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A Prospective Study of Long-term Intake of Dietary Fiber and Risk of Crohn's Disease and Ulcerative Colitis

ASHWIN N. ANANTHAKRISHNAN,[1] HAMED KHALILI,[1] GAUREE G. KONIJETI,[1] LESLIE M. HIGUCHI,[2] PUNYANGANIE DE SILVA,[1] JOSHUA R. KORZENIK,[3] CHARLES S. FUCHS,[2,4] WALTER C. WILLETT,[5,6] JAMES M. RICHTER,[1] and ANDREW T. CHAN[1,4]

[1]Division of Gastroenterology, Massachusetts General Hospital and Harvard Medical School, Boston; [2]Division of Gastroenterology and Nutrition, Children's Hospital Boston and Harvard Medical School, Boston; [3]Division of Gastroenterology and [4]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston; [5]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston; and [6]Department of Nutrition, Harvard School of Public Health, Boston, Massachusetts

BACKGROUND & AIMS: Increased intake of dietary fiber has been proposed to reduce the risk of inflammatory bowel disease (Crohn's disease [CD] and ulcerative colitis [UC]). However, few prospective studies have examined associations between long-term intake of dietary fiber and risk of incident CD or UC. **METHODS:** We collected and analyzed data from 170,776 women, followed up over 26 years, who participated in the Nurses' Health Study, followed up for 3,317,425 person-years. Dietary information was prospectively ascertained via administration of a validated semiquantitative food frequency questionnaire every 4 years. Self-reported CD and UC were confirmed through review of medical records. Cox proportional hazards models, adjusting for potential confounders, were used to calculate hazard ratios (HRs). **RESULTS:** We confirmed 269 incident cases of CD (incidence, 8/100,000 person-years) and 338 cases of UC (incidence, 10/100,000 person-years). Compared with the lowest quintile of energy-adjusted cumulative average intake of dietary fiber, intake of the highest quintile (median of 24.3 g/day) was associated with a 40% reduction in risk of CD (multivariate HR for CD, 0.59; 95% confidence interval, 0.39–0.90). This apparent reduction appeared to be greatest for fiber derived from fruits; fiber from cereals, whole grains, or legumes did not modify risk. In contrast, neither total intake of dietary fiber (multivariate HR, 0.82; 95% confidence interval, 0.58–1.17) nor intake of fiber from specific sources appeared to be significantly associated with risk of UC. **CONCLUSIONS: Based on data from the Nurses' Health Study, long-term intake of dietary fiber, particularly from fruit, is associated with lower risk of CD but not UC. Further studies are needed to determine the mechanisms that mediate this association.**

Keywords: Population-Based Study; Diet; Fruits; Vegetables.

To date, 163 distinct genetic polymorphisms associated with risk of either Crohn's disease (CD) or ulcerative colitis (UC) have been identified, with many loci involved in regulation of the innate or adaptive immune response to the gut microbiome or maintenance of the intestinal epithelial barrier.[1,2] The external environment may also influence disease development by modification of the gut immune response, altering the composition of the microbiome, or disruption of epithelial barrier integrity. Secular changes in the external environment, such as the westernization of lifestyle, may explain observed temporal and geographic variations in incidence and distribution of disease as well as changes seen with migration.[3,4]

Diet has been long purported to modify risk of CD or UC.[5,6] However, the role of specific dietary components in the etiopathogenesis of inflammatory bowel disease (IBD) remains unclear, with studies variably implicating carbohydrates, proteins, fats, and dietary fiber.[5–11] Among these food groups, a role for dietary fiber in the predisposition to IBD appears to have particularly compelling biologic plausibility. For example, fermentable fiber is metabolized by intestinal bacteria to short-chain fatty acids, which inhibit nuclear factor $\kappa\beta$ and transcription of proinflammatory mediators.[12] In addition, fiber plays a vital role in the maintenance of intestinal barrier function.[13]

Previous investigation of the association between dietary fiber and risk of CD or UC has been limited for several reasons. First, retrospective ascertainment of preillness diet is subject both to recall bias and the alteration of dietary patterns related to symptoms of the disease preceding formal diagnosis.[11] Second, studies of specific dietary macronutrients require cohorts of sufficient size to examine individual associations as well as the influence of different sources of dietary fiber in the context of consumption of other foods in a typical diet. Third, prior studies have been limited to the pediatric IBD population[11] or have assessed diet at a single time point,[5,6] thus inadequately capturing the expected variation in long-term dietary patterns that occur over adult life.

