diet on the pathogenesis of CD.

Prior studies have investigated the association between certain dietary patterns and development of CD and UC[9–11,27]. Dietary patterns resembling the Western diet–characterized by higher intake of red meat, high-fat dairy, and refined grains–have been proposed to trigger the onset of intestinal inflammation by inducing changes in gut microbiome, altering host homeostasis and regulating T-cell immune response[28,29]. An analysis of a prospective cohort found that individuals who consumed a diet high in sugar and soft drinks and low in vegetables had a higher risk of UC but not CD[10]. In a

case-control analysis, D'Souza *et al.*[11] applied factor analyses and identified 4 sex-specific dietary patterns, among which a diet high in consumption of meats, fatty foods, and desserts, resembling the Western dietary pattern, conferred increased risk for developing CD among girls. In contrast, diets rich in fruit, vegetables, legumes, whole grains, fish, and poultry–resembling a more prudent and Mediterranean dietary pattern with high fiber and marine ω-3 content–may have anti-inflammatory effects. A case-control[11] and 2 cohort studies[9,27] found that consumption of these diets is associated with lower risk of CD. A limitation of the above studies is that diet was assessed at a single time point (thereby precluding effect of changing diet) and the association of change in diet could not be assessed. In addition, most of the studied dietary patterns were derived based on co-clustering of different food groups rather than based on the associations of foods with inflammatory markers. Here, by identifying a combination of food groups predictive of circulating markers of inflammation, we provide a more robust evidence base behind the association of these foods with inflammation and IBD.

Proinflammatory and anti-inflammatory food groups among the components of EDIP score have been variably associated previously with either CD or UC[26,30–37]. The most robust evidence lies in the association with fiber-rich foods. Both case-control[36] and prospective cohort studies[26] have suggested that diets rich in fruit and vegetables are

inversely associated with CD. This is mechanistically supported by experimental evidence[38]. High fiber intake from fruit and vegetables is associated with increase in the production of short-chain fatty acids (SCFAs) such as butyrate which modulate intestinal inflammation through several mechanisms, including suppressing the lipopolysaccharide- and cytokine-stimulated production of proinflammatory mediators, inhibiting expression of adhesion molecules, and reducing the production of chemokines by neutrophils and macrophages[38]. Fiber may contribute to maintenance of epithelial barrier integrity by reducing translocation of intestinal pathogens across Peyer's patches and colonic lymphoid follicles[39,40]. Furthermore, cruciferous vegetables contain natural ligands for aryl hydrocarbon receptor, a transcription factor whose expression has been inversely associated with intestinal inflammation[41]. The association of EDIP score with risk of CD, however, does not appear to be mediated solely by dietary fiber since in our study, the association remained unchanged upon additional adjustment for fiber intake. While alcohol intake itself has not been robustly associated with IBD, a number of *in vitro*[42] and animal studies[43] have demonstrated an anti-inflammatory property of resveratrol, a natural (poly) phenol found in red wine. There are likely a variety of mechanisms behind the beneficial effects of resveratrol, including inhibition of NF-κB activation, decreased cyclooxygenase-2 expression, prostaglandin (PG) E_2, PGD_2 levels and neutrophil infiltration, reduction of proinflammatory cytokines (e.g., TNF-α), and attenuation of reactive species production[44].

The potential role of this antioxidant was supported by a prospective cohort study[45] which demonstrated an inverse association between resveratrol intake and CD. Interestingly, and perhaps counter to its position as a calorie-dense processed food, in the derivation of the EDIP score, pizza intake demonstrated a significant inverse association with inflammatory markers. One potential explanation for this is the abundance of bioavailable lycopene in cooked tomato paste compared to uncooked fresh tomatoes. Lycopene is an unsaturated carotenoid with antioxidant and anti-inflammatory properties[46]. Its absorption may be facilitated by its lipophilic character and the high levels of fat in pizza, thereby rendering pizza as having strong anti-inflammatory potential.

