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High School Diet and Risk of Crohn's Disease and Ulcerative Colitis

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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.
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Abstract

Introduction—Diet may play an important role in the pathogenesis of Crohn's disease (CD) and ulcerative colitis (UC), yet there are few prospective studies of dietary factors. None have examined the association between adolescent diet and risk of inflammatory bowel diseases (IBD; CD and UC).

Methods—This study included women enrolled in Nurses' Health Study II who completed a validated high school dietary questionnaire in 1998. We examined the effect of dietary patterns (prudent or western diet) and individual components of each patterns. We documented incident cases of CD and UC through 2011 based on physician review of medical records and used Cox proportional hazards models adjusting for confounders to estimate hazard ratios (HR) and confidence intervals (CI) for CD and UC.

Results—Over 763,229 person-years of follow-up, we identified 70 incident cases of CD and 103 cases of UC. Compared to women in the lowest quartile of a prudent diet score (characterized by greater intake of fruits, vegetables, and fish), women in the highest quartile had a 53% lower risk of CD (Hazard ratio (HR) 0.47, 95% confidence interval (CI) 0.23 – 0.98; P_{trend}=0.04). Specifically, greater intake of fish (P_{trend}=0.01) and fiber (P_{trend}=0.06) were associated with lower risk of CD. In contrast, Western diet score was not associated with risk of CD. Neither dietary patterns nor individual food or nutrient groups was associated with UC.

Conclusion—Adolescent diet is associated with risk of CD, but not UC, offering insights into disease pathogenesis.

Keywords

Crohn's disease; ulcerative colitis; diet; iron; fiber

INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) (inflammatory bowel diseases, IBD) are chronic immunologically mediated diseases affecting 1.5 million in the United States, 2.2 million in Europe, and several thousands more worldwide[1, 2]. They develop at the complex intersection of predisposing genetic polymorphisms, gut microbial dysbiosis, immunologic abnormalities and the external environment. However, our understanding of the precise pathogenesis and the source of the majority of the variance in disease risk is limited[3]. The external environment remains particularly challenging to study due to limitations of case-control examinations of such associations and the paucity of prospective cohort studies.

Diet has been long proposed as being important in the pathogenesis of these diseases[4]. It may exert its effect through panoply of mechanisms including influence on microbial composition and establishment of gut enterotypes[5], facilitating expansion of specific pathobionts[6], contributing to the integrity of the intestinal barrier[7] as well as a direct effect of dietary ligands on immune response[8]. In children and adults, a diet high in fiber, particularly from fruits and vegetables, has been inversely associated with risk of CD[9–11] and a high ω3, low ω6 polyunsaturated fatty acid (PUFA) diet with UC[12–15]. The association with other dietary constituents including carbohydrates, saturated fats, and

sweetened beverages is less robust and data are conflicting[16, 17]. A key unanswered question in disease pathogenesis is the importance of the timing of exposure. While case-control studies have utilized assessment of diet immediately pre-diagnosis (thereby subject to bias from reverse causation), cohort studies examining diets have largely relied on habitual adult diet. No prior studies have examined whether dietary patterns or individual dietary constituents during adolescence are associated with risk of CD and UC. Such associations have been described for colorectal adenomas[18, 19], and are supported by biological plausibility owing to the previously described sustained effect of early life influences on the establishment of the gut microbiome and immune responses[20]. Identifying such associations would offer additional insights into disease pathogenesis and importantly may suggest avenues for prevention prior to the years of peak incidence of disease.

Consequently, we performed this study utilizing the strengths of a large prospective cohort of women who provided validated and detailed data on their usual dietary intake during high school to (i) examine the influence of high school dietary patterns, specifically a prudent diet characterized by high intake of fruits, vegetables, and fish or a western diet (high intake of desserts and sweets, snack foods, red and processed meat), and risk of incident UC and CD; and (ii) to define the association with specific food groups and dietary nutrients constituting major components of these broad dietary patterns.

METHODS

Study Population

The Nurses Health Study II is a prospective cohort that began in 1989 when 116,686 female registered nurses between the ages of 25–42 years were enrolled. The women were followed biennially through questionnaires ascertaining health status, personal and environmental exposures with follow-up rates exceeding 90%[21]. Diet was assessed using a semi-quantitative food frequency questionnaire (FFQ) first in 1991 and subsequently every 4 years. In 1997, women were asked if they were willing to complete an additional detailed food frequency questionnaire about usual diet during high school. Just over half the women enrolled in NHS II (55%, n=64,380) indicated willingness to do so among whom 83% (n=47,355) returned the high school dietary food frequency questionnaire (HS-FFQ). Women who completed the HS-FFQ were between the ages of 35–51 years at the time of completion and had similar baseline dietary intake compared to those who did not complete the questionnaire[18, 19]. After exclusion of women who reported a history of IBD or cancer (excluding non-melanoma skin cancers) prior to enrollment in NHS II or had died prior to the assessment of dietary intake, our study included 39,511 women.

