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

Ashwin N. Ananthakrishnan, M.D., M.P.H.[1], **Hamed Khalili, M.D.**[1], **Gauree G. Konijeti, M.D., M.P.H.**[1], **Leslie M. Higuchi, M.D., M.P.H.**[2], **Punyanganie de Silva, M.B.B.S, M.R.C.P**[1], **Joshua R. Korzenik, M.D.**[3], **Charles S. Fuchs, M.D., M.P.H.**[2,5], **Walter C. Willett, M.D., Dr.P.H.**[4,6], **James M. Richter, M.D.**[1], and **Andrew T. Chan, M.D., M.P.H.**[1,5]

[1]Division of Gastroenterology, Massachusetts General Hospital and Harvard Medical School, Boston, MA

[2]Division of Gastroenterology and Nutrition, Children's Hospital Boston and Harvard Medical School, Boston, MA

[3]Division of Gastroenterology, Brigham and Women' Hospital and Harvard Medical School, Boston, MA

[4]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA

Correspondence Ashwin N Ananthakrishnan, MD, MPH, Massachusetts General Hospital Crohn's and Colitis center, 165 Cambridge Street, 9th Floor, Boston, MA 02114, Phone: 617-726-0267, Fax: 617-726-3080, aananthakrishnan@partners.org.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Disclosures
Ashwin N. Ananthakrishnan – Scientific advisory board for Prometheus Inc, and Janssen, Inc.
Hamed Khalili – none
Gauree Konijeti - none
Leslie M. Higuchi- none
Punyanganie de Silva – none
Joshua R Korzenik - none
James M. Richter- Consultant for Policy Analysis, Inc.
Charles S. Fuchs- none
Walter C. Willett - none
Andrew T. Chan- Consultant for Bayer HealthCare, Millennium Pharmaceuticals, Pfizer Inc.,, Pozen Inc.

Author Contributions
Ashwin N. Ananthakrishnan - study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis; obtained funding; study supervision.
Hamed Khalili - acquisition of data; analysis and interpretation of data; critical revision of the manuscript for important intellectual content.
Gauree G Konijeti - acquisition of data; critical revision of the manuscript for important intellectual content
Leslie M. Higuchi- acquisition of data; critical revision of the manuscript for important intellectual content.
Punyanganie de Silva - acquisition of data; critical revision of the manuscript for important intellectual content.
Joshua R Korzenik – interpretation of data; critical revision of the manuscript for important intellectual content.
Charles S. Fuchs- study concept and design; critical revision of the manuscript for important intellectual content; study supervision.
Walter C. Willett - study concept and design; acquisition of data; critical revision of the manuscript for important intellectual content;
James M. Richter- study concept and design, acquisition of data; critical revision of the manuscript for important intellectual content.
Andrew T. Chan- study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis; obtained funding; study supervision

5Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

6Department of Nutrition, Harvard School of Public Health

Abstract

Background & Aims—Increased intake of dietary fiber has been proposed to reduce risk of inflammatory bowel diseases (Crohn's disease [CD], 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 over 26 y, who participated in the Nurses' Health Study, followed for 3,317,425 person-y. Dietary information was prospectively ascertained via administration of a validated semi-quantitative food frequency questionnaire every 4 y. 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-y) and 338 cases of UC (incidence 10/100,000 person-y). Compared to 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 [CI], 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% CI 0.58–1.17) nor intake of fiber from specific sources appeared to be significantly associated with risk of UC.

Conclusion—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

INTRODUCTION

To date, a total of 163 distinct genetic polymorphisms associated with risk of either CD or 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 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].

The 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 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 NF   and transcription of pro-inflammatory 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 had been limited for several reasons. First, retrospective ascertainment of pre-illness diet is subject both to recall bias as well as 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 two large, well-characterized cohorts of women, with validated outcomes and periodic assessments of diet across the adult lifespan, to examine the association between long-term intake of dietary fiber and risk of incident CD and UC. Furthermore, we examined the impact of fiber intake from different sources to shed light on the specific mechanisms through which dietary fiber intake may modulate risk of disease.