In contrast to food groups with anti-inflammatory properties, food groups that are positively associated with EDIP score are characterized by calorie-dense foods high in animal proteins, saturated fats, and glycemic carbohydrates, such as red meat, refined grain, and high-energy soft drinks[14]. Plausible explanations of red meat's role in gut inflammation include the generation of potentially toxic substances such as ammonia, amines, N-nitroso compounds, phenols, cresols, and hydrogen sulfide from high consumption of amino acids and heme contained in red meat products[47]. Increased dietary heme intake may also form reactive oxygen species and cause colonic epithelial damage and DNA strand breaks[48]. However, contrary to our findings, epidemiologic studies have mostly demonstrated an

association between red meat intake and UC[49]. In addition, patients with CD have an abnormal expression of carcinoembryonic antigen-related cell adhesion molecule (CEACAM) 6, a receptor for adherent-invasive *Escherichia coli* (AIEC), in the ileal epithelium[50]. Martinez-Medina *et al.*[29] showed that a diet high in fat and sugar alters the composition of intestinal microbiota and host homeostasis (e.g., increased intestinal permeability and TNF-α secretion) in CEACAM10 transgenic mice, leading to a higher ability of AIEC to colonize the gut mucosa and induce inflammation.

Our findings also shed light on the dynamic interplay between diet and disease risk. When we examined diet at 2 different time points in relation to future risk of disease, we noted that even among those who consumed a baseline diet with low inflammatory potential, modification to a proinflammatory diet was associated with a significant increase in disease risk. Furthermore, participants who persistently consumed a proinflammatory diet remained at a higher risk for CD, while the risk for those who switched to a diet with low inflammatory potential were no longer statistically different from that of those whose EDIP scores remained low at both time points. Together, our results demonstrated that dietary changes dynamically alter subsequent disease risk, thereby rendering dietary modification an attractive intervention for disease prevention.

A few hypotheses may explain the exclusive association of EDIP with CD. First, diet may be more relevant and have a stronger effect biologically in CD compared to UC. Most prior epidemiologic studies on dietary risk factors have identified associations with CD but not UC (except for ω-3/ω-6 polyunsaturated fatty acids [PUFAs])[9,11,27]. Dietary intervention studies such as exclusive enteral nutrition (EEN) have demonstrated efficacy in CD with no rigorous studies in UC[51,52]. Second, exposure to luminal content (microbiome or metabolites) may be more pertinent in CD. Fecal diversion is often more effective in resolving inflammation in CD[53]. In contrast, systemic factors (immunologic or epithelial barrier defects) may play a greater role in UC[54]. Third, dietary factors more relevant to UC such as ω-3 and ω-6 PUFAs were not found to be associated with systemic inflammatory markers in our cohorts and consequently not factored into the calculation of EDIP score. Finally, the difference in findings may reflect a specificity of effect of dietary ligands and metabolites on the small intestine rather the colon. This may also potentially explain the stronger association with ileal CD compared to colonic CD. While the exact mechanisms of ileal compared to colonic involvement in CD remains to be robustly determined, studies have demonstrated that differences in genetic variants or microbial composition may confer this location specificity[55,56]. Indeed, depletion of butyrate producers such as *Faecalibacterium prauznitzii* or increased abundance of *Escherichia coli* are more notable in ileal CD compared to colonic CD, suggesting perhaps a stronger diet-microbiome-phenotype link for

this location[57,58]. Few studies examined whether disease location influences response to dietary therapy, though the evidence is conflicting. While 2 studies suggested that there is poorer response to EEN in isolated colonic CD when compared to CD with small bowel involvement[59,60], one study found no such difference[61]. A meta-analysis concluded that there was insufficient data to evaluate the effectiveness of EEN based on disease location[62]. It must also be acknowledged that most studies of successful dietary therapies for treatment of IBD have been in children[51,52,59,63].

