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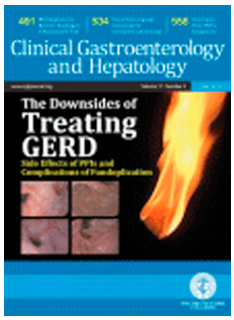

DIETARY GLUTEN INTAKE IS NOT ASSOCIATED WITH RISK OF INFLAMMATORY BOWEL DISEASE IN U.S. ADULTS WITHOUT CELIAC DISEASE

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DIETARY GLUTEN INTAKE IS NOT ASSOCIATED WITH RISK OF INFLAMMATORY BOWEL DISEASE IN U.S. ADULTS WITHOUT CELIAC DISEASE

Short title: Gluten intake and risk of inflammatory bowel disease

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Abbreviations: Crohn's disease (CD), low fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP), gluten-free diet (GFD), Health Professionals Follow-up Study (HPFS), Inflammatory bowel disease (IBD), Nurses' Health Study (NHS), Nurses' Health Study II (NHSII), semi-quantitative food frequency questionnaire (SFFQ), ulcerative colitis (UC)

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Author Contributions
EWL, ATC and HK were involved in the study concept and design. EWL, KEB, ANA, PL, JRR, and HK participated in acquisition of data. EWL, KLI and HK were involved in statistical analysis. EWL and HK had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. EWL, BL, KLI, ANA, JFL, WCW, ATC, PL and HK participated in interpretation of data. EWL and HK performed drafting of the manuscript. All authors participated in critical revision of the manuscript.

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ABSTRACT

Background & Aims: Diet is thought to play a role in the development of inflammatory bowel disease (IBD), though the relationship between gluten intake and risk of IBD has not been explored. The aim of this study was to determine the relationship between gluten intake and risk of incident Crohn's disease (CD) and ulcerative colitis (UC).

Methods: We performed a prospective cohort study of 208,280 US participants from the Nurses' Health Study (NHS; 1986-2016), NHSII (1991-2017), and Health Professionals Follow-up Study (1986-2016) who did not have IBD at baseline or celiac disease, and who completed semi-quantitative food frequency questionnaires. We used Cox proportional hazards modeling to estimate the risk of IBD according to quintiles of cumulative average energy-adjusted dietary gluten intake over follow-up period.

Results: We documented 337 CD cases and 447 UC cases over 5,115,265 person-years of follow-up. Dietary gluten intake was not associated with risk of IBD. Compared to participants in the lowest quintile of gluten intake, the adjusted hazard-ratios and 95% confidence intervals (CI) for participants in the highest quintile of gluten intake were 1.16 (95% CI: 0.82-1.64; P_{trend} = 0.41) for CD and 1.04 (95% CI: 0.75-1.44; P_{trend} = 0.64) for UC. Adjusting for primary sources of gluten intake did not materially change our estimates.

Conclusions: In three large adult US prospective cohorts, gluten intake was not associated with risk of CD or UC. Our findings are reassuring at a time when consumption of gluten has been increasingly perceived as a trigger for chronic gastrointestinal diseases.

Keywords: inflammatory bowel disease, Crohn's disease, ulcerative colitis, gluten

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INTRODUCTION:

Inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are chronic inflammatory diseases of the gastrointestinal tract that result from a dysregulated immune response to environmental and microbial stimuli in a genetically susceptible host[1,2]. Though over 200 susceptibility loci have been identified, the total variance of IBD risk explained by known genetic factors is less than 14%, highlighting the significance of environmental factors in disease development[3,4]. Diet is thought to play a role in IBD pathogenesis, likely due to influence on gut microbiome composition, mucosal barrier function, and mucosal inflammation[5].

Gluten, the dietary trigger for celiac disease, is a protein in wheat, barley, and rye. Gluten-free diets (GFD) have gained popularity, even among those without celiac disease. A recent national health and nutrition examination surveys (NHANES) survey estimated that by 2014, 2.7 million US adults without celiac disease adhered to a GFD, increasing by over 3-fold since 2009[6]. This may be due to gastrointestinal symptoms attributed to gluten intake, as in non-celiac gluten sensitivity, or overlap of GFD with low fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP) diet, which is known to aid symptoms of irritable bowel syndrome[7]. Others suggest that GFD, popularized by media and consumer-directed marketing are utilized by patients because of perceived health benefits[8].

IBD is associated with an increased risk for celiac disease[9], though non-celiac gluten sensitivity is also common in those with IBD[10]. Some patients with IBD report improvements in clinical symptoms following dietary gluten restriction[11]. This may be due to undiagnosed celiac disease, which constitutes a substantial portion of celiac cases [12], or an effect of gluten on IBD activity. Evidence for the role of gluten in gut inflammation, independent of celiac disease, is scant,

though one study of mice with chemical-induced colitis showed an increase in gut inflammation in mice fed wheat gluten compared to those on standard diet [13].

Therefore, there is a need to examine the relationship between dietary gluten and risk of IBD in adults without celiac disease. These studies may help inform dietary strategies for prevention of IBD. Additionally, empiric gluten avoidance is likely not without consequence. We have previously shown that avoidance of gluten from whole but not refined grains may affect cardiovascular disease risk [14]. Increased whole grain consumption has also been linked to decreased risk for type 2 diabetes mellitus and mortality [15,16]. Finally, indiscriminate exclusion diets have been linked to malnutrition and disordered-eating [17,18]. Thus, in this study, we explored the relationship between dietary gluten intake and risk of IBD in three large prospective US cohorts of men and women.

METHODS:

Study Population

We included participants in the Nurses' Health Study (NHS), NHSII and Health Professionals Follow-Up Study (HPFS) (**Supplementary Material**). Briefly, NHS is a prospective cohort study of 121,700 female nurses (ages 30-55 years) enrolled in 1976, while NHSII was established in 1989 and enrolled 116,429 female nurses (ages 25-42 years). HPFS enrolled 51,529 US male physicians (ages 40-75 years) starting in 1986. Participants completed baseline and biennial questionnaires on lifestyle factors, anthropometric measurements, and medical information. Overall follow up rates for these cohorts have been reported as 90% (NHS), 85% (NHSII), and 93% (HPFS)[19,20].

We included participants who completed baseline semi-quantitative food frequency questionnaires (SFFQ) in 1986 (NHS, HPFS) and 1991 (NHSII). We excluded participants with self-reported celiac disease at any time (n = 660), IBD at baseline (n = 120), missing or implausible baseline body mass index (BMI < 10 kg/m^2; n = 1,487), and missing or implausible caloric intake (< 600 or > 3500 kcal/day for women, < 800 or > 4200 kcal/day for men). Baseline characteristics of those who completed SFFQ are similar to the entire cohort [21].

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, and the IRB allowed participants' completion of questionnaires to be considered as implied consent.

Ascertainment of IBD diagnosis

Ascertainment of IBD has been previously described in detail[22] (**Supplementary Material**). Briefly, in all cohorts, self-reported diagnosis of CD or UC was confirmed by two gastroenterologists blinded to exposure information through detailed review of medical records.