To address these limitations, we performed a prospective study using 2 large, well-characterized cohorts of women, with validated outcomes and periodic assessments of diet across the adult life span, to examine the association between long-term intake of dietary fiber and risk of

Abbreviations used in this paper: AhR, aryl hydrocarbon receptor; CD, Crohn's disease; CI, confidence interval; FFQ, food frequency questionnaire; HR, hazard ratio; IBD, inflammatory bowel disease; IQR, interquartile range; NHS, Nurses' Health Study; NSAID, nonsteroidal anti-inflammatory drug; UC, ulcerative colitis.

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incident CD and UC. Furthermore, we examined the effect of fiber intake from different sources to shed light on the specific mechanisms through which dietary fiber intake may modulate risk of disease.

Patients and Methods

Study Population

Our study included participants from the Nurses' Health Study (NHS) I and II. The NHS I is a prospective cohort of 121,700 female registered nurses between the ages of 30 and 55 years at recruitment in 1976. The NHS II includes 116,686 female registered nurses between the ages of 25 and 42 years at enrollment in 1989. Both cohorts are followed up with detailed biennial questionnaires ascertaining environmental exposures and health outcomes with a follow-up rate of approximately 90%. The present study included women who completed a detailed semiquantitative dietary food frequency questionnaire (FFQ) in 1984 in NHS I and in 1991 in NHS II. Women who died before the first dietary questionnaire, had a diagnosis of cancer (except nonmelanoma skin cancer), or received a diagnosis of IBD before the baseline diet questionnaire were excluded. The study was approved by the institutional review board of Partners Healthcare.

Dietary Assessment

Intake of dietary fiber and other nutrients was assessed using validated, self-administered, semiquantitative FFQs administered in 1984, 1986, 1990, 1994, 1998, 2002, and 2006 in NHS I and 1991, 1995, 1999, 2003, and 2007 in NHS II. The 1984 FFQ included a total of 121 items, which was expanded to 136 items in 1986 and subsequent years.[14–16] For each food item, a commonly used portion size was specified and participants were asked how often they consumed the food on average over the past year. Nutrient intake was calculated by multiplying the frequency of consumption of each food item by the nutrient content based on tables provided by the Department of Agriculture. Total dietary fiber was calculated based on the method of the Association of Official Analytic Chemists. Nutrient intake was adjusted for total energy intake by the residual method. Fiber supplements were not assessed until 1994 but were taken by less than 6% of women. The 1984 FFQ also contained 15 questions on fruit consumption comprising 20 fruits and 28 questions on vegetable consumption, with similar patterns repeated on subsequent questionnaires through 2002.[14–16] Prior studies have shown the validity of the FFQ. The correlation between total dietary fiber intake measured by the FFQ and weighted records was 0.61.[17] Fiber intake from various sources correlated well with weighed portions for white bread (0.71), cold cereal (0.79), apples (0.80), bananas (0.79), tomatoes (0.73), and broccoli (0.69).[18]

Ascertainment of CD and UC

Details about the confirmation of CD and UC have been described in previous reports.[19–25] In brief, 2735 women from NHS I since 1976 and 2541 women from NHS II since 1989 self-reported a diagnosis of CD or UC on a biennial questionnaire through 2010 in NHS I and 2009 in NHS II. Self-report was followed by a detailed supplementary questionnaire inviting further information on IBD type, date of diagnosis, disease behavior, and history of treatment, as well as requesting permission to obtain medical records from the treating physician. Among the 3415 women who were still alive, did not have a diagnosis of IBD before the start date of the study, and could be contacted, 1549 subsequently denied the diagnosis based on this more detailed description of the diseases. Among the remaining 1866 patients, permission to view medical records was obtained from 1532. Medical records were reviewed by 2 board-certified gastroenterologists blinded to the exposure status. A diagnosis of CD or UC was confirmed based on accepted clinical criteria comprising typical symptoms of 4 weeks or longer and confirmatory endoscopic, surgical, histologic, and radiographic findings.[26,27] Disagreements between the 2 reviewers occurred infrequently and were resolved through consensus. Among those with sufficient medical records, a diagnosis of chronic colitis was rejected in 312 women and a diagnosis of non-IBD chronic colitis was made in 192. After excluding cases with missing information on date of diagnosis (n = 17) or dietary fiber (n = 53), our final cohort for analysis included 269 incident cases of CD and 338 cases of UC.