Ascertainment of High School Diet

The ascertainment of high school diet using the HS-FFQ has been described in detail in previous publications[18, 19, 22]. In brief, the HS-FFQ was a 124-item questionnaire ascertaining dietary intake during high school (ages 13–17 years; grades 9–12) and included food items commonly eaten when participants attended high school. The HS-FFQ was validated in two steps. First, a subset of 333 NHS II participants were re-administered the HS-FFQ 4 years later; results demonstrated good correlation with initial self-report (mean

Spearman correlation coefficient 0.60) supporting consistency of data[23]. Second, 80 young adults who were children of NHS II participants completed three 24-hour dietary recalls and the Youth Adolescent Questionnaire (YAQ) FFQ between the ages of 13–18 years and were administered the HS-FFQ 10 years later. The mean correlation for nutrient intake between 24-hour diet recalls and HS-FFQ was 0.69 and between HS-FFQ and YAQ was 0.58[24].

High school dietary patterns were generated by grouping HS-FFQ items into 37 food groups and applying factor analysis using the SAS procedure PROC FACTOR with orthogonal rotation procedure varimax as described previously[19, 25]. This factor analysis aggregated food groups based on the degree of correlation between the food items in the data set. We identified two dietary patterns, a prudent pattern (characterized by high intake of vegetables, fruit, better quality grains, fish, and poultry) and a western pattern (characterized by high intake of desserts, sweets, snacks, red and processed meat, refined grains and fries). A dietary pattern score was generated for each participant by summing weighted intakes of food groups, adjusted for energy consumption using the residual method. We also examined associations between individual constituents of diet included total carbohydrates, total and animal fats, total and animal protein, fiber, servings per day of fruits and vegetables as well as fish and CD or UC. All food groups were modeled as quartiles of intake except for fish which was categorized into previously described categories (< 10g/day, 10–20g/day, 20–30g/day, and ≥ 30g/day) owing to a skewed distribution[18].

Habitual adult dietary intake was assessed using a 131-item FFQ ascertaining intake during the previous 12 months[26–28]. The response categories for these questions were similar to the HS-FFQ. For each food item, a commonly used portion size was specified and participants asked about the average frequency of consumption over the past year. Nutrient intake was calculated by multiplying frequency of consumption with the nutrient content of each food item. Dietary fiber was calculated based on the method of the Association of Official Analytic Chemists. Intake was adjusted for total energy intake by the residual method. Dietary food groups were divided into quartiles as described above for high school diet.

Ascertainment of incident CD and UC

Details about identification of incident cases of CD and UC have been reported previously[11, 12, 29–31]. In brief, in each biennial questionnaire, participants were asked to self-report a diagnosis of CD and UC. Women who self-identified as having these diseases were mailed a supplemental questionnaire with a more detailed description of the diseases and inquired further about details of their disease including duration of symptoms, method of diagnosis, disease-related complications, and medical and surgical treatments. From participants who provided consent, medical records were obtained and independently reviewed by two board certified gastroenterologists to confirm the diagnosis and type of IBD. Disagreements were infrequent and adjudicated by consensus. All medical record review was blinded to exposures. A diagnosis of CD or UC was made based upon accepted criteria including a history of symptoms of 4 weeks or longer in duration, and supportive endoscopy, histopathology, radiology, and operative findings[32–34].

Among the women who completed the high school dietary questionnaire, during the study period (1991 – 2011), 690 women self-reported a diagnosis of IBD. After excluding those

who were deceased (n = 3), were unable to be contacted (n=57) or who subsequently denied the diagnosis on the more detailed supplementary questionnaire (n=234), medical records were obtained for 300 women who permitted review. A diagnosis of chronic colitis was rejected in 72 women and non-IBD indeterminate colitis was diagnosed in 39. After excluding those with missing information on relevant covariates (n=16), our final case population consisted of 70 incident cases of CD and 103 incident cases of UC.

Covariates

Biennially updated information was collected on potentially relevant exposures including smoking[30], oral contraceptive use[35], menopausal status and use of menopausal hormone therapy[31], non-steroid anti-inflammatory drug use[36], and dietary intake of fiber[11] and vitamin D[29] using the SFFQ. Habitual dietary intake of various nutrients during adulthood was modeled as a cumulative average up to each biennial questionnaire cycle. Body mass index (BMI) was calculated by dividing the weight (in kilograms) by the square of the height (in meters) and baseline BMI at cohort entry was adjusted for as a covariate. Physical activity was assessed every four years as previously described and reported as metabolic equivalent hours per week[37].