Assessment of gluten intake and covariates

In each cohort, SFFQs were administered every four years and assessed patterns of food intake during the previous year. Participants reported how often they consumed standard portions (e.g. one cup for cereals, one slice for bread, etc) of various food items, ranging from "never or less than once a month" to "6 or more times per day". Based on food intake, nutrient intake was calculated using the Harvard Food Composition Database.

We have previously detailed our method for estimating dietary gluten intake [14,23]. Briefly, the expected protein content of wheat, rye, and barley of food items was multiplied by a conservative conversion factor of 75% to account for the gluten content of protein[23]. Trace

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sources of gluten, such as that found in condiments, were not included. In two recent validation studies nested within NHSII (n = 732) and HPFS (n = 650), compared to 7-day dietary records, the energy-adjusted Spearman correlation coefficients for gluten intake derived from SFFQ were 0.55 (0.48-0.61) and 0.58 (0.52 - 0.64), respectively, demonstrating the validity of SFFQ in measuring dietary gluten intake[23].

We used the residual method to derive energy-adjusted gluten accounting for total caloric intake, which reduces the effect of extraneous variation in nutrient reporting[24]. Additionally, we calculated cumulative average of energy-adjusted gluten intake, to reduce measurement errors, account for individual variation in gluten intake over time, and better represent long-term dietary patterns.

We also assessed the following covariates: BMI, physical activity, smoking status, non-steroidal anti-inflammatory drug (NSAID) use, oral contraceptive use, menopausal hormone therapy, appendectomy, family history of IBD and Alternate Healthy Eating Index (AHEI). Detailed information regarding ascertainment of these variables is included in the **Supplementary Material.**

Statistical Analysis

Person-time was calculated from return of baseline questionnaire to date of IBD diagnosis, date of last returned questionnaire, death, or end of follow up (2016 for NHS, HPFS; 2017 for NHSII), whichever occurred first. We modeled gluten intake as cohort-specific quintiles of cumulative average energy adjusted intake but also assessed the relationship between more recent (simple updated) and baseline energy-adjusted intake. We used Cox proportional hazards modeling to estimate hazard ratios (HR) and 95% confidence intervals (CI). The proportional hazards assumption was tested as described in the **Supplementary Material**. All models were

stratified by age (months), time-period (in 2-year intervals), and cohort (NHS, NHSII, or HPFS). We adjusted models for BMI (< 25, 25 - < 30, or ≥ 30 kg/m^2), smoking status (never, past, or current), regular NSAID use (yes/no), oral contraceptive use (never, past or current), menopausal hormone therapy (never, past, current, or pre-menopausal), appendectomy (yes/no), AHEI (quintiles), physical activity (quintiles) and family history of IBD (yes/no). All variables except family history of IBD were time-varying covariates. We tested for non-linear association between gluten intake and risk of IBD using previously described methods[25].

In exploratory analyses, we examined gluten intake and risk of IBD according to strata of BMI (< 25 or ≥ 25 kg/m^2), baseline median age (< 45 or ≥ 45 years), smoking status (ever/never), and family history of IBD (yes/no) and evaluated for presence of effect modification using log likelihood ratio. We performed several sensitivity analyses including 4- and 8-year lag analyses, adjustment for primary sources of gluten, controlling for sugar intake, and substitution of AHEI with fruit and vegetables (**Supplementary Materials**). All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC). Statistical significance was defined as a p value < 0.05 using two-tailed tests.

RESULTS:

We included 208,280 participants in our study (NHS: 72,474; NHSII: 94,074; and HPFS: 41,732). **Table 1** and **Supplementary Table 1** show baseline characteristics of the pooled and individual cohorts, respectively, by quintiles of baseline gluten intake. Mean daily cumulative average gluten intake remained stable from baseline to follow up (5.7g (SD 2.2) and 6.0g (SD 1.6), respectively). At baseline, compared to participants in the lowest quintile of gluten intake, participants in the highest quintile had higher intake of whole and refined grains and were less likely to be current smokers. Baseline characteristics were otherwise similar.

Through the end of follow up, we documented 337 CD cases and 447 UC cases over 5,115,265 person-years. Mean time from enrollment to diagnosis of IBD was 15.7 years (SD 6.5). We observed no heterogeneity in the association between gluten intake and risk of CD or UC across cohorts (all $P_{interaction} > 0.77$) and therefore conducted pooled analysis by combining individual-level data from all cohorts. The risk of CD and UC according to quintiles of gluten intake are shown in **Table 2** (pooled cohort) and **Supplementary Tables 2-4** (individual cohorts). In our pooled analysis, we did not observe an association between cumulative average intake of gluten and risk of CD or UC in either age-adjusted or multivariable-adjusted analysis. For those in the highest quintile of gluten intake, the MV-adjusted HR (aHR) was 1.16 (95% CI 0.82-1.64; $P_{trend} = 0.41$) for CD and 1.04 (95% CI 0.75-1.44; $P_{trend} = 0.64$) for UC compared to those in the lowest quintile. Similarly, we found no association between simple-updated or baseline gluten intake and risk of IBD (all $P_{trend} > 0.37$). There was no non-linear association between gluten intake and risk of CD and UC (all $P_{non\text{-}linear} > 0.46$, **Supplementary Figure 1**).

Sensitivity analysis:

In sensitivity analyses, we adjusted for primary sources of gluten (**Table 2**). When adjusting for refined grains, and therefore with the variance of gluten intake explained by whole grain intake, there was no association between cumulative average gluten intake and risk of IBD [aHR for highest compared to lowest quintile: 0.96 (95% CI 0.62-1.49; $P_{trend} = 0.78$) for CD and 1.16 (95% CI 0.77-1.74; $P_{trend} = 0.33$) for UC]. Similarly, when adjusting for whole grains, and therefore with the variance of gluten intake explained by refined grain intake, there was no association between cumulative average gluten intake and risk of IBD [aHR for highest compared to lowest quintile: 1.16 (95% CI 0.81-1.67; $P_{trend} = 0.45$) for CD and 1.00 (95% CI 0.71-1.40; $P_{trend} = 0.82$) for UC]. Adjustment for cereal fiber did not materially alter the

association between gluten intake and IBD risk (all $P_{trend} > 0.29$). Similarly, there was no association between whole- or refined-grain-adjusted gluten and risk of CD or UC using the residual model (all $P_{trend} > 0.09$).

Replacement of AHEI with daily servings of fruit and vegetables did not materially change our estimates (all $P_{trend} > 0.49$), nor did additional adjustment for added sugar (all $P_{trend} > 0.21$). Finally, 4- and 8-year lagged analyses showed no relationship between gluten intake and risk of CD and UC (all $P_{trend} > 0.06$; **Table 3**).