Covariates

Detailed information on cigarette smoking,[21] menopausal status,[22] use of oral contraceptives,[23] use of postmenopausal hormones,[22] use of aspirin, use of nonsteroidal anti-inflammatory drugs (NSAIDs),[19] and weight was collected every 2 years. Smoking, use of oral contraceptives, and use of postmenopausal hormones were modeled as time-varying covariates based on biennially updated estimates. Consistent with prior analysis, to avoid modification of weight by disease symptoms, body mass index (in kilograms per square meter) was modeled according to the baseline diet questionnaire (1984 for NHS I, 1989 for NHS II). Covariates were selected for inclusion a priori based on prior or suspected association with CD or UC based on the literature and prior data from our cohorts.[19–23]

Statistical Analysis

Participants contributed follow-up time from the date of return of the baseline FFQ (1984 in NHS I, 1991 in NHS II) to the date of diagnosis of CD or UC, death, or the return of the last questionnaire, whichever came first. A Cox proportional hazards model adjusting for potential confounders was used to estimate the multivariate hazard ratios (HRs) and 95% confidence intervals (CIs). Our main exposure, dietary fiber intake, was modeled as a cumulative average of intake through the questionnaire preceding the diagnosis and was stratified into quintiles, consistent with prior analyses using these cohorts.[14] Cumulative average intake provides the most stable estimate of adult diet in studies involving repeated measurements.[28] Tests for linear trend were conducted using the median value for each quintile as a continuous variable in the regression models. Because we observed no significant heterogeneity for the association of dietary fiber intake with CD or UC separately in NHS I and NHS II ($P > .30$), the cohorts were pooled for the final analysis, adjusting for cohort. To account for the potential modification of diet by development of symptoms before the formal diagnosis of disease, we conducted a lag analysis in which we used exposure information derived at least 2 questionnaire cycles before a follow-up interval. We performed formal tests for interaction between fiber intake and other potential risk factors by introducing a cross-product interaction term in the multivariate model. All models satisfied the proportionality of hazards assumption. We used SAS software 9.1 for all analyses (SAS

Institute, Cary, NC). A 2-sided P value of $<.05$ was considered statistically significant.

Results

Our study included 76,738 women in NHS I and 94,038 women in NHS II, among whom we documented 269 cases of CD (incidence, 8 per 100,000 person-years) and 338 cases of UC (incidence, 10 per 100,000 person-years) over 26 years encompassing 3,317,425 person-years of follow-up. The median age at diagnosis was 54 years (range, 29–82 years) for CD and 52 years (range, 29–85 years) for UC. At baseline, the median cumulative average intake of fiber ranged from 11 g/day in the lowest quintile to 25 g/day in the highest quintile. Whole grains and vegetables comprised the largest sources of dietary fiber. Table 1 shows the characteristics of the women according to quintile of fiber intake. Women in the highest quintile of cumulative fiber intake were more likely to be never smokers, less likely to have a body mass index $\geq$30 kg/m^2, or less likely to regularly use aspirin. Intake of other nutrients also varied by intake of fiber; women in the highest quintile had lower consumption of total fat and higher intake of dietary carbohydrates and proteins.

We observed that a high cumulative average intake of dietary fiber was associated with a lower incidence of CD in women (Table 2), although the association was not clearly linear. Compared with women in the lowest quintile of fiber intake, women in the highest quintile of fiber intake had a significantly reduced risk of CD (multivariate HR, 0.59; 95% CI, 0.39–0.90). In contrast, there was no statistically significant association between the intake of dietary fiber and UC (HR, 0.82; 95% CI, 0.58–1.17). We also observed differential associations according to the source of fiber intake. The strongest inverse association with CD was observed for intake of fiber from fruits (HR, 0.57; 95% CI, 0.38–0.85) for women in the highest quintile (median intake, 6.4 g/day; interquartile range [IQR], 5.7–7.6 g/day) compared with those in the lowest quintile (median, 1.4 g/day; IQR, 1.0–1.7 g/day). We also found numerically reduced but not statistically significant associations for all vegetables (HR, 0.74; 95% CI, 0.50–1.07) or cruciferous vegetables

Table 1. Baseline Characteristics of the Study Population According to Quintile of Dietary Fiber Intake