There are several strengths to our study. First, we prospectively collected detailed information on dietary exposure at several time points using validated FFQs. This minimizes the potential for recall bias as noted in case-control studies. Second, our cases were confirmed through detailed medial record review. Third, the detailed data on numerous exposures allowed us to adjust for multiple confounding factors. Fourth, the EDIP score characterizes the inflammatory potential of diet by predicting levels of circulating inflammatory markers[14]. Given that inflammation is a pivotal pathway through which diet modifies the risk of chronic diseases as well as a central characteristic of IBD, this score serves as a useful tool to elucidate the diet-disease relationship from a mechanistic perspective.

We acknowledge several limitations as well. First, self-reported dietary and lifestyle data are subject to measurement error. However, prior studies evaluating the relative validity of FFQ data have shown good correlations between FFQs and diet records[17,18], suggesting that dietary intake is generally well-measured and suited for large prospective studies. Second, we cannot exclude the possibility of unmeasured or residual confounding due to the observational nature of our study. Third, the median age of IBD diagnosis is higher than other population-based cohorts, which is in part due to the long follow-up of these studies that allowed new diagnoses to be captured well into the seventh and eighth decades of life. However, women were eligible for enrollment in the NHS and the NHS II beginning at age 30 and 25 years, respectively, and thus we were able to capture younger-onset disease as well. In addition, studies have not identified environmental factors to be different between younger-onset and older-onset IBD and many of our previously described associations have been replicated in pediatric populations. Furthermore, our findings were unchanged after excluding those diagnosed after age 60 years. Last, our study participants were mostly white health professionals. Although studies of dietary risk factors have not revealed a strong ethnicity-specific association, extrapolating our findings to individuals of other ethnicity should be performed with caution.

In conclusion, we demonstrate that consumption of diets with high inflammatory

potential is associated with an increased risk of developing CD. Our findings support the importance of diet in modulating intestinal inflammation and IBD risk. Strategies to mitigate chronic inflammation through avoidance or reduced intake of proinflammatory foods may be considered for disease prevention.

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Figure 1. Multivariable associations of cumulative average empirical dietary inflammatory pattern score and risk of Crohn's disease according to disease location. Disease location was categorized according the Montréal classification. *P* for trend was calculated using cumulative average EDIP score as a continuous variable.

Figure 2. Multivariable associations of 8-year change in EDIP score with risk of Crohn's disease and ulcerative colitis. Participants' 8-year change in EDIP score was calculated by subtracting the baseline EDIP score from the updated EDIP score 8 years after baseline.

Table 1. Age- and cohort-standardized basic characteristics of study participants according to quartiles of cumulative average EDIP score[a]

Variable	Cumulative average EDIP score[b]			
	Quartile 1	Quartile 2	Quartile 3	Quartile 4
EDIP score, median (IQR)	-0.30 (-0.42, -0.23)	-0.08 (-0.12, -0.04)	0.08 (0.04, 0.13)	0.31 (0.24, 0.44)
Age at baseline, years, mean (SD)	44.8 (9.9)	44.9 (10.5)	44.7 (10.6)	44.2 (10.4)
Female, %	77	81	82	83
Race, %				
Southern European/Mediterranean	19	19	19	18
Scandinavian	9	8	7	7
Other Caucasian	66	66	65	64
Asian, Hispanic, African, or others	6	7	9	11
Smoking status, %				
Never smoker	51	59	63	64
Past smoker	35	30	26	24
Current smoker	14	11	11	12
Body mass index, kg/m^2, mean (SD)	25.1 (4.5)	25.8 (4.9)	26.5 (5.4)	28.0 (6.3)
Physical activity[c], MET-hr/wk, mean (SD)	23.5 (22.6)	21.2 (20.6)	19.9 (20.1)	18.8 (20.2)
Nonsteroidal anti-inflammatory drug, %	42	41	41	43
Oral contraceptive pill, %				
Never user/men	42	43	43	43
Ever user	58	57	57	57
Hormone replacement therapy, %				
Premenopausal	30	29	29	28
Postmenopausal never user/men	39	39	39	41
Postmenopausal past user	16	17	17	17
Postmenopausal current user	15	15	15	14
Dietary factor, mean (SD)				
Calorie, kcal/d	1803.2 (482.7)	1739.4 (470.9)	1773.8 (480.1)	1963.5 (529.7)
Total fiber, g/d	19.7 (5.8)	19.5 (5.5)	18.8 (5.3)	17.7 (5.2)
ω-3 polyunsaturated fatty acids, g/d	1.3 (0.4)	1.3 (0.4)	1.3 (0.4)	1.3 (0.4)
ω-6 polyunsaturated fatty acids, g/d	10.2 (2.6)	10.4 (2.5)	10.4 (2.5)	10.4 (2.6)