METHODS

Study Population

Our study included participants from the Nurses Health Study I & II (NHS I & II). The NHS I is a prospective cohort of 121,700 female registered nurses between the ages of 30–55 years at recruitment in 1976. The NHS II includes 116,686 female registered nurses of age 25–42 years at enrollment in 1989. Both cohorts are followed with detailed biennial questionnaires ascertaining environmental exposures and health outcomes with a rate of follow-up of approximately 90%. The present study included women who completed a detailed semi-quantitative dietary food frequency questionnaire (FFQ) in 1984 in NHS I and 1991 in NHS II. Women who were deceased prior to the first dietary questionnaire, had a diagnosis of cancer (except non-melanoma skin cancer) or were diagnosed with IBD prior to this 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 semi-quantitative food frequency questionnaires (FFQ) 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, 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 an average over the past year. Nutrient intakes were calculated by multiplying the frequency of consumption of each food item by the nutrient content based on the tables provided by the Department of Agriculture. Total dietary fiber was calculated based on the method of the Association of Official Analytic Chemists (AOAC). Nutrient intake was adjusted for total energy intake by the residual method. Fiber supplements were not assessed till 1994 but were taken by fewer 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 demonstrated 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 publications[19–25]. In brief, since 1976 2,735 women from NHS I and since 1989 2,541 women from NHS II self-reported a diagnosis of CD or UC on a biennial questionnaire through 2010 in NHSI and 2009 in NHSII. 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 3,415 women who were still alive, were not diagnosed with IBD prior to the start date of the study and could be contacted, 1,549 subsequently denied the diagnosis based on this more detailed description of the diseases. Among the remaining 1,866 patients, permission to view medical records was obtained in 1,532. Medical records were reviewed by two 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 two 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 of UC.

Covariates

Detailed information on cigarette smoking[21], menopausal status[22], use of oral contraceptives[23], post-menopausal hormone use[22], aspirin, non-steroidal anti-inflammatory drugs (NSAIDs)[19], and weight were collected every 2 years. Smoking, OC use, and hormone use 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 (BMI) (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 till 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 (CI). Our main exposure, dietary fiber intake, was modeled as 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. As we observed no significant heterogeneity for the association of dietary fiber intake with CD or UC separately in NHS I and NHS II ($p > 0.30$), the cohorts were pooled together for the final analysis, adjusting for cohort. To account for the potential modification of diet by development of symptoms prior to the formal diagnosis of disease, we conducted a lag analysis in which we used exposure information derived at least two 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 two-sided p-value of < 0.05 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 of 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 grams (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 presents 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 BMI 30kg/m^2 or be regular users of aspirin. Intake of other nutrients also varied by fiber intake; women in the highest quintile had a lower consumption of total fat and a higher intake of dietary carbohydrates and proteins.