	Quintile 1 (n = 34,229)	Quintile 2 (n = 33,815)	Quintile 3 (n = 34,097)	Quintile 4 (n = 34,360)	Quintile 5 (n = 33,810)
Median total fiber intake (IQR) (*g/day*)	11.6 (10.3–12.6)	14.5 (13.7–15.4)	16.8 (15.8–17.6)	19.4 (18.5–20.3)	24.0 (22.4–26.8)
Mean age (SD) (*y*)	41.9 (8.8)	42.3 (8.9)	43.0 (9.1)	43.4 (9.4)	44.4 (9.7)
White race (%)	96	97	97	97	97
Smoking status (%)					
Never smoker	49	55	56	58	59
Past smoker	23	25	27	28	30
Current smoker	28	20	16	13	11
Ever oral contraceptive use (%)	69	69	69	68	68
Postmenopausal (%)	31	31	30	31	32
Postmenopausal hormone use (%)[a]					
Never users	57	55	55	52	52
Past users	20	21	21	21	19
Current users	23	24	24	28	29
Body mass index (*kg/m^2*) (%)					
<20.0	16	14	14	13	15
20.0–24.9	50	51	52	53	54
25.0–29.9	21	22	22	22	21
≥30.0	13	13	12	11	10
Regular use of aspirin[b] (%)	19	19	19	17	15
Regular use of NSAIDs[b] (%)	11	11	11	12	12
Mean fiber intake from various sources (SD) (*g/day*)					
Fruits	1.7 (1.0)	2.5 (1.3)	3.2 (1.6)	4.1 (1.9)	5.8 (3.1)
Vegetables	4.0 (1.4)	5.3 (1.5)	6.2 (1.8)	7.3 (2.2)	10.0 (4.1)
Cruciferous vegetables	0.6 (0.4)	0.8 (0.5)	0.9 (0.6)	1.1 (0.7)	1.6 (1.3)
Whole grains	8.4 (7.2)	12.6 (9.2)	16.0 (10.9)	20.7 (13.3)	30.3 (20.5)
Cereals	3.3 (1.3)	4.1 (1.6)	4.7 (1.9)	5.5 (2.3)	7.2 (4.4)
Bran	1.8 (2.2)	2.9 (3.0)	3.9 (3.8)	5.5 (5.1)	9.2 (9.5)
Legumes	0.5 (0.6)	0.7 (0.7)	0.8 (0.8)	1.0 (0.9)	1.5 (1.6)
Mean total fat intake (SD) (*g/day*)	66.6 (12.2)	65.7 (9.9)	63.6 (9.2)	60.8 (9.0)	55.0 (9.8)
Mean carbohydrate intake (SD) (*g/day*)	191 (44)	197 (35)	203 (32)	212 (32)	231 (36)
Mean total protein intake (SD) (*g/day*)	76.5 (17.6)	78.8 (15.8)	80.1 (15.4)	81.7 (15.4)	81.9 (16.3)

NOTE. Baseline characteristics according to the 1984 questionnaire for NHS I and the 1991 questionnaire for NHS II. Dietary fiber categories according to energy-adjusted intake. The US Department of Agriculture and National Academy of Sciences recommend intake of at least 21 g/day of fiber for women and 30 g/day for men.

[a]Percentages among postmenopausal women.

[b]Regular use was defined as intake of ≥5 times per month.

Table 2. Risk of CD and UC According to Quintile of Total Dietary Fiber Intake

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	*P* value (linear trend)
Daily fiber intake (g), median (IQR)	12.7 (11.4–13.6)	15.5 (14.9–16.0)	17.7 (17.1–18.2)	20.1 (19.4–20.8)	24.3 (22.8–26.8)	
Person-years of follow-up	675,994	673,043	673,390	671,533	671,588	
CD						
No. of cases	68	50	51	64	37	
Age-adjusted incidence[a]	10	7	8	9	5	
Age-adjusted HR (95% CI)	1.0	0.71 (0.49–1.03)	0.73 (0.50–1.05)	0.91 (0.65–1.29)	0.53 (0.35–0.80)	.02
Multivariate HR (95% CI)[b]	1.0	0.73 (0.50–1.06)	0.78 (0.54–1.13)	0.97 (0.68–1.38)	0.59 (0.39–0.90)	.08
UC						
No. of cases	74	65	66	72	63	
Age-adjusted incidence[a]	11	10	10	10	9	
Age-adjusted HR (95% CI)	1.0	0.86 (0.62–1.20)	0.86 (0.61–1.20)	0.94 (0.68–1.31)	0.83 (0.59–1.16)	.41
Multivariate HR (95% CI)[b]	1.0	0.87 (0.62–1.22)	0.86 (0.62–1.21)	0.94 (0.67–1.31)	0.82 (0.58–1.17)	.41

NOTE. Cumulative average energy-adjusted intake from the 1984 questionnaire for NHS I and the 1991 questionnaire for NHS II.
[a]Per 100,000 person-years.
[b]Adjusted for age, cohort, smoking (never, past, current), body mass index (<20 kg/m^2, 20–24.9 kg/m^{2}k, 25–29 kg/m^2, >30 kg/m^2), use of oral contraceptives (never, ever), use of postmenopausal hormone therapy (premenopausal, postmenopausal hormone never user, past user, current user), regular use of NSAIDs (yes, no), and regular use of aspirin (yes, no).