Red meat, IU/wk	5.0 (3.1)	5.3 (3.1)	6.0 (3.3)	7.9 (4.4)

Abbreviations: EDIP, Empirical dietary inflammatory pattern; IQR, interquartile range; MET, metabolic equivalent of task; SD, standard deviation.

[a]The basic characteristics are presented by quartiles of cumulative average EDIP score. 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. All variables are presented across person-time except for age.

[b]Average of the available EDIP scores from baseline until the current cycle.

[c]Physical activity was represented by the product sum of the MET of each specific recreational activity and hours spent on that activity per week.

Table 2. Age-adjusted and multivariable associations of cumulative average EDIP score with risk of Crohn's disease and ulcerative colitis

	Cumulative average EDIP score[a]				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P_{trend}[e]
Crohn's disease					
No. of cases	71	70	79	108	
Person-year	1234232	1235503	1237597	1242606	
Age-adjusted HR (95% CI)[b]	1 (reference)	1.00 (0.72-1.40)	1.10 (0.79-1.52)	1.49 (1.10-2.02)	0.01
Multivariable-adjusted HR (95% CI)[c]	1 (reference)	1.02 (0.73-1.43)	1.11 (0.80-1.54)	1.51 (1.10-2.07)	0.01
Multivariable- + fiber-adjusted HR (95% CI)[d]	1 (reference)	1.03 (0.74-1.43)	1.12 (0.80-1.55)	1.51 (1.10-2.08)	0.01
Ulcerative colitis					
No. of cases	104	97	114	113	
Person-year	1234232	1235503	1237597	1242606	
Age-adjusted HR (95% CI)[b]	1 (reference)	0.90 (0.68-1.18)	1.02 (0.78-1.34)	0.96 (0.73-1.26)	0.99
Multivariable-adjusted HR (95% CI)[c]	1 (reference)	0.93 (0.70-1.23)	1.08 (0.82-1.42)	1.03 (0.78-1.36)	0.62
Multivariable- + fiber-adjusted HR (95% CI)[d]	1 (reference)	0.93 (0.70-1.23)	1.08 (0.82-1.42)	1.03 (0.77-1.36)	0.64

Abbreviations: BMI, body mass index; CI, confidence interval; EDIP, Empirical dietary inflammatory pattern; HR, hazard ratio; HPFS, Health Professionals Follow-up Study; MET, metabolic equivalent of task; NSAID, nonsteroidal anti-inflammatory drug; NHS, Nurses' Health study.

[a]Average of the available EDIP scores from baseline until the current cycle.

[b]Cox proportional hazards model stratified by age (continuous, month), cohort (NHS, NHS II, HPFS), and time period (in 2-year intervals).

[c]Further adjusted for race (Southern European/Mediterranean, Scandinavian, other Caucasian, other races), smoking (never smoker, past smoker, current smoker), BMI (<18.5, 18.5-24.9, 25-29.9, ≥30 kg/m^2), physical activity (in quintiles, MET-hr/wk), regular NSAID use (no, yes), oral contraceptive pill (never user/men, ever user), and hormonal replacement therapy (premenopausal, postmenopausal never user/men, postmenopausal past user, postmenopausal current user).

[d]Further adjusted for total fiber intake (in quartiles, g/d).

[e]*P* for trend was calculated using the EDIP score as a continuous variable.