Exploratory analysis:

We examined the association between gluten intake and risk of IBD according to strata of baseline age, BMI, smoking status and family history of IBD **(Tables 4 and 5).** We did not observe any effect modification according to BMI, smoking status, or family history in CD or UC (all $P_{interaction} > 0.27$). However, the association between gluten intake and risk of CD appeared to be modified by age at baseline ($P_{interaction} = 0.049$). For participants aged ≥ 45 years, those in the highest quintile of gluten intake had an aHR of 1.49 (95% CI: 0.85-2.63; $P_{trend} = 0.06$) for risk of CD compared to those in the lowest quintile. This association reached significance after additional adjustment for whole grains and cereal fiber ($P_{trend} = 0.02$ for each), but not after additional adjustment for refined grains ($P_{trend} = 0.54$). The associations were similar when using refined-grain-adjusted gluten ($P_{trend} = 0.53$) and slightly attenuated when using whole grain-adjusted gluten ($P_{trend} = 0.06$). Among those < 45 years at baseline, we observed no association between gluten intake and risk of CD (aHR for the highest quintile = 0.92 (95% CI 0.59-1.42), $P_{trend} = 0.35$), including after additional adjustment for refined grains, whole grains or cereal fiber (all $P_{trend} > 0.21$). There was no evidence of effect modification according to baseline age for UC ($P_{interaction} = 0.83$).

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DISCUSSION:

In three large adult US prospective cohorts, we found no association between long-term intake of gluten and risk of subsequent IBD. The lack of an association was consistent across various exposure time-windows and subgroups defined by IBD risk factors.

Our study represents the first investigation of the relationship between long-term gluten intake and risk of incident IBD. Interestingly, prior studies have shown that many patients with IBD report non-celiac gluten sensitivity and improved symptoms with GFD [10,11]. These observations raise important questions regarding the biological mechanisms that underpin the relationship between gluten and gastrointestinal symptoms. In an animal model of colitis, mice fed gluten had increased intestinal mucosal inflammation, permeability, and bacterial translocation when compared to mice fed standard diet[13]. In contrast, among healthy participants without celiac disease, consumption of high amount of gluten did not result in malabsorption or an acute inflammatory response in intestinal biopsies [26]. Therefore, as previously suggested, it is possible that non-gluten-components, such as FODMAPs or non-gluten wheat proteins, may explain gastrointestinal symptoms commonly attributed to gluten[7,27].

GFDs have gained popularity in those without celiac disease [6]. However, GFD may result in changes in diet quality. For example, we have previously demonstrated that avoidance of gluten from whole but not refined grain may affect cardiovascular disease risk [14]. Dietary grain source has also been implicated in systemic inflammation and intestinal microbiota composition. A diet high in refined grain has been associated with increased levels of C-reactive protein (CRP), interleukin 6 (IL-6) and soluble intracellular cell adhesion molecule 1 (sICAM-1) [28,29]. In contrast, a diet high in whole grain is associated with a reduction in tumor necrosis factor-alpha (TNF-alpha), IL-6 and CRP [30,31] and increased abundance of anti-inflammatory short chain fatty

acid (SCFA)-producing microbes, reflected by increased Firmicutes to Bacteroidetes ratios[32,33]. Two randomized dietary intervention studies demonstrated that changes in circulating inflammatory markers accompanying whole-grain diet coincided with alterations in gut microbiota composition [31,33]. Additionally, *Faecalibacterium prausnitzii* and *Prevotella copri*, previously implicated in CD pathogenesis, are increased in abundance with whole grain consumption and decreased with refined grain consumption[30,34]. Thus, empiric gluten avoidance, particularly from whole grains may have significant negative biological and health consequences.

In exploratory analysis we found that increased consumption of gluten from refined but not whole grains was associated with increased risk of CD among older adults. This may be related to the pro-inflammatory effects of refined grains rather than gluten itself. In support of this, when adjusting our models for refined grain, the association between gluten and CD risk in those aged ≥ 45 years was fully attenuated (**Table 4**), while refined grain itself was associated with increased CD risk in this group (aHR = 1.78, 95% CI 1.06 – 2.99 for highest quintile, P_{trend} = 0.03). That these findings were limited to older adults may be related to a greater role of environment in older-onset CD compared to younger-onset disease[35]. Aging has been linked to marked reduction in microbial diversity and immunosenescence [36,37]. Therefore, it is plausible that the known pro-inflammatory effect of refined grain on the gut microbiome and immune function is significantly augmented in older adults[38].

Our study has several strengths. Dietary data were collected prospectively every 4 years over nearly 30 years, accounting for long-term changes in dietary intake and minimizing the possibility of recall or selection biases. We confirmed all cases of CD and UC through medical record review, minimizing the possibility of outcome misclassification. Additionally, we

accounted for important confounders using detailed and validated information on lifestyle, medication and dietary factors. Finally, our study spanned a broad age range, with mean baseline age of 36 years in NHSII to 53 years in NHS and HPFS, allowing us to examine the effects of gluten intake according to younger versus older age.

Our study also has several limitations. There is measurement error with the use of SFFQ for estimating nutrient intake. However, our validation study demonstrated moderate to good correlation between SFFQ and diet records for estimating gluten intake[5]. SFFQ data could not capture if participants were on strict GFD, thus we could not examine the relationship between a GFD and risk of IBD. As most gluten consumption in the US comes from wheat products, we cannot fully assess the impact of gluten from sources such as barley and rye. We also did not consider minor sources of gluten such as soy sauce or condiments, though we expect these sources to have minimal contribution to total gluten intake. We also note that the baseline age in our cohort is higher than the average age of IBD onset in the US, thus younger-onset IBD may be under-represented. However, baseline age for NHSII participants ranged from 26-46 years which allowed us to also capture younger-onset cases. Participants in our cohorts are also health care professionals and are largely white and female, thus generalizability may be limited. We also acknowledge that the positive association in exploratory analysis may represent a type 1 error related to multiple comparisons or residual confounding due to unavailability of important risk factors such as antibiotics use in our cohorts.

CONCLUSION:

Long-term intake of gluten did not confer an increased risk of developing IBD in adults US, even among high-risk participants with a family history of IBD. Our findings do not support the theory that gluten contributes to IBD development. This is important because of the established

health benefits of a diet rich in whole grains. Our observation that gluten from refined grains may be associated with an increased risk of CD in older adults warrants confirmation in further prospective studies. Thus, gluten should not be empirically avoided in persons without celiac disease for the purpose of preventing IBD.

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Table 1. Age-adjusted baseline demographics of pooled cohort by quintiles of energy-adjusted gluten intake.