(HR, 0.78; 95% CI, 0.54–1.13) (Table 3). In contrast, intake of fiber from whole grain, bran, or legumes did not appear to be associated with risk of CD. We performed subgroup analysis by location of CD according to the Montreal classification. Although the numbers of women with each disease location was small and precluded statistically meaningful comparisons, we observed the strongest effect of total fiber intake for ileocolonic CD (HR, 0.47; 95% CI, 0.22–1.00). The association was stronger for disease with any ileal involvement (HR, 0.50; 95% CI, 0.29–0.86) compared with CD with any colonic disease (HR, 0.62; 95% CI, 0.38–1.01). Similar results were

Table 3. Risk of CD Associated With Fiber Intake From Specific Dietary Sources

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	*P* value (linear trend)
Fruits						
No. of cases	73	49	54	53	40	
Age-adjusted HR (95% CI)	1.0	0.65 (0.45–0.93)	0.70 (0.49–1.00)	0.67 (0.47–0.96)	0.51 (0.35–0.76)	.003
Multivariate HR (95% CI)[a]	1.0	0.69 (0.48–0.99)	0.75 (0.52–1.08)	0.74 (0.51–1.06)	0.57 (0.38–0.85)	.02
Vegetables						
No. of cases	66	49	49	58	47	
Age-adjusted HR (95% CI)	1.0	0.75 (0.52–1.09)	0.70 (0.48–1.02)	0.89 (0.62–1.27)	0.72 (0.49–1.04)	.22
Multivariate HR (95% CI)[a]	1.0	0.76 (0.53–1.10)	0.69 (0.48–1.01)	0.88 (0.61–1.25)	0.74 (0.50–1.07)	.25
Cruciferous vegetables						
No. of cases	64	49	54	50	52	
Age-adjusted HR (95% CI)	1.0	0.71 (0.49–1.03)	0.81 (0.56–1.17)	0.75 (0.52–1.09)	0.80 (0.55–1.15)	.40
Multivariate HR (95% CI)[a]	1.0	0.70 (0.48–1.02)	0.81 (0.56–1.17)	0.75 (0.52–1.09)	0.78 (0.54–1.13)	.35
Cereals						
No. of cases	63	45	54	60	47	
Age-adjusted HR (95% CI)	1.0	0.69 (0.47–1.01)	0.82 (0.57–1.19)	0.92 (0.64–1.33)	0.72 (0.49–1.06)	.40
Multivariate HR (95% CI)[a]	1.0	0.72 (0.49–1.07)	0.89 (0.61–1.29)	1.05 (0.72–1.51)	0.85 (0.57–1.26)	.95
Whole grain						
No. of cases	53	65	42	58	51	
Age-adjusted HR (95% CI)	1.0	1.15 (0.80–1.66)	0.77 (0.51–1.16)	1.04 (0.71–1.52)	0.94 (0.63–1.40)	.65
Multivariate HR (95% CI)[a]	1.0	1.17 (0.81–1.69)	0.81 (0.53–1.22)	1.14 (0.77–1.68)	1.07 (0.71–1.60)	.79
Bran						
No. of cases	56	54	53	62	44	
Age-adjusted HR (95% CI)	1.0	0.91 (0.62–1.32)	0.87 (0.59–1.28)	1.04 (0.72–1.51)	0.75 (0.50–1.12)	.26
Multivariate HR (95% CI)[a]	1.0	0.93 (0.64–1.36)	0.92 (0.63–1.36)	1.13 (0.77–1.66)	0.85 (0.56–1.28)	.65
Legumes						
No. of cases	55	59	49	52	54	
Age-adjusted HR (95% CI)	1.0	1.04 (0.72–1.50)	0.87 (0.59–1.28)	0.94 (0.63–1.38)	0.99 (0.67–1.46)	.90
Multivariate HR (95% CI)[a]	1.0	1.02 (0.70–1.48)	0.88 (0.60–1.30)	0.95 (0.64–1.40)	0.98 (0.66–1.44)	.88

NOTE. Cumulative average energy-adjusted intake from the 1984 questionnaire for NHS I and the 1991 questionnaire for NHS II.
[a]Adjusted for age, cohort, smoking (never, past, current), body mass index (<20 kg/m^2, 20–24.9 kg/m^2, 25–29 kg/m^2, >30 kg/m^2), use of oral contraceptives (never, ever), use of postmenopausal hormone therapy (premenopausal, postmenopausal hormone never user, past user, current user), regular use of NSAIDs (yes, no), and regular use of aspirin (yes, no).

seen with analysis for fiber intake from fruit. We also observed no similar protective effect with intake of different sources of fiber and UC (Table 4). We further examined if the lack of association with UC was due to requirement of a higher threshold of fiber intake; however, we observed no statistically significant effect across a range of plausible thresholds for the extreme quintile.