We observed that 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 to women with the lowest quintile of fiber intake, women in the highest quintile of fiber intake had a significantly reduced risk of CD (multivariate hazard ratio (HR) 0.59, 95% confidence interval (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 fiber intake from fruits (HR 0.57, 95%CI 0.38 – 0.85) for women in the highest quintile (median intake 6.4g/day; interquartile range (IQR) 5.7 – 7.6g/day) compared to those in the lowest quintile (median 1.4g/day, IQR 1.0 – 1.7g/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 vegetable (HR 0.78, 95% CI 0.54 – 1.13) (Table 3). In contrast, fiber intake 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 to CD with any colonic disease (HR 0.62, 95% CI 0.38 – 1.01). Similar results were 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. As 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 four years prior to a two-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 hazard ratios 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 to 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 CD risk whereas fiber intake from whole grains or legumes had no effect on risk of CD or UC. The median fiber intake from fruits in the highest quintile of fruit intake was 6.4 grams/ day, which is the equivalent of just over two 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 reduced proportion of firmicutes and bacteroides[29–32]. While much of the adult gut microbial diversity may be attained by the age of 4 years, the adult microbiome remains susceptible to the influence of diet[29]. Indeed, dietary patterns have been proposed to explain over half the variation in the adult intestinal microbiome[29]. Recent studies have demonstrated 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 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 NF   and transcription of pro-inflammatory mediators[12]. Several genetic susceptibility loci for IBD are associated with maintaining intestinal barrier function and an increase in mucosa-associated adherent, invasive *E coli* has been demonstrated in patients with CD[35]. Roberts *et al* showed that soluble plant fiber inhibits the translocation of *E coli* across Peyer's patches[13]. This maintenance of intestinal barrier specific to soluble fiber may account for our findings that the protective effect of fiber appears 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 CD pathogenesis 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 (DSS) colitis than wild type of mice, and have a distinct pattern of intestinal colonization by *Bacteroides*[36, 40, 41]. In particular, a component of cruciferous vegetables, indole-3-carbinol (I3C) activates the AhR, and attenuates DSS-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 timepoint, and limited sample size, yielding inconsistent results as summarized by recent reviews[5, 6]. A few studies have demonstrated 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 timepoints across adult lifespan as well as specific sources of fiber, in relation to 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 fewer than 25% of the risk alleles being 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 two. Apart from the overall gut dysbiosis in IBD patients, there are likely pathogenic differences between the two diseases itself[31, 44] which could account for the differential effect of dietary fiber. We observed a statistically significant protective association of with the highest quintile of dietary fiber intake compared with the lowest. However, the association did not appear 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 due to 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[28] point. Third, our CD and UC cases were confirmed through detailed medical record review by two 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 IBD incidence in younger age groups. Second, our cohort consisted entirely of women, mostly of Caucasian race. However, there are limited data to suggest a differential effect of environmental exposures on IBD risk based on race or sex. Furthermore, we have previously demonstrated that the overall IBD incidence 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 4–8 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 (i.e. symptoms preceding a formal diagnosis of CD leading to modifications in fiber intake). First, our study design uses exposure data collected from the two-year questionnaire cycle prior to the date of diagnosis. Thus, our primary analysis already incorporates a lag of 2–4 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]. Second, our primary exposure is the cumulative average intake of total fiber as well as fiber from specific sources from all questionnaires prior to 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 hazard ratio may potentially suggest that recent fiber intake (within 4–8 years of diagnosis, and prior to the onset of symptoms) may encompass the more relevant latency period by which fiber may influence risk of CD (e.g. through shifts in the microbiome or alterations in mucosal immunity). Fourth, 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 results. While it is possible that women in the highest quintile of fiber intake may have other healthy behaviors which may confound the results, it is notable that in similarly designed analyses within our prospective cohorts, we did not observe any significant inverse associations between fiber intake and colorectal cancer, an endpoint in which potential confounding healthy behaviors such as physical activity are more strongly associated with risk[14].

In conclusion, we demonstrate that high long-term intake of dietary fiber was associated with a reduction in 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 aryl hydrocarbon receptor. Further studies exploring these potential mechanisms as well a potential role for dietary fiber in the prevention or treatment of CD merits further study.

Acknowledgments

REFERENCES

1. Khor B, Gardet A, Xavier RJ. Genetics and pathogenesis of inflammatory bowel disease. Nature. 2011; 474:307–317. [PubMed: 21677747]