Characteristics [a]	Quintiles of baseline energy-adjusted gluten intake				
	1 (lowest) N = 41,287	**2** N = 41,628	**3** N = 41,703	**4** N = 41,814	**5 (highest)** N = 41,848
Age (years)	45.7 (10.9)	45.2 (10.7)	45.2 (10.6)	45.1 (10.6)	45.4 (10.7)
Sex (% female)	81	80	80	80	80
Body mass index (kg/m^2)	25.4 (5.1)	25.2 (4.9)	25.1 (4.8)	25.0 (4.7)	24.5 (4.6)
Alternate Healthy Eating Index score	50.1 (11.9)	49.9 (11.2)	50.1 (11.0)	50.4 (11.1)	52.2 (11.3)
Physical activity, MET-hours/week	18.7 (25.8)	18.2 (24.7)	18.1 (23.5)	17.9 (23.3)	19.2 (26.3)
Smoking status (%)					
Never	51	54	55	56	57
Past smoker	30	30	31	31	32
Current smoker	20	16	14	13	11
Regular NSAIDs use (%) [b]	18	18	18	17	16
History of appendectomy (%)	20	19	19	19	18
History of oral contraceptive use (%) [c]	63	63	63	62	62
Menopausal hormone use [c]					
Pre-menopausal (%)	68	68	69	69	69
Never used (%)	16	16	16	16	15
Past user (%)	7	7	6	6	7
Current user (%)	9	9	9	9	9
Family history of IBD (%)	3	4	4	4	4
Gluten intake (g/day) [d]	3.1 (0.8)	4.5 (0.6)	5.5 (0.6)	6.6 (0.8)	8.8 (1.9)
Whole grains (g/day) [d]	13.1 (14.4)	14.9 (12.9)	17.0 (13.2)	20.0 (14.5)	28.5 (20.5)
Refined grains (g/day) [d]	38.2 (17.4)	48.5 (13.1)	55.4 (14.0)	62.4 (15.7)	74.8 (22.9)

MET metabolic equivalent of task. **NSAID** non-steroidal anti-inflammatory drug. **IBD** inflammatory bowel disease. Missing data: physical activity (<1%), smoking status (3%), oral contraceptives (3.4%), menopausal hormones (3.4%). [a] All values other than age standardized to the age distribution of the study population. Values are mean (standard deviation) unless stated otherwise. Values may not sum to 100% due to rounding. [b] NSAIDs use in year 1990 for NHS and 1995 for NHSII. [c] For female participants only. [d] Energy-adjusted.

Table 2. Energy-adjusted gluten intake and risk of Crohn's disease and ulcerative colitis in the pooled cohort.

	Quintiles of energy-adjusted gluten intake					P_{trend}
	1 (lowest)	**2**	**3**	**4**	**5 (highest)**	
CUMULATIVE AVERAGE						
Crohn's Disease						
Cases	61	66	71	67	72	
Person-years	926,287	1,043,311	1,067,128	1,066,781	1,011,758	
Age-adjusted HR (95% CI)	1 (ref)	0.96 (0.68-1.36)	1.02 (0.72-1.43)	0.96 (0.67-1.35)	1.09 (0.77-1.53)	0.66
MV-adjusted HR (95% CI) [a]	1 (ref)	0.97 (0.68-1.37)	1.03 (0.73-1.46)	0.99 (0.70-1.40)	1.16 (0.82-1.64)	0.41
MV-adjusted HR + cereal fiber [a,b]	1 (ref)	0.99 (0.69-1.41)	1.07 (0.75-1.53)	1.04 (0.71-1.52)	1.27 (0.84-1.92)	0.29
Gluten from whole grains [a,c]	1 (ref)	0.92 (0.64-1.32)	0.95 (0.66-1.36)	0.87 (0.59-1.29)	0.96 (0.62-1.49)	0.78
Gluten from refined grains [a,d]	1 (ref)	0.97 (0.68-1.37)	1.03 (0.73-1.46)	0.99 (0.69-1.41)	1.16 (0.81-1.67)	0.45
Ulcerative Colitis						
Cases	71	91	103	102	80	
Person-years	926,287	1,043,311	1,067,128	1,066,781	1,011,758	
Age-adjusted HR (95% CI)	1 (ref)	1.16 (0.85-1.59)	1.29 (0.95-1.75)	1.28 (0.94-1.73)	1.06 (0.77-1.46)	0.56
MV-adjusted HR (95% CI) [a]	1 (ref)	1.14 (0.83-1.55)	1.25 (0.92-1.70)	1.25 (0.92-1.70)	1.04 (0.75-1.44)	0.64
MV-adjusted HR + cereal fiber [a,b]	1 (ref)	1.12 (0.81-1.53)	1.21 (0.89-1.65)	1.19 (0.86-1.64)	0.96 (0.66-1.38)	0.99
Gluten from whole grains [a,c]	1 (ref)	1.17 (0.85-1.61)	1.32 (0.95-1.82)	1.34 (0.95-1.89)	1.16 (0.77-1.74)	0.33
Gluten from refined grains [a,d]	1 (ref)	1.13 (0.83-1.54)	1.24 (0.91-1.68)	1.22 (0.90-1.68)	1.00 (0.71-1.40)	0.82
SIMPLE UPDATED [e]						
Crohn's Disease						
Cases	64	70	63	62	78	
Person-years	1,018,233	1,025,127	1,027,732	1,021,087	1,023,086	
Age-adjusted HR (95% CI)	1 (ref)	1.10 (0.78-1.54)	0.97 (0.68-1.37)	0.96 (0.67-1.36)	1.21 (0.87-1.68)	0.50
MV-adjusted HR (95% CI) [a]	1 (ref)	1.11 (0.79-1.56)	0.99 (0.70-1.40)	0.98 (0.69-1.39)	1.25 (0.89-1.75)	0.37
MV-adjusted HR + cereal fiber [a,b]	1 (ref)	1.12 (0.79-1.58)	1.01 (0.71-1.44)	1.01 (0.70-1.46)	1.32 (0.91-1.91)	0.30
Gluten from whole grains [a,c]	1 (ref)	1.07 (0.76-1.51)	0.94 (0.65-1.34)	0.91 (0.62-1.32)	1.11 (0.75-1.63)	0.94
Gluten from refined grains [a,d]	1 (ref)	1.11 (0.79-1.56)	0.99 (0.70-1.40)	0.98 (0.69-1.40)	1.25 (0.88-1.76)	0.40
Ulcerative Colitis						
Cases	91	71	96	102	87	
Person-years	1,018,233	1,025,127	1,027,732	1,021,087	1,023,086	
Age-adjusted HR (95% CI)	1 (ref)	0.78 (0.57-1.06)	1.05 (0.79-1.40)	1.14 (0.86-1.51)	0.96 (0.71-1.29)	0.40
MV-adjusted HR (95% CI) [a]	1 (ref)	0.76 (0.56-1.04)	1.02 (0.77-1.36)	1.11 (0.83-1.47)	0.94 (0.59-1.26)	0.50
MV-adjusted HR + cereal fiber [a,b]	1 (ref)	0.75 (0.55-1.03)	1.00 (0.75-1.34)	1.07 (0.80-1.44)	0.89 (0.64-1.22)	0.73
Gluten from whole grains [a,c]	1 (ref)	0.77 (0.56-1.06)	1.05 (0.78-1.42)	1.16 (0.85-1.57)	1.00 (0.71-1.41)	0.29
Gluten from refined grains [a,d]	1 (ref)	0.76 (0.55-1.03)	1.01 (0.76-1.35)	1.09 (0.82-1.45)	0.91 (0.67-1.23)	0.62
BASELINE [f]						
Crohn's Disease						
Cases	70	74	54	72	67	
Person-years	989,017	1,021,634	1,030,932	1,037,266	1,036,417	
Age-adjusted HR (95% CI)	1 (ref)	1.04 (0.75-1.44)	0.75 (0.52-1.07)	1.01 (0.72-1.40)	0.95 (0.68-1.32)	0.70
MV-adjusted HR (95% CI) [a]	1 (ref)	1.05 (0.76-1.46)	0.76 (0.53-1.08)	1.03 (0.74-1.43)	1.01 (0.72-1.42)	0.98
MV-adjusted HR + cereal fiber [a,b]	1 (ref)	1.05 (0.76-1.47)	0.76 (0.53-1.09)	1.04 (0.73-1.46)	1.02 (0.70-1.49)	0.98
Gluten from whole grains [a,c]	1 (ref)	1.01 (0.72-1.40)	0.70 (0.49-1.01)	0.92 (0.65-1.31)	0.86 (0.58-1.25)	0.36
Gluten from refined grains [a,d]	1 (ref)	1.05 (0.75-1.46)	0.75 (0.53-1.08)	1.02 (0.73-1.43)	1.00 (0.70-1.41)	0.91
Ulcerative Colitis						
Cases	89	84	79	110	85	
Person-years	989,017	1,021,634	1,030,932	1,037,266	1,036,417	
Age-adjusted HR (95% CI)	1 (ref)	0.92 (0.68-1.24)	0.86 (0.63-1.16)	1.19 (0.90-1.58)	0.93 (0.69-1.25)	0.69
MV-adjusted HR (95% CI) [a]	1 (ref)	0.91 (0.67-1.23)	0.84 (0.62-1.14)	1.18 (0.89-1.56)	0.93 (0.69-1.26)	0.68
MV-adjusted HR + cereal fiber [a,b]	1 (ref)	0.90 (0.66-1.21)	0.83 (0.61-1.12)	1.14 (0.85-1.52)	0.88 (0.63-1.22)	0.96
Gluten from whole grains [a,c]	1 (ref)	0.92 (0.68-1.25)	0.86 (0.63-1.18)	1.21 (0.90-1.64)	0.97 (0.69-1.37)	0.48