Table 3. Age-adjusted and multivariable associations of recent EDIP score with risk of Crohn's disease and ulcerative colitis

	Recent EDIP score[a]				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P_{trend}[e]
Crohn's disease					
No. of cases	62	84	85	97	
Person-year	1234319	1236896	1233935	1244787	
Age-adjusted HR (95% CI)[b]	1 (reference)	1.35 (0.97-1.88)	1.35 (0.97-1.88)	1.49 (1.08-2.06)	0.02
Multivariable-adjusted HR (95% CI)[c]	1 (reference)	1.37 (0.98-1.91)	1.36 (0.98-1.90)	1.49 (1.07-2.06)	0.03
Multivariable- + fiber-adjusted HR (95% CI)[d]	1 (reference)	1.37 (0.99-1.91)	1.37 (0.98-1.90)	1.48 (1.07-2.07)	0.04
Ulcerative colitis					
No. of cases	98	115	98	117	
Person-year	1234319	1236896	1233935	1244787	
Age-adjusted HR (95% CI)[b]	1 (reference)	1.13 (0.86-1.48)	0.94 (0.71-1.25)	1.05 (0.79-1.37)	0.49
Multivariable-adjusted HR (95% CI)[c]	1 (reference)	1.16 (0.89-1.53)	0.99 (0.74-1.32)	1.11 (0.84-1.47)	0.25
Multivariable- + fiber-adjusted HR (95% CI)[d]	1 (reference)	1.16 (0.89-1.53)	0.99 (0.74-1.32)	1.11 (0.84-1.47)	0.26

Abbreviations: BMI, body mass index; CI, confidence interval; EDIP, Empirical dietary inflammatory pattern; HR, hazard ratio; HPFS, Health Professionals Follow-up Study; MET, metabolic equivalent of task; NSAID, nonsteroidal anti-inflammatory drug; NHS, Nurses' Health study.

[a]EDIP score within 4 years prior to the current follow-up cycle.

[b]Cox proportional hazards model stratified by age (continuous, month), cohort (NHS, NHS II, HPFS), and time period (in 2-year intervals).

[c]Further adjusted for race (Southern European/Mediterranean, Scandinavian, other Caucasian, other races), smoking (never smoker, past smoker, current smoker), BMI (<18.5, 18.5-24.9, 25-29.9, ≥30 kg/m^2), physical activity (in quintiles, MET-hr/wk), regular NSAID use (no, yes), oral contraceptive pill (never user/men, ever user), and hormonal replacement therapy (premenopausal, postmenopausal never user/men, postmenopausal past user, postmenopausal current user).

[d]Further adjusted for total fiber intake (in quartiles, g/d).

[e]*P* for trend was calculated using the EDIP score as a continuous variable.

Table 4. Age-adjusted and multivariable associations of baseline EDIP score with risk of Crohn's disease and ulcerative colitis

	Baseline EDIP Score[a]				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P_{trend}[e]
Crohn's disease					
No. of cases	73	79	73	103	
Person-year	1235068	1236774	1238132	1239964	
Age-adjusted HR (95% CI)[b]	1 (reference)	1.11 (0.80-1.53)	1.03 (0.74-1.43)	1.43 (1.05-1.95)	0.004
Multivariable-adjusted HR (95% CI)[c]	1 (reference)	1.15 (0.83-1.59)	1.07 (0.76-1.49)	1.45 (1.06-2.00)	0.004
Multivariable- + fiber-adjusted HR (95% CI)[d]	1 (reference)	1.15 (0.83-1.59)	1.07 (0.76-1.49)	1.45 (1.05-2.00)	0.005
Ulcerative colitis					
No. of cases	102	97	113	116	
Person-year	1234319	1236896	1233935	1244787	
Age-adjusted HR (95% CI)[b]	1 (reference)	0.91 (0.69-1.20)	1.03 (0.78-1.35)	1.04 (0.79-1.37)	0.69
Multivariable-adjusted HR (95% CI)[c]	1 (reference)	0.94 (0.71-1.25)	1.07 (0.81-1.41)	1.10 (0.83-1.46)	0.44
Multivariable- + fiber-adjusted HR (95% CI)[d]	1 (reference)	0.94 (0.71-1.25)	1.07 (0.81-1.41)	1.10 (0.83-1.46)	0.45

Abbreviations: BMI, body mass index; CI, confidence interval; EDIP, Empirical dietary inflammatory pattern; HR, hazard ratio; HPFS, Health Professionals Follow-up Study; MET, metabolic equivalent of task; NSAID, nonsteroidal anti-inflammatory drug; NHS, Nurses' Health study.