2. Jostins L, Ripke S, Weersma RK, Duerr RH, McGovern D, Hun KY, Lee JC, Schumm LP, Sharma Y, Anderson CA, Essers J, Mitrovic M, Ning K, Cleynen I, Theatre E, Spain SL, Raychaudhuri S, Goyette P, Wei Z, Abraham C, Achkar JP, Ahmad T, Amineinejad L, Ananthakrishnan AN, Andersen V, Andrews JM, Baidoo L, Balschun T, Cohain A, Cichon S, D'Amato M, De Jong DJ, Devaney KL, Dubinsky M, Edwards C, Ellinghaus D, Ferguson LR, Franchimont D, Fransen K, Gearry R, Gieger C, Karlsen J, Haritunians T, Hart A, Hawkey C, Hedl M, Hu X, Karlsen TH, Kupinskas L, Kugathasan S, Latiano A, Laukens D, Lawrance IC, Lees CW, Louis E, Mahy G, Mansfield J, Morgan AR, Mowat C, Newman W, Palmieri O, Ponsioen CY, Potocnik U, Prescott NJ, Regueiro MD, Rotter JI, Russell RK, Sanderson JD, Sans M, Satsangi J, Schreiber S, Simms LA, Sventoraityte J, Targan SR, Taylor K, Tremelling M, Verspaget HW, De Vos M, Wijmenga C, Wilson DC, Winkelmann J, Xavier RJ, S Z, Zhang B, Zhang CK, Zhao H, Consortium TIIG, Silverberg MS, Annese V, Hakonarson H, Brant SR, Radford-Smith G, Mathew CG, Rioux JD, Schadt EE, Daly M, Franke A, Parkes M, Vermeire S, Barret JC, et al. Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. Nature. 2012 in press.

3. Williams CN. Does the incidence of IBD increase when persons move from a low- to a high-risk area? Inflamm Bowel Dis. 2008; 14(Suppl 2):S41–S42. [PubMed: 18816730]

4. Thia KT, Loftus EV, Sandborn WJ, Yang SK Jr. An update on the epidemiology of inflammatory bowel disease in Asia. Am J Gastroenterol. 2008; 103:3167–3182. [PubMed: 19086963]

5. Chapman-Kiddell CA, Davies PS, Gillen L, Radford-Smith GL. Role of diet in the development of inflammatory bowel disease. Inflamm Bowel Dis. 2010; 16:137–151. [PubMed: 19462428]

6. Hou JK, Abraham B, El-Serag H. Dietary intake and risk of developing inflammatory bowel disease: a systematic review of the literature. Am J Gastroenterol. 2011; 106:563–573. [PubMed: 21468064]

7. Geerling BJ, Dagnelie PC, Badart-Smook A, Russel MG, Stockbrugger RW, Brummer RJ. Diet as a risk factor for the development of ulcerative colitis. Am J Gastroenterol. 2000; 95:1008–1013. [PubMed: 10763951]

8. Gentschew L, Ferguson LR. Role of nutrition and microbiota in susceptibility to inflammatory bowel diseases. Mol Nutr Food Res. 2012; 56:524–535. [PubMed: 22495981]

9. Jantchou P, Morois S, Clavel-Chapelon F, Boutron-Ruault MC, Carbonnel F. Animal protein intake and risk of inflammatory bowel disease: The E3N prospective study. Am J Gastroenterol. 2010; 105:2195–2201. [PubMed: 20461067]

10. Sakamoto N, Kono S, Wakai K, Fukuda Y, Satomi M, Shimoyama T, Inaba Y, Miyake Y, Sasaki S, Okamoto K, Kobashi G, Washio M, Yokoyama T, Date C, Tanaka H. Dietary risk factors for inflammatory bowel disease: a multicenter case-control study in Japan. Inflamm Bowel Dis. 2005; 11:154–163. [PubMed: 15677909]

11. Amre DK, D'Souza S, Morgan K, Seidman G, Lambrette P, Grimard G, Israel D, Mack D, Ghadirian P, Deslandres C, Chotard V, Budai B, Law L, Levy E, Seidman EG. Imbalances in dietary consumption of fatty acids, vegetables, and fruits are associated with risk for Crohn's disease in children. Am J Gastroenterol. 2007; 102:2016–2025. [PubMed: 17617201]