Gluten from refined grains [a,d]	1 (ref)	0.91 (0.67-1.22)	0.84 (0.62-1.14)	1.16 (0.87-1.54)	0.90 (0.66-1.23)	0.83

CI Confidence interval, **HR** hazard ratio, **MV** multivariable. [a] Models adjusted for BMI (<25, 25-30, ≥30 kg/m2), smoking status (never, past, current), Alternate Healthy Eating Index score (quintiles), physical activity (quintiles), non-steroidal anti-inflammatory drug use, history of appendectomy (yes/no), and family history of IBD (yes/no). [b] Additionally adjusted for cereal fiber. [c] Additionally adjusted for refined grains. [d] Additionally adjusted for whole grains. [e] Gluten intake updated every 4 years. [f] Gluten intake at baseline: 1986 (NHS, HPFS) and 1991 (NHSII).

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Table 3. Risk of ulcerative colitis and Crohn's disease for the pooled cohort, using cumulative averages of energy-adjusted gluten as exposure with a 4-and 8-year lagged period.

	Quintiles of cumulative average of energy-adjusted gluten intake					P_{trend}
	1 (lowest)	2	3	4	5 (highest)	
4 YEAR LAG						
Crohn's Disease						
Cases	52	63	57	65	55	
Person-years	782,870	875,670	895,211	896,738	856,872	
Age-adjusted HR (95% CI)	1 (ref)	1.12 (0.78-1.62)	0.98 (0.68-1.44)	1.13 (0.78-1.63)	0.98 (0.67-1.44)	0.94
MV-adjusted HR (95% CI) [a]	1 (ref)	1.13 (0.78-1.63)	0.98 (0.67-1.43)	1.15 (0.80-1.66)	1.03 (0.70-1.52)	0.85
Gluten from whole grains [a]	1 (ref)	1.06 (0.72-1.54)	0.88 (0.59-1.31)	0.99 (0.65-1.49)	0.81 (0.50-1.32)	0.40
Gluten from refined grains [a]	1 (ref)	1.13 (0.78-1.63)	0.98 (0.67-1.44)	1.16 (0.80-1.68)	1.04 (0.70-1.56)	0.81
Ulcerative Colitis						
Cases	55	85	68	91	71	
Person-years	782,870	875,670	895,211	896,738	856,872	
Age-adjusted HR (95% CI)	1 (ref)	1.41 (1.00-1.98)	1.10 (0.77-1.57)	1.48 (1.06-2.07)	1.22 (0.85-1.73)	0.30
MV-adjusted HR (95% CI) [a]	1 (ref)	1.39 (0.99-1.96)	1.08 (0.76-1.55)	1.46 (1.04-2.05)	1.23 (0.86-1.75)	0.27
Gluten from whole grains [a]	1 (ref)	1.48 (1.04-2.10)	1.20 (0.82-1.76)	1.69 (1.15-2.49)	1.53 (0.97-2.40)	0.06
Gluten from refined grains [a]	1 (ref)	1.38 (0.98-1.94)	1.07 (0.75-1.53)	1.44 (1.02-2.02)	1.19 (0.82-1.72)	0.37
8 YEAR LAG						
Crohn's Disease						
Cases	32	52	42	64	39	
Person-years	637,569	708,298	725,682	728,401	699,336	
Age-adjusted HR (95% CI)	1 (ref)	1.52 (0.98-2.36)	1.21 (0.77-1.93)	1.85 (1.21-2.84)	1.17 (0.73-1.86)	0.31
MV-adjusted HR (95% CI) [a]	1 (ref)	1.52 (0.98-2.37)	1.23 (0.77-1.95)	1.87 (1.22-2.87)	1.23 (0.77-1.98)	0.21
Gluten from whole grains [a]	1 (ref)	1.45 (0.92-2.27)	1.13 (0.69-1.83)	1.65 (1.02-2.68)	1.02 (0.57-1.83)	0.70
Gluten from refined grains [a]	1 (ref)	1.51 (0.97-2.36)	1.21 (0.76-1.93)	1.83 (1.19-2.83)	1.19 (0.73-1.94)	0.28
Ulcerative Colitis						
Cases	51	67	49	71	50	
Person-years	637,569	708,298	725,682	728,401	699,336	
Age-adjusted HR (95% CI)	1 (ref)	1.21 (0.84-1.75)	0.86 (0.58-1.28)	1.26 (0.88-1.81)	0.93 (0.63-1.37)	0.83
MV-adjusted HR (95% CI) [a]	1 (ref)	1.19 (0.82-1.71)	0.84 (0.56-1.24)	1.24 (0.86-1.79)	0.93 (0.63-1.39)	0.87
Gluten from whole grains [a]	1 (ref)	1.29 (0.88-1.88)	0.96 (0.63-1.47)	1.50 (0.98-2.29)	1.23 (0.75-2.04)	0.29
Gluten from refined grains [a]	1 (ref)	1.19 (0.82-1.71)	0.84 (0.56-1.24)	1.24 (0.86-1.79)	0.93 (0.62-1.40)	0.88

[a] Models are adjusted for same variables as in Table 2.