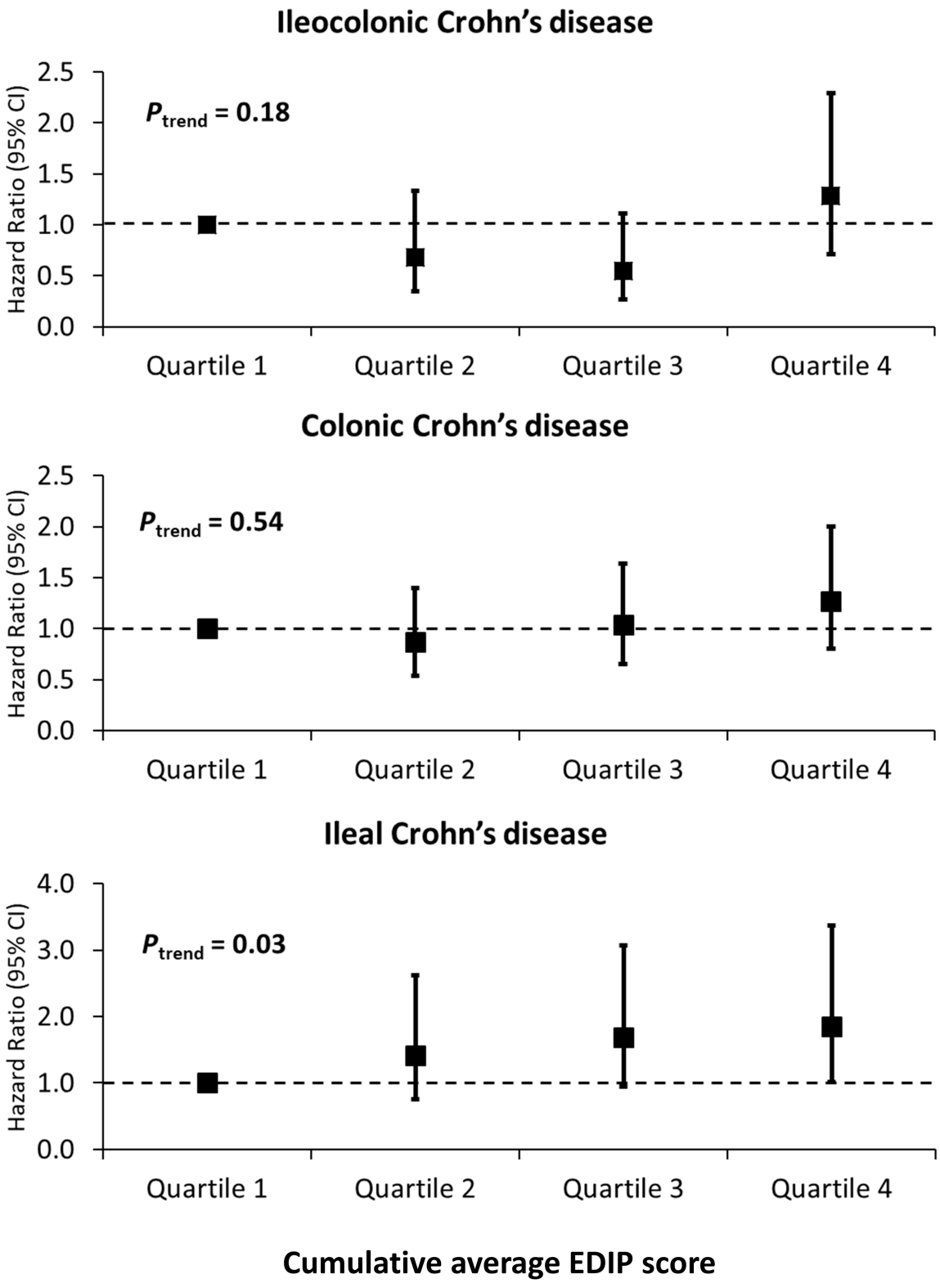
[a]EDIP score at baseline (1984 in the NHS; 1991 in the NHS II; 1986 in the HPFS).