12. Maslowski KM, Mackay CR. Diet, gut microbiota and immune responses. Nat Immunol. 2011; 12:5–9. [PubMed: 21169997]

13. Roberts CL, Keita AV, Duncan SH, O'Kennedy N, Soderholm JD, Rhodes JM, Campbell BJ. Translocation of Crohn's disease Escherichia coli across M-cells: contrasting effects of soluble plant fibres and emulsifiers. Gut. 2010; 59:1331–1339. [PubMed: 20813719]

14. Fuchs CS, Giovannucci EL, Colditz GA, Hunter DJ, Stampfer MJ, Rosner B, Speizer FE, Willett WC. Dietary fiber and the risk of colorectal cancer and adenoma in women. N Engl J Med. 1999; 340:169–176. [PubMed: 9895396]

15. Michels KB, Giovannucci E, Chan AT, Singhania R, Fuchs CS, Willett WC. Fruit and vegetable consumption and colorectal adenomas in the Nurses' Health Study. Cancer Res. 2006; 66:3942–3953. [PubMed: 16585224]

16. Michels KB, Fuchs CS, Giovannucci E, Colditz GA, Hunter DJ, Stampfer MJ, Willett WC. Fiber intake and incidence of colorectal cancer among 76,947 women and 47,279 men. Cancer Epidemiol Biomarkers Prev. 2005; 14:842–849. [PubMed: 15824154]

17. Willett WC, Sampson L, Stampfer MJ, Rosner B, Bain C, Witschi J, Hennekens CH, Speizer FE. Reproducibility and validity of a semiquantitative food frequency questionnaire. Am J Epidemiol. 1985; 122:51–65. [PubMed: 4014201]

18. Salvini S, Hunter DJ, Sampson L, Stampfer MJ, Colditz GA, Rosner B, Willett WC. Food-based validation of a dietary questionnaire: the effects of week-to-week variation in food consumption. Int J Epidemiol. 1989; 18:858–867. [PubMed: 2621022]

19. Ananthakrishnan AN, Higuchi LM, Huang ES, Khalili H, Richter JM, Fuchs CS, Chan AT. Aspirin, Nonsteroidal Anti-inflammatory Drug Use, and Risk for Crohn Disease and Ulcerative Colitis: A Cohort Study. Ann Intern Med. 2012; 156:350–359. [PubMed: 22393130]

20. Ananthakrishnan AN, Khalili H, Higuchi LM, Bao Y, Korzenik JR, Giovannucci EL, Richter JM, Fuchs CS, Chan AT. Higher predicted vitamin d status is associated with reduced risk of Crohn's disease. Gastroenterology. 2012; 142:482–489. [PubMed: 22155183]

21. Higuchi LM, Khalili H, Chan AT, Richter JM, Bousvaros A, Fuchs CS. A Prospective Study of Cigarette Smoking and the Risk of Inflammatory Bowel Disease in Women. American Journal of Gastroenterology. 2012; 107:1399–1406. [PubMed: 22777340]

22. Khalili H, Higuchi LM, Ananthakrishnan AN, Manson JE, Feskanich D, Richter JM, Fuchs CS, Chan AT. Hormone Therapy Increases Risk of Ulcerative Colitis but not Crohn's Disease. Gastroenterology. 2012; 143:1199–1206. [PubMed: 22841783]

23. Khalili H, Higuchi LM, Ananthakrishnan AN, Richter JM, Feskanich D, Fuchs CS, Chan AT. Oral Contraceptives, Reproductive Factors, and Risk of Inflammatory Bowel Disease. Gut. 2012 in press.

24. Khalili H, Huang ES, Ananthakrishnan AN, Higuchi L, Richter JM, Fuchs CS, Chan AT. Geographical variation and incidence of inflammatory bowel disease among US women. Gut. 2012; 61:1686–1692. [PubMed: 22241842]

25. Ananthakrishnan AN, Khalili H, Pan A, Higuchi LM, de Silva P, Richter JM, Fuchs CS, Chan AT. Association between depressive symptoms and incidence of Crohn's disease and ulcerative colitis: results from the nurses' health study. Clin Gastroenterol Hepatol. 2013; 11:57–62. [PubMed: 22944733]