Table 4. Gluten intake and risk of Crohn's disease according to baseline age, body mass index, smoking status, and family history.

	Quintiles of cumulative average energy-adjusted gluten intake					P_{trend}	$P_{interaction}$
	1 (lowest)	2	3	4	5 (highest)		
Age < 45							0.049
Cases	41	41	36	30	41		
Person-years	514,656	585,627	599,177	602,690	575,310		
Age-adjusted HR (95% CI)	1 (ref)	0.88 (0.57-1.36)	0.76 (0.48-1.19)	0.63 (0.39-1.01)	0.88 (0.57-1.36)	0.27	
MV-adjusted HR (95% CI) [a]	1 (ref)	0.88 (0.57-1.35)	0.75 (0.48-1.18)	0.63 (0.39-1.01)	0.92 (0.59-1.42)	0.35	
MV-adjusted HR + cereal fiber [a]	1 (ref)	0.88 (0.57-1.37)	0.76 (0.47-1.21)	0.64 (0.38-1.06)	0.94 (0.55-1.60)	0.42	
Gluten from whole grains [a]	1 (ref)	0.85 (0.54-1.33)	0.71 (0.44-1.15)	0.58 (0.34-0.99)	0.81 (0.45-1.47)	0.21	
Gluten from refined grains [a]	1 (ref)	0.86 (0.56-1.33)	0.73 (0.47-1.15)	0.61 (0.37-0.98)	0.86 (0.54-1.36)	0.23	
Age ≥ 45							
Cases	20	25	35	37	31		
Person-years	411,631	457,684	467,951	464,091	436,448		
Age-adjusted HR (95% CI)	1 (ref)	1.11 (0.62-2.00)	1.53 (0.88-2.66)	1.64 (0.95-2.82)	1.45 (0.83-2.55)	0.08	
MV-adjusted HR (95% CI) [a]	1 (ref)	1.09 (0.61-1.97)	1.52 (0.88-2.64)	1.64 (0.95-2.83)	1.49 (0.85-2.63)	0.06	
MV-adjusted HR + cereal fiber [a]	1 (ref)	1.15 (0.63-2.09)	1.64 (0.93-2.91)	1.84 (1.02-3.31)	1.81 (0.93-3.50)	0.02	
Gluten from whole grains [a]	1 (ref)	1.01 (0.56-1.83)	1.32 (0.75-2.33)	1.33 (0.74-2.39)	1.09 (0.57-2.11)	0.54	
Gluten from refined grains [a]	1 (ref)	1.12 (0.62-2.03)	1.58 (0.91-2.76)	1.75 (1.00-3.04)	1.69 (0.93-3.07)	0.02	
Body mass index < 25 kg/m^2							0.63
Cases	37	34	38	42	49		
Person-years	522,076	595,745	624,113	647,720	651,772		
Age-adjusted HR (95% CI)	1 (ref)	0.79 (0.50-1.26)	0.84 (0.53-1.32)	0.89 (0.57-1.39)	1.03 (0.67-1.58)	0.65	
MV-adjusted HR (95% CI) [a]	1 (ref)	0.79 (0.49-1.26)	0.85 (0.54-1.34)	0.91 (0.58-1.41)	1.11 (0.72-1.70)	0.44	
MV-adjusted HR + cereal fiber [a]	1 (ref)	0.81 (0.50-1.30)	0.89 (0.56-1.42)	0.96 (0.60-1.56)	1.22 (0.73-2.06)	0.33	
Gluten from whole grains [a]	1 (ref)	0.77 (0.48-1.24)	0.82 (0.51-1.32)	0.85 (0.52-1.40)	1.01 (0.58-1.74)	0.83	
Gluten from refined grains [a]	1 (ref)	0.79 (0.49-1.26)	0.86 (0.54-1.35)	0.91 (0.58-1.43)	1.11 (0.71-1.76)	0.46	
Body mass index ≥ 25 kg/m^2							
Cases	24	32	33	25	23		
Person-years	404,212	447,566	443,015	419,061	359,985		
Age-adjusted HR (95% CI)	1 (ref)	1.21 (0.71-2.05)	1.26 (0.74-2.13)	1.01 (0.57-1.77)	1.08 (0.61-1.93)	0.96	
MV-adjusted HR (95% CI) [a]	1 (ref)	1.19 (0.70-2.02)	1.19 (0.70-2.03)	1.02 (0.58-1.80)	1.10 (0.62-1.96)	0.98	
MV-adjusted HR + cereal fiber [a]	1 (ref)	1.23 (0.71-2.11)	1.26 (0.72-2.21)	1.10 (0.59-2.05)	1.24 (0.61-2.51)	0.72	
Gluten from whole grains [a]	1 (ref)	1.09 (0.63-1.87)	1.02 (0.57-1.80)	0.82 (0.43-1.55)	0.78 (0.37-1.64)	0.34	
Gluten from refined grains [a]	1 (ref)	1.19 (0.69-2.03)	1.19 (0.70-2.04)	1.02 (0.57-1.81)	1.09 (0.59-2.00)	0.999	
Never smoker							0.49
Cases	31	31	31	34	35		
Person-years	491,693	575,498	598,206	609,022	593,707		
Age-adjusted HR (95% CI)	1 (ref)	0.86 (0.52-1.42)	0.84 (0.51-1.39)	0.88 (0.54-1.44)	0.93 (0.57-1.52)	0.87	
MV-adjusted HR (95% CI) [a]	1 (ref)	0.82 (0.50-1.35)	0.81 (0.49-1.34)	0.86 (0.53-1.40)	0.92 (0.56-1.50)	0.87	
MV-adjusted HR + cereal fiber [a]	1 (ref)	0.85 (0.51-1.41)	0.86 (0.51-1.44)	0.93 (0.54-1.59)	1.05 (0.57-1.90)	0.79	
Gluten from whole grains [a]	1 (ref)	0.79 (0.48-1.31)	0.76 (0.45-1.27)	0.78 (0.46-1.32)	0.78 (0.43-1.42)	0.48	
Gluten from refined grains [a]	1 (ref)	0.81 (0.49-1.35)	0.81 (0.49-1.34)	0.85 (0.52-1.40)	0.91 (0.54-1.52)	0.82	
Past or current smoker							
Cases	30	35	40	33	37		
Person-years	434,594	467,813	468,922	457,759	418,051		
Age-adjusted HR (95% CI)	1 (ref)	1.07 (0.66-1.75)	1.23 (0.76-1.97)	1.03 (0.63-1.70)	1.27 (0.78-2.06)	0.43	
MV-adjusted HR (95% CI) [a]	1 (ref)	1.09 (0.67-1.78)	1.23 (0.77-1.99)	1.05 (0.63-1.72)	1.32 (0.81-2.14)	0.36	
MV-adjusted HR + cereal fiber [a]	1 (ref)	1.11 (0.68-1.83)	1.28 (0.78-2.10)	1.11 (0.65-1.89)	1.44 (0.81-2.58)	0.29	
Gluten from whole grains [a]	1 (ref)	1.03 (0.62-1.71)	1.13 (0.68-1.88)	0.92 (0.52-1.62)	1.08 (0.57-2.05)	0.98	
Gluten from refined grains [a]	1 (ref)	1.09 (0.67-1.79)	1.24 (0.77-2.01)	1.06 (0.64-1.76)	1.34 (0.81-2.24)	0.35	