We also performed sensitivity analyses to confirm the consistency of our associations. Because various dietary macronutrients are not consumed in isolation, we introduced intake of carbohydrates, proteins, and fats into our multivariate model and did not observe a change in the association with dietary fiber. We also considered the possibility that symptoms of CD and UC may precede a formal diagnosis of CD by several months, thereby influencing dietary intake. Thus, we used the dietary assessment derived at least 4 years before a 2-year follow-up interval to conduct a lag analysis and observed only weak attenuation of the association between overall fiber intake and CD (HR, 0.75; 95% CI, 0.50–1.11) but not fiber intake from fruits (HR, 0.62; 95% CI, 0.42–0.92) or vegetables (HR, 0.71; 95% CI, 0.48–1.04). We also observed no differential association between dietary fiber intake and CD according to subgroups defined by smoking, oral contraceptive use, or body mass index. We also additionally adjusted for quintiles of physical activity and vitamin D intake and did not observe any change in our HRs for total dietary fiber (HR, 0.64; 95% CI, 0.42–0.98) or fiber intake from fruits (HR, 0.61; 95% CI, 0.41–0.92).

Discussion

In this large prospective study, we found that women in the highest quintile of cumulative intake of dietary fiber had a reduced risk of developing CD, but not UC, compared with those in the lowest quintile. Furthermore, specific sources of dietary fiber appeared to have differential associations. Dietary fiber intake from fruits and possibly vegetables reduced the risk of CD, whereas fiber intake from whole grains or legumes had no effect on the risk of CD or UC. The median fiber intake from fruits in the highest quintile of fruit intake was 6.4 g/day, which is the equivalent of slightly more than 2 medium-sized apples or bananas.

Plausible mechanisms exist to support the association between fiber intake and risk of CD. There is a dysbiosis of the gut microbiome in patients with IBD primarily characterized by reduced bacterial diversity, enrichment of Enterobacteriaceae, and a reduced proportion of *Firmicutes* and *Bacteroides*.[29–32] Although much of the adult gut microbial diversity may be attained by the age of 4 years, the adult microbiome remains susceptible to the influence

Table 4. Risk of UC Associated With Fiber Intake From Specific Dietary Sources

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	*P* value (trend)
Fruits						
No. of cases	70	72	72	66	58	
Age-adjusted HR (95% CI)	1.0	1.02 (0.74–1.42)	1.01 (0.73–1.41)	0.99 (0.71–1.38)	0.81 (0.57–1.15)	.12
Multivariate HR (95% CI)[a]	1.0	1.00 (0.72–1.39)	0.97 (0.69–1.35)	0.95 (0.67–1.33)	0.78 (0.54–1.12)	.15
Vegetables						
No. of cases	63	71	76	69	59	
Age-adjusted HR (95% CI)	1.0	1.10 (0.79–1.54)	1.18 (0.85–1.65)	1.08 (0.77–1.52)	0.90 (0.63–1.28)	.40
Multivariate HR (95% CI)[a]	1.0	1.08 (0.77–1.51)	1.16 (0.83–1.61)	1.04 (0.74–1.47)	0.88 (0.61–1.25)	.35
Cruciferous vegetables						
No. of cases	59	81	62	73	63	
Age-adjusted HR (95% CI)	1.0	1.22 (0.88–1.71)	1.00 (0.70–1.42)	1.18 (0.84–1.66)	1.00 (0.70–1.42)	.70
Multivariate HR (95% CI)[a]	1.0	1.20 (0.86–1.67)	0.95 (0.67–1.35)	1.13 (0.80–1.60)	0.95 (0.67–1.36)	.64
Cereals						
No. of cases	57	70	76	64	71	
Age-adjusted HR (95% CI)	1.0	1.24 (0.87–1.76)	1.31 (0.93–1.86)	1.12 (0.78–1.61)	1.24 (0.86–1.76)	.50
Multivariate HR (95% CI)[a]	1.0	1.26 (0.88–1.79)	1.34 (0.94–1.90)	1.14 (0.79–1.65)	1.26 (0.88–1.81)	.46
Whole grain						
No. of cases	56	75	66	71	70	
Age-adjusted HR (95% CI)	1.0	1.36 (0.96–1.92)	1.18 (0.82–1.69)	1.28 (0.89–1.83)	1.26 (0.87–1.81)	.42
Multivariate HR (95% CI)[a]	1.0	1.36 (0.96–1.93)	1.18 (0.82–1.70)	1.28 (0.89–1.84)	1.27 (0.88–1.83)	.42
Bran						
No. of cases	60	75	71	62	70	
Age-adjusted HR (95% CI)	1.0	1.25 (0.89–1.76)	1.15 (0.81–1.63)	1.04 (0.72–1.49)	1.13 (0.79–1.61)	.99
Multivariate HR (95% CI)[a]	1.0	1.26 (0.89–1.77)	1.15 (0.81–1.64)	1.05 (0.72–1.51)	1.13 (0.79–1.63)	.97
Legumes						
No. of cases	65	65	67	63	78	
Age-adjusted HR (95% CI)	1.0	1.01 (0.72–1.43)	1.04 (0.73–1.46)	1.04 (0.73–1.49)	1.26 (0.90–1.77)	.15
Multivariate HR (95% CI)[a]	1.0	1.01 (0.71–1.42)	1.03 (0.73–1.45)	1.03 (0.72–1.46)	1.23 (0.87–1.72)	.21