26. Baumgart DC, Sandborn WJ. Crohn's disease. Lancet. 2012; 380:1590–1605. [PubMed: 22914295]

27. Ordas I, Eckmann L, Talamini M, Baumgart DC, Sandborn WJ. Ulcerative colitis. Lancet. 2012; 380:1606–1619. [PubMed: 22914296]

28. Hu FB, Stampfer MJ, Rimm E, Ascherio A, Rosner BA, Spiegelman D, Willett WC. Dietary fat and coronary heart disease: a comparison of approaches for adjusting for total energy intake and modeling repeated dietary measurements. Am J Epidemiol. 1999; 149:531–540. [PubMed: 10084242]

29. Brown K, DeCoffe D, Molcan E, Gibson DL. Diet-induced dysbiosis of the intestinal microbiota and the effects on immunity and disease. Nutrients. 2012; 4:1095–1119. [PubMed: 23016134]

30. Nagalingam NA, Lynch SV. Role of the microbiota in inflammatory bowel diseases. Inflamm Bowel Dis. 2012; 18:968–984. [PubMed: 21936031]

31. Morgan XC, Tickle TL, Sokol H, Gevers D, Devaney KL, Ward DV, Reyes JA, Shah SA, LeLeiko N, Snapper SB, Bousvaros A, Korzenik J, Sands BE, Xavier RJ, Huttenhower C. Dysfunction of the intestinal microbiome in inflammatory bowel disease and treatment. Genome Biol. 2012; 13:R79. [PubMed: 23013615]

32. Spor A, Koren O, Ley R. Unravelling the effects of the environment and host genotype on the gut microbiome. Nat Rev Microbiol. 2011; 9:279–290. [PubMed: 21407244]

33. De Filippo C, Cavalieri D, Di Paola M, Ramazzotti M, Poullet JB, Massart S, Collini S, Pieraccini G, Lionetti P. Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa. Proc Natl Acad Sci U S A. 2010; 107:14691–14696. [PubMed: 20679230]

34. Wu GD, Chen J, Hoffmann C, Bittinger K, Chen YY, Keilbaugh SA, Bewtra M, Knights D, Walters WA, Knight R, Sinha R, Gilroy E, Gupta K, Baldassano R, Nessel L, Li H, Bushman FD, Lewis JD. Linking long-term dietary patterns with gut microbial enterotypes. Science. 2011; 334:105–108. [PubMed: 21885731]

35. Kotlowski R, Bernstein CN, Sepehri S, Krause DO. High prevalence of Escherichia coli belonging to the B2+D phylogenetic group in inflammatory bowel disease. Gut. 2007; 56:669–675. [PubMed: 17028128]

36. Monteleone I, MacDonald TT, Pallone F, Monteleone G. The aryl hydrocarbon receptor in inflammatory bowel disease: linking the environment to disease pathogenesis. Curr Opin Gastroenterol. 2012; 28:310–313. [PubMed: 22450895]

37. Gu YZ, Hogenesch JB, Bradfield CA. The PAS superfamily: sensors of environmental and developmental signals. Annu Rev Pharmacol Toxicol. 2000; 40:519–561. [PubMed: 10836146]

38. Li Y, Innocentin S, Withers DR, Roberts NA, Gallagher AR, Grigorieva EF, Wilhelm C, Veldhoen M. Exogenous stimuli maintain intraepithelial lymphocytes via aryl hydrocarbon receptor activation. Cell. 2011; 147:629–640. [PubMed: 21999944]

39. Kiss EA, Vonarbourg C, Kopfmann S, Hobeika E, Finke D, Esser C, Diefenbach A. Natural aryl hydrocarbon receptor ligands control organogenesis of intestinal lymphoid follicles. Science. 2011; 334:1561–1565. [PubMed: 22033518]

40. Li J, Norgard B, Precht DH, Olsen J. Psychological stress and inflammatory bowel disease: a follow-up study in parents who lost a child in Denmark. Am J Gastroenterol. 2004; 99:1129–1133. [PubMed: 15180736]