No family history							0.29
Cases	51	52	61	58	61		
Person-years	892,124	1,000,070	1,020,764	1,022,061	968,681		
Age-adjusted HR (95% CI)	1 (ref)	0.91 (0.62-1.34)	1.05 (0.72-1.52)	1.00 (0.68-1.46)	1.10 (0.76-1.59)	0.50	
MV-adjusted HR (95% CI) [a]	1 (ref)	0.91 (0.62-1.35)	1.07 (0.73-1.55)	1.03 (0.71-1.51)	1.17 (0.80-1.70)	0.30	
MV-adjusted HR + cereal fiber [a]	1 (ref)	0.95 (0.64-1.41)	1.14 (0.77-1.68)	1.14 (0.76-1.72)	1.38 (0.87-2.17)	0.12	
Gluten from whole grains [a]	1 (ref)	0.87 (0.59-1.28)	0.97 (0.66-1.44)	0.90 (0.60-1.37)	0.95 (0.60-1.52)	0.93	
Gluten from refined grains [a]	1 (ref)	0.92 (0.62-1.35)	1.07 (0.74-1.56)	1.04 (0.71-1.52)	1.18 (0.80-1.75)	0.31	
Positive family history							
Cases	10	14	10	9	11		
Person-years	34,163	43,241	46,364	44,720	43,077		
Age-adjusted HR (95% CI)	1 (ref)	1.06 (0.45-2.52)	0.66 (0.26-1.66)	0.60 (0.23-1.56)	0.71 (0.28-1.80)	0.24	
MV-adjusted HR (95% CI) [a]	1 (ref)	0.94 (0.39-2.29)	0.62 (0.24-1.61)	0.53 (0.19-1.42)	0.74 (0.29-1.89)	0.29	
MV-adjusted HR + cereal fiber [a]	1 (ref)	0.90 (0.37-2.21)	0.59 (0.22-1.55)	0.47 (0.16-1.37)	0.64 (0.22-1.83)	0.22	
Gluten from whole grains [a]	1 (ref)	0.91 (0.36-2.27)	0.58 (0.21-1.65)	0.48 (0.15-1.52)	0.64 (0.18-2.35)	0.29	
Gluten from refined grains [a]	1 (ref)	0.93 (0.38-2.27)	0.61 (0.23-1.59)	0.51 (0.18-1.41)	0.70 (0.26-1.91)	0.27	

[a] Models are adjusted for the same variables as Table 2 minus the strata variable.

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Table 5. Gluten intake and risk of ulcerative colitis according to baseline age, body mass index, smoking status, and family history.