NOTE. Cumulative average energy-adjusted intake from the 1984 questionnaire for NHS I and the 1991 questionnaire for NHS II.

[a]Adjusted for age, cohort, smoking (never, past, current), body mass index (<20 kg/m^2, 20–24.9 kg/m^2, 25–29 kg/m^2, >30 kg/m^2), use of oral contraceptives (never, ever), use of postmenopausal hormone therapy (premenopausal, postmenopausal hormone never user, past user, current user), regular use of NSAIDs (yes, no), and regular use of aspirin (yes, no).

of diet.[29] Indeed, dietary patterns have been proposed to explain more than half of the variation in the adult intestinal microbiome.[29] Recent studies have shown a significant difference in the composition of intestinal microflora between children from Europe and Africa, with some of the difference postulated to be due to differences in consumption of dietary fiber.[33] Furthermore, intake of dietary fiber may differentially favor certain phylogenic groups of bacteria over others.[34] Thus, dietary fiber, through its effect on intestinal microbial composition, could potentially modify the risk of CD.

Interestingly, the protective effect of dietary fiber was seen predominantly for fiber intake from fruits. There are a few potential mechanisms to explain the specificity of this association. First, fiber from fruits tends to be soluble or fermentable fibers. This fermentable fiber is metabolized by intestinal bacteria to short-chain fatty acids, which inhibit nuclear factor $\kappa\beta$ and transcription of proinflammatory mediators.[12] Several genetic susceptibility loci for IBD are associated with maintaining intestinal barrier function, and an increase in mucosa-associated adherent, invasive *Escherichia coli* has been shown in patients with CD.[35] Roberts et al showed that soluble plant fiber inhibits the translocation of *E coli* across Peyer patches.[13] This maintenance of the intestinal barrier specific to soluble fiber may account for our findings that the protective effect of fiber appears to be primarily associated with soluble fiber from fruits but not whole grains, bran, or cereals. Furthermore, the effect of soluble fibers on prevention of bacterial translocation and the suggested role of enteroinvasive bacteria in the pathogenesis of CD also supports the specificity of the protective effect with CD but not UC.

A second mechanism that could explain the association with dietary fiber, particularly with some fruits and cruciferous vegetables, is mediated through the aryl hydrocarbon receptor (AhR)[36]. The AhR, abundantly expressed in intestinal intraepithelial lymphocytes, mediates protection against environmental antigens by binding to a nuclear translocator and activating dioxin- or xenobiotic-response element sequences.[36–39] Mice deficient in AhR are more susceptible to dextran sodium sulfate–induced colitis than wild-type mice and have a distinct pattern of intestinal colonization by *Bacteroides*.[36,40,41] In particular, a component of cruciferous vegetables, indole-3-carbinol, activates the AhR and attenuates dextran sodium sulfate–induced colitis in mice maintained on a vegetable-free diet.[36]

Prior retrospective studies examining the association between dietary fiber, fruit, or vegetable intake have had several limitations, including recall bias, assessment of diet at a single time point, and limited sample size, yielding inconsistent results as summarized by recent reviews.[5,6] A few studies have shown a protective effect for total dietary fiber,[11,42] with others finding no such association.[10] To our knowledge, the present study is the first to prospectively examine the association between long-term intake of total dietary fiber, assessed at several time points across the adult life span as well as specific sources of fiber, and the risk of CD and UC.