41. Monteleone I, Rizzo A, Sarra M, Sica G, Sileri P, Biancone L, MacDonald TT, Pallone F, Monteleone G. Aryl hydrocarbon receptor-induced signals up-regulate IL-22 production and inhibit inflammation in the gastrointestinal tract. Gastroenterology. 2011; 141:237–248. 248 e1. [PubMed: 21600206]

42. Reif S, Klein I, Lubin F, Farbstein M, Hallak A, Gilat T. Pre-illness dietary factors in inflammatory bowel disease. Gut. 1997; 40:754–760. [PubMed: 9245929]

43. Andersson RE, Olaison G, Tysk C, Ekbom A. Appendectomy and protection against ulcerative colitis. N Engl J Med. 2001; 344:808–814. [PubMed: 11248156]

44. Bibiloni R, Mangold M, Madsen KL, Fedorak RN, Tannock GW. The bacteriology of biopsies differs between newly diagnosed, untreated, Crohn's disease and ulcerative colitis patients. J Med Microbiol. 2006; 55:1141–1149. [PubMed: 16849736]

45. Mahid SS, Minor KS, Soto RE, Hornung CA, Galandiuk S. Smoking and inflammatory bowel disease: a meta-analysis. Mayo Clin Proc. 2006; 81:1462–1471. [PubMed: 17120402]

46. Romberg-Camps MJ, Hesselink-van de Kruijs MA, Schouten LJ, Dagnelie PC, Limonard CB, Kester AD, Bos LP, Goedhard J, Hameeteman WH, Wolters FL, Russel MG, Stockbrugger RW. Inflammatory Bowel Disease in South Limburg (the Netherlands) 1991–2002: Incidence, diagnostic delay, and seasonal variations in onset of symptoms. J Crohns Colitis. 2009; 3:115–124. [PubMed: 21172254]

47. Vavricka SR, Spigaglia SM, Rogler G, Pittet V, Michetti P, Felley C, Mottet C, Braegger CP, Rogler D, Straumann A, Bauerfeind P, Fried M, Schoepfer AM. Systematic evaluation of risk factors for diagnostic delay in inflammatory bowel disease. Inflamm Bowel Dis. 2011; 18:496–505. [PubMed: 21509908]

48. Ng SC, Tang W, Ching JY, Wong M, Chow CM, Hui AJ, Wong TC, Leung VK, Tsang SW, Yu HH, Li MF, Ng KK, Kamm MA, Studd C, Bell S, Leong R, de Silva HJ, Kasturiratne A, Mufeena MN, Ling KL, Ooi CJ, Tan PS, Ong D, Goh KL, Hilmi I, Pisespongsa P, Manatsathit S, Rerknimitr R, Aniwan S, Wang YF, Ouyang Q, Zeng Z, Zhu Z, Chen MH, Hu PJ, Wu K, Wang X, Simadibrata M, Abdullah M, Wu JC, Sung JJ, Chan FK. Incidence and phenotype of inflammatory bowel disease based on results from the Asia-pacific Crohn's and colitis epidemiology study. Gastroenterology. 2013; 145:158–165. e2. [PubMed: 23583432]

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 (in years) (standard deviation)	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
Post-menopausal (%)	31	31	30	31	32
Post-menopausal hormone use (%)[†]					
Never Users	57	55	55	52	52
Past Users	20	21	21	21	19
Current Users	23	24	24	28	29
Body Mass Index (%)					
< 20.0 kg/m2	16	14	14	13	15
20.0 – 24.9 kg/m2	50	51	52	53	54
25.0 – 29.9 kg/m2	21	22	22	22	21
30.0 kg/m2	13	13	12	11	10
Regular aspirin use[±] (%)	19	19	19	17	15
Regular NSAID use[±] (%)	11	11	11	12	12
Mean fiber intake from various sources (g/day) (SD)					
Fruits	1.7(1.0)	2.5(1.3)	3.2(1.6)	4.1(1.9)	5.8(3.1)