[b]Cox proportional hazards model stratified by age (continuous, month), cohort (NHS, NHS II, HPFS), and time period (in 2-year intervals).

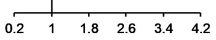
[c]Further adjusted for race (Southern European/Mediterranean, Scandinavian, other Caucasian, other races), smoking (never smoker, past smoker, current smoker), BMI (<18.5, 18.5-24.9, 25-29.9, ≥30 kg/m^2), physical activity (in quintiles, MET-hr/wk), regular NSAID use (no, yes), oral contraceptive pill (never user/men, ever user), and hormonal replacement therapy (premenopausal, postmenopausal never user/men, postmenopausal past user, postmenopausal current user).

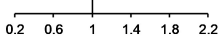
[d]Further adjusted for total fiber intake (in quartiles, g/d).

[e]*P* for trend was calculated using the EDIP score as a continuous variable.


Ileocolonic Crohn's disease
Hazard Ratio (95% CI)
2.5
2.0
1.5
1.0
0.5
0.0
P_{trend} = 0.18
Quartile 1
Quartile 2
Quartile 3
Quartile 4
Colonic Crohn's disease
Hazard Ratio (95% CI)
2.5
2.0
1.5
1.0
0.5
0.0
P_{trend} = 0.54
Quartile 1
Quartile 2
Quartile 3
Quartile 4
Ileal Crohn's disease
Hazard Ratio (95% CI)
4.0
3.0
2.0
1.0
0.0
P_{trend} = 0.03
Quartile 1
Quartile 2
Quartile 3
Quartile 4
Cumulative average EDIP score

Eight-year change in EDIP	Person-year	Crohn's disease: No. of cases	Crohn's disease: Multivariable-adjusted HR (95% CI)	Ulcerative colitis: No. of cases	Ulcerative colitis: Multivariable-adjusted HR (95% CI)
Low-low	556541	29	1 (reference)	52	1 (reference)
Low-moderate	306593	22	1.34 (0.77-2.35)	29	0.99 (0.63-1.57)
Low-high	147789	16	2.02 (1.09-3.75)	14	1.02 (0.56-1.86)
Moderate-low	294738	16	1.13 (0.61-2.10)	19	0.67 (0.39-1.14)
Moderate-moderate	422103	21	1.01 (0.57-1.79)	29	0.80 (0.51-1.28)
Moderate-high	291721	20	1.34 (0.75-2.39)	19	0.73 (0.43-1.24)
High-low	157572	12	1.50 (0.76-2.98)	11	0.72 (0.37-1.39)
High-moderate	280499	19	1.34 (0.74-2.42)	25	1.00 (0.61-1.64)
High-high	569518	50	1.72 (1.07-2.78)	44	0.91 (0.60-1.38)





What You Need to Know

BACKGROUND AND CONTEXT: Few studies have examined the association of composite dietary determinants of inflammation on the risk of Crohn's disease and ulcerative colitis.

NEW FINDINGS: Dietary patterns with high inflammatory potential were associated with increased risk of Crohn's disease but not ulcerative colitis. The effect with Crohn's disease was dynamic, where a shift from low to high inflammatory potential of diet and a persistently proinflammatory diet were both associated with greater disease risk.

LIMITATIONS: These findings are based on observational data. The median age of diagnosis in this study is higher than other population-based cohorts.

IMPACT: Given the importance of diet in modulating intestinal inflammation and risk of inflammatory bowel disease, strategies to mitigate chronic inflammation through avoidance or reduced intake of proinflammatory foods may be considered for disease prevention.

Lay Summary

Inflammation is a potential mechanism linking diet and development of inflammatory bowel disease. Dietary patterns with high inflammatory potential can increase the risk of developing Crohn's disease.