	Quintiles of cumulative average energy-adjusted gluten intake					P_{trend}	$P_{interaction}$
	1 (lowest)	2	3	4	5 (highest)		
Age < 45							0.83
Cases	48	52	65	59	53		
Person-years	514,656	585,627	599,177	602,690	575,310		
Age-adjusted HR (95% CI)	1 (ref)	0.98 (0.66-1.46)	1.19 (0.82-1.73)	1.07 (0.73-1.57)	1.02 (0.69-1.50)	0.81	
MV-adjusted HR (95% CI) [a]	1 (ref)	0.98 (0.66-1.45)	1.18 (0.81-1.72)	1.07 (0.73-1.57)	1.02 (0.68-1.51)	0.80	
MV-adjusted HR + cereal fiber [a]	1 (ref)	0.95 (0.64-1.41)	1.12 (0.76-1.64)	0.99 (0.66-1.47)	0.89 (0.57-1.38)	0.71	
Gluten from whole grains [a]	1 (ref)	1.03 (0.69-1.55)	1.28 (0.85-1.93)	1.21 (0.77-1.88)	1.22 (0.73-2.06)	0.34	
Gluten from refined grains [a]	1 (ref)	0.97 (0.65-1.43)	1.15 (0.79-1.67)	1.02 (0.69-1.51)	0.94 (0.62-1.41)	0.88	
Age ≥ 45							
Cases	23	39	38	43	27		
Person-years	411,631	457,684	467,951	464,091	436,448		
Age-adjusted HR (95% CI)	1 (ref)	1.56 (0.93-2.62)	1.46 (0.87-2.46)	1.69 (1.02-2.80)	1.12 (0.64-1.95)	0.66	
MV-adjusted HR (95% CI) [a]	1 (ref)	1.51 (0.90-2.53)	1.43 (0.85-2.40)	1.68 (1.01-2.80)	1.13 (0.65-1.98)	0.57	
MV-adjusted HR + cereal fiber [a]	1 (ref)	1.49 (0.89-2.52)	1.41 (0.82-2.40)	1.64 (0.96-2.82)	1.09 (0.58-2.05)	0.66	
Gluten from whole grains [a]	1 (ref)	1.48 (0.88-2.51)	1.39 (0.81-2.40)	1.62 (0.93-2.84)	1.07 (0.55-2.08)	0.75	
Gluten from refined grains [a]	1 (ref)	1.51 (0.90-2.53)	1.43 (0.85-2.41)	1.69 (1.01-2.83)	1.14 (0.63-2.05)	0.54	
Body mass index < 25 kg/m^2							0.90
Cases	48	49	67	64	56		
Person-years	522,076	595,745	624,113	647,720	651,772		
Age-adjusted HR (95% CI)	1 (ref)	0.93 (0.62-1.39)	1.20 (0.83-1.74)	1.10 (0.76-1.60)	0.96 (0.65-1.41)	0.89	
MV-adjusted HR (95% CI) [a]	1 (ref)	0.92 (0.62-1.37)	1.20 (0.82-1.74)	1.13 (0.77-1.64)	1.01 (0.68-1.49)	0.63	
MV-adjusted HR + cereal fiber [a]	1 (ref)	0.90 (0.60-1.35)	1.15 (0.79-1.69)	1.06 (0.71-1.58)	0.91 (0.58-1.43)	0.98	
Gluten from whole grains [a]	1 (ref)	0.95 (0.63-1.43)	1.27 (0.85-1.89)	1.22 (0.80-1.87)	1.14 (0.70-1.87)	0.34	
Gluten from refined grains [a]	1 (ref)	0.92 (0.61-1.37)	1.19 (0.81-1.73)	1.11 (0.76-1.63)	0.98 (0.65-1.47)	0.74	
Body mass index ≥ 25 kg/m^2							
Cases	23	42	36	38	24		
Person-years	404,212	447,566	443,015	419,061	359,985		
Age-adjusted HR (95% CI)	1 (ref)	1.64 (0.99-2.74)	1.45 (0.86-2.46)	1.60 (0.95-2.69)	1.17 (0.66-2.09)	0.67	
MV-adjusted HR (95% CI) [a]	1 (ref)	1.61 (0.96-2.68)	1.44 (0.85-2.43)	1.56 (0.93-2.64)	1.15 (0.65-2.05)	0.72	
MV-adjusted HR + cereal fiber [a]	1 (ref)	1.56 (0.93-2.62)	1.36 (0.79-2.35)	1.45 (0.83-2.54)	1.02 (0.52-1.98)	0.97	
Gluten from whole grains [a]	1 (ref)	1.60 (0.94-2.72)	1.43 (0.81-2.53)	1.55 (0.85-2.85)	1.14 (0.55-2.38)	0.81	
Gluten from refined grains [a]	1 (ref)	1.57 (0.94-2.63)	1.39 (0.81-2.36)	1.48 (0.87-2.52)	1.05 (0.58-1.92)	0.98	
Never smoker							0.27
Cases	29	38	49	53	43		
Person-years	491,693	575,498	598,206	609,022	593,707		
Age-adjusted HR (95% CI)	1 (ref)	1.16 (0.72-1.89)	1.43 (0.90-2.26)	1.49 (0.94-2.34)	1.26 (0.78-2.01)	0.21	
MV-adjusted HR (95% CI) [a]	1 (ref)	1.15 (0.71-1.87)	1.39 (0.87-2.20)	1.46 (0.92-2.30)	1.25 (0.78-2.01)	0.22	
MV-adjusted HR + cereal fiber [a]	1 (ref)	1.12 (0.69-1.83)	1.33 (0.83-2.13)	1.38 (0.85-2.22)	1.13 (0.66-1.93)	0.46	
Gluten from whole grains [a]	1 (ref)	1.20 (0.73-1.96)	1.50 (0.92-2.44)	1.63 (0.98-2.73)	1.49 (0.82-2.69)	0.10	
Gluten from refined grains [a]	1 (ref)	1.14 (0.70-1.85)	1.37 (0.86-2.18)	1.43 (0.90-2.27)	1.20 (0.73-1.97)	0.29	
Past or current smoker							
Cases	42	53	54	49	37		
Person-years	434,594	467,813	468,922	457,759	418,051		
Age-adjusted HR (95% CI)	1 (ref)	1.20 (0.80-1.80)	1.21 (0.81-1.82)	1.13 (0.75-1.72)	0.94 (0.60-1.47)	0.75	
MV-adjusted HR (95% CI) [a]	1 (ref)	1.18 (0.79-1.78)	1.19 (0.79-1.79)	1.11 (0.73-1.67)	0.92 (0.59-1.43)	0.66	
MV-adjusted HR + cereal fiber [a]	1 (ref)	1.15 (0.76-1.73)	1.13 (0.75-1.72)	1.03 (0.66-1.60)	0.82 (0.49-1.36)	0.42	
Gluten from whole grains [a]	1 (ref)	1.18 (0.77-1.80)	1.19 (0.76-1.84)	1.10 (0.68-1.78)	0.91 (0.51-1.62)	0.74	
Gluten from refined grains [a]	1 (ref)	1.17 (0.78-1.76)	1.16 (0.77-1.75)	1.07 (0.70-1.62)	0.86 (0.54-1.37)	0.48	

No family history							0.56
Cases	60	79	94	85	71		
Person-years	892,124	1,000,070	1,020,764	1,022,061	968,681		
Age-adjusted HR (95% CI)	1 (ref)	1.21 (0.87-1.70)	1.40 (1.01-1.94)	1.26 (0.91-1.76)	1.12 (0.79-1.57)	0.55	
MV-adjusted HR (95% CI) [a]	1 (ref)	1.21 (0.86-1.69)	1.40 (1.01-1.94)	1.27 (0.91-1.77)	1.13 (0.80-1.60)	0.48	
MV-adjusted HR + cereal fiber [a]	1 (ref)	1.20 (0.85-1.68)	1.37 (0.98-1.91)	1.23 (0.86-1.75)	1.07 (0.72-1.60)	0.69	
Gluten from whole grains [a]	1 (ref)	1.22 (0.86-1.72)	1.42 (1.00-2.00)	1.29 (0.89-1.88)	1.17 (0.76-1.80)	0.46	
Gluten from refined grains [a]	1 (ref)	1.20 (0.86-1.69)	1.38 (1.00-1.92)	1.25 (0.89-1.75)	1.10 (0.77-1.58)	0.60	
Positive family history							
Cases	11	12	9	17	9		
Person-years	34,163	43,241	46,364	44,720	43,077		
Age-adjusted HR (95% CI)	1 (ref)	0.89 (0.38-2.10)	0.52 (0.21-1.33)	1.23 (0.55-2.76)	0.58 (0.23-1.46)	0.57	
MV-adjusted HR (95% CI) [a]	1 (ref)	0.80 (0.34-1.91)	0.52 (0.20-1.32)	1.26 (0.55-2.86)	0.60 (0.24-1.52)	0.71	
MV-adjusted HR + cereal fiber [a]	1 (ref)	0.75 (0.31-1.81)	0.44 (0.17-1.14)	0.96 (0.40-2.29)	0.38 (0.13-1.08)	0.20	
Gluten from whole grains [a]	1 (ref)	0.90 (0.36-2.20)	0.63 (0.23-1.73)	1.64 (0.63-4.31)	0.90 (0.27-2.98)	0.59	
Gluten from refined grains [a]	1 (ref)	0.80 (0.34-1.93)	0.49 (0.19-1.25)	1.18 (0.52-2.69)	0.49 (0.18-1.30)	0.46	

[a] Models are adjusted for the same varaibles as Table 2 minus the strata variable.

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WHAT YOU NEED TO KNOW

BACKGROUND: Diet plays a role in inflammatory bowel disease (IBD) pathogenesis. Some patients with IBD report gastrointestinal symptoms with gluten intake. However, the relationship between gluten intake and risk of IBD is unknown.

FINDINGS: Our study suggests that gluten intake does not confer increased risk for development of Crohn's disease or ulcerative colitis.

IMPLICATIONS FOR PATIENT CARE: Empiric gluten avoidance, which may have adverse health effects, should not be recommended for the purpose of preventing IBD.

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