Our results are in agreement with most prior studies that have not identified an association of dietary fiber, fruit, or vegetable intake and risk of UC.[5,6] The reason for the potential divergent effect of fiber on CD as compared with UC merits further exploration. Recent genetic studies suggest a substantial overlap in genetic risk alleles for CD and UC, with less than 25% of the risk alleles distinct for each disease. In contrast, most environmental factors that have been examined, particularly through rigorous prospective studies, have revealed an association with either CD[20,21,23,25] or UC,[22,43] with few risk factors that are shared between the 2 diseases. Apart from the overall gut dysbiosis in patients with IBD, there are likely pathogenic differences between the 2 diseases[31,44] that could account for the differential effect of dietary fiber. We observed a statistically significant protective association with the highest quintile of dietary fiber intake compared with the lowest. However, the association did not appear to be clearly linear, suggesting that there may be a threshold of minimum fiber consumption associated with lower risk. This merits study in future analyses.

There are several strengths to our study. We used a prospective, validated dietary instrument, minimizing biases related to differential recall in the ascertainment of dietary intake and reverse causation due to modification of diet as a result of symptoms of CD. Second, assessment of diet through repeated questionnaires every 4 years minimized misclassification of dietary intake over extended follow-up and permitted a more stable estimate of long-term intake than studies that depend on assessment of diet at a single time point.[28] Third, our cases of CD and UC were confirmed through detailed medical record review by 2 board-certified gastroenterologists. Fourth, the medical background of the women participating in the study increased our confidence in the accuracy of assessment of exposures and potential confounders. Last, we were able to adjust for a large number of potential confounders.

We acknowledge that our study has a few limitations. First, our results are limited to IBD with onset at older ages. Additional studies are needed to examine the association of fiber intake with the incidence of IBD in younger age groups. Second, our cohort consisted entirely of women, mostly white. However, there are limited data to suggest a differential effect of environmental exposures on the risk of IBD based on race or sex. Furthermore, we have previously shown that the overall incidence of IBD in our cohorts is comparable to other population-based studies, and many of the environmental exposures described in our cohorts[21] are consistent with those reported from populations encompassing both men and women.[45] Third, we observed some attenuation in the magnitude of association of total fiber with CD in an analysis introducing a lag of 4 to 8 years between the final time point of assessment of diet and the diagnosis of CD or UC. However, this attenuation is unlikely to be explained by reverse causation (ie, symptoms

preceding a formal diagnosis of CD leading to modifications in fiber intake). Our study design used exposure data collected from the 2-year questionnaire cycle before the date of diagnosis. Thus, our primary analysis already incorporates a lag of 2 to 4 years between the last assessment of fiber intake and subsequent disease diagnosis. This lag period in our primary analysis is well beyond the mean lag between symptom onset and diagnosis identified in other cohorts.[46–48] In addition, our primary exposure is the cumulative average intake of total fiber as well as fiber from specific sources from all questionnaires before diagnosis, considered a more stable estimate of long-term diet. This also minimizes the likelihood that our associations can be explained by extreme variation in fiber intake reported on a single questionnaire before diagnosis. Thus, one can reasonably exclude the possibility of reverse causality completely explaining our findings in the vast majority of patients with both CD and UC. We do believe that the attenuation of the HR potentially suggests that recent fiber intake (within 4–8 years of diagnosis and before the onset of symptoms) may encompass the more relevant latency period by which fiber may influence the risk of CD (eg, through shifts in the microbiome or alterations in mucosal immunity). Also, the number of cases across each quintile was relatively limited, precluding statistically meaningful subgroup analysis across disease phenotypes. Last, as with all observational studies, we cannot exclude the possibility that an unmeasured confounder could account for the results. Although it is possible that women in the highest quintile of fiber intake may have other healthy behaviors that may confound the results, it is notable that in similarly designed analyses in our prospective cohorts, we did not observe any significant inverse associations between fiber intake and colorectal cancer, an end point in which potential confounding healthy behaviors such as physical activity are more strongly associated with risk.[14]

In conclusion, we show that high long-term intake of dietary fiber was associated with a reduction in the risk of CD, particularly for fiber intake from fruits and potentially from overall vegetables and cruciferous vegetables. This association supports experimental findings suggesting the importance of dietary fiber in modulating the gut microbiome or as a source of AhR. Further studies exploring these potential mechanisms as well a potential role for dietary fiber in the prevention or treatment of CD are needed.

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Reprint requests

Address requests for reprints to: Ashwin N. Ananthakrishnan, MD, MPH, Massachusetts General Hospital Crohn's and Colitis Center, 165 Cambridge Street, 9th Floor, Boston, Massachusetts 02114. e-mail: aananthakrishnan@partners.org; fax: (617) 726-3080.

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Conflicts of interest

The authors disclose the following: Dr Ananthakrishnan is a member of the scientific advisory board for Prometheus and Janssen. Dr Richter is a consultant for Policy Analysis. Dr Chan is a consultant for Bayer HealthCare, Millennium Pharmaceuticals, Pfizer, and Pozen. The remaining authors disclose no conflicts.

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