	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)
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 (g/day) (SD)	66.6 (12.2)	65.7 (9.9)	63.6 (9.2)	60.8 (9.0)	55.0 (9.8)
Mean carbohydrate intake (g/day)(SD)	191 (44)	197 (35)	203 (32)	212 (32)	231 (36)
Mean total protein intake (g/day) (SD)	76.5(17.6)	78.8(15.8)	80.1(15.4)	81.7(15.4)	81.9(16.3)

SD – standard deviation; NSAID – non-steroidal anti-inflammatory drugs; g/day – grams per day; IQR – interquartile range

[†]Baseline characteristics according to the 1984 questionnaire for Nurses Health Study I and 1991 questionnaire for Nurses Health Study II.

Dietary fiber categories according to energy-adjusted intake.

[ĵ]Percentages among postmenopausal women

[±]regular use was defined as intake of 5 or more times per month

The United States Department of Agriculture and National Academy of Sciences recommend an intake of at least 21 grams/day of fiber for women and 30 grams/day for men.

Table 2

Risk of Crohn's disease and ulcerative colitis according to quintile of total dietary fiber intake[†]

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P(linear trend)
Daily fiber intake (in grams) [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	
Crohn's disease						
Number of cases	68	50	51	64	37	
Age-adjusted incidence [#]	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)	0.02
Multivariate HR (95% CI) [†]	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)	0.08
Ulcerative colitis						
Number of cases	74	65	66	72	63	
Age-adjusted incidence [#]	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)	0.41
Multivariate HR (95% CI) [†]	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)	0.41

NSAID – non-steroidal anti-inflammatory drugs, HR – hazard ratio, CI – confidence interval, IQR – interquartile range

[‡]Cumulative average energy-adjusted intake from 1984 (NHS I) or 1991 (NHS II)

[#] per 100,000 person-years

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

Table 3

Risk of Crohn's disease associated with fiber intake from specific dietary sources[‡]

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P(linear trend)
Fruits						
Number 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)	0.003
Multivariate HR (95% CI) [†]	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)	0.02
Vegetables						
Number 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)	0.22
Multivariate HR (95% CI) [†]	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)	0.25
Cruciferous vegetables						
Number 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)	0.40
Multivariate HR (95% CI) [†]	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)	0.35
Cereals						
Number 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)	0.40
Multivariate HR (95% CI) [†]	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)	0.95
Whole grain						
Number 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)	0.65
Multivariate HR (95% CI) [†]	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)	0.79
Bran						
Number 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)	0.26

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P(linear trend)
Multivariate HR (95% CI) [†]	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)	0.65
Legumes						
Number 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)	0.90
Multivariate HR (95% CI) [†]	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)	0.88

[‡] Cumulative average energy-adjusted intake from 1984 (NHS I) or 1991 (NHS II)

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

Ananthakrishnan et al.

Page 17

Table 4

Risk of ulcerative colitis associated with fiber intake from specific dietary sources[†]

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P(trend)
Fruits						
Number 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)	0.12
Multivariate HR (95% CI) [†]	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)	0.15
Vegetables						
Number 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)	0.40
Multivariate HR (95% CI) [†]	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)	0.35
Cruciferous vegetables						
Number 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)	0.70
Multivariate HR (95% CI) [†]	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)	0.64
Cereals						
Number 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)	0.50
Multivariate HR (95% CI) [†]	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)	0.46
Whole grain						
Number 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)	0.42
Multivariate HR (95% CI) [†]	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)	0.42
Bran						
Number 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)	0.99

Gastroenterology. Author manuscript; available in PMC 2014 November 01.

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P(trend)
Multivariate HR (95% CI) [†]	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)	0.97
Legumes						
Number 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)	0.15
Multivariate HR (95% CI) [†]	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)	0.21

[‡] Cumulative average energy-adjusted intake from 1984 (NHS I) or 1991 (NHS II)

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