Statistical Analysis

All participants contributed person-time from the date of return of the 1991 questionnaire to the month of diagnosis of IBD, death, date of completion of the last questionnaire, or June 1, 2011, whichever came first. Age-adjusted incidence rates for CD and UC were calculated using the Mantel-Haenszel adjustment of age-specific incidences in 5-year age categories. Cox proportional hazards models adjusting for relevant covariates were used to calculate the independent association between quartiles of high-school dietary exposures and risk of IBD. The statistical significance of trend across quartiles was assessed by modeling the median intake within each quartile as a continuous variable. Covariates were selected for adjustment in the multivariable model based on significance on univariate analysis or prior results in published literature demonstrating significant association. All models satisfied the proportional hazards assumption. For high-school dietary factors that were significant in the adjusted Cox models, we repeated the analyses adjusting for habitual dietary intake of the relevant food group or nutrient during adulthood to assess the independence of high-school intake. A two-sided p-value < 0.05 indicated independent statistical significance. This study was approved by the Institutional Review Board of Brigham and Women's Hospital and Partners Healthcare.

RESULTS

Over 763,229 person-years (p-y) of follow-up of 39,511 women, there were 70 new cases of CD (incidence 9 per 100,000 p-y) and 103 cases of UC (incidence 14 per 100,000 p-y). The median age of diagnosis was 46 years for CD (range 29 – 63 years) and 45 years for UC (range 31 – 64 years). The mean age at baseline was 37 years and most women were white (97%). The majority were premenopausal (92%), had current or past use of oral contraceptives (84%) and were non-smokers (67%). Compared to women in the lowest quartile of prudent diet, those in the highest quartile had higher adult and high school fiber

and carbohydrate intake and lower intake of fat (Table 1). Intake of protein during adulthood or high school was similar across all quartiles of prudent diet. Women in the highest quartile of the prudent diet score had higher consumption of fruits, vegetables and fish during high school and adulthood. In contrast, women in the highest quartile of western diet had lower intake of fish, carbohydrates, and fiber (Table 1).

First, we examined the association between a prudent or western dietary pattern during high school and risk of CD and UC. Compared to women in the lowest quartile of a prudent dietary pattern, we observed a 53% lower risk of CD among those with the highest prudent dietary pattern quartile (hazard ratio (HR) 0.47, 95% confidence interval (CI) 0.23 – 0.98; P_{trend}=0.04) when compared to those in the lowest quartile.

In order to determine which individual components of a dietary pattern may drive observed associations, we then examined the individual components contributing to a high prudent diet score to determine if specific food groups that are major components of a prudent diet most strongly associated with risk of CD. Compared to women who consumed < 10g/day of fish during high school, those with an intake of ≥ 30g/day had a 57% lower risk of CD (HR 0.43, 95% CI 0.21 – 0.90; P_{trend}=0.01). The association with high school intake of fish was not materially altered even after adjusting for adult fish intake (P_{trend}=0.03) or adult intake of dietary n–3 PUFA (P_{trend}=0.01). Adult intake of fish was not independently associated with risk of CD. High intake of dietary fiber during high school was non-significantly inversely associated with risk of CD. Compared to women in the lowest quartile of high school dietary fiber, women in the highest quartile had a lower incidence of CD even adjusting for adult fiber intake (multivariable-adjusted HR 0.55, 95% CI 0.27 – 1.12; P_{trend}=0.06) (Table 2). Additionally, our findings were suggestive of an inverse association between vegetable intake and risk of CD, but none of the results reached statistical significance (highest vs. lowest quartile HR 0.50, 95% CI 0.25 – 1.03, P_{trend}=0.11). Fruit intake was not associated with risk of CD. Restriction of analysis only to cases (n=40) diagnosed after the return of the high school FFQ in 1998 yielded a similar association for prudent diet (Q4 vs. Q1 HR 0.33, 95% CI 0.10 – 1.10, P_{trend}=0.06). As previously reported, adult dietary patterns were not found to be associated with risk of CD or UC in our cohort[38]. In addition, adjustment for adult dietary patterns did not modify the association with high school dietary patterns, individual food groups, or macronutrients.

We did not observe a significant association between Western diet and risk of CD. However, we did find a non-significant increase in risk of CD with higher intake of dietary heme-iron during high school (HR 1.62, 95% CI 0.81 – 3.23, P_{trend}=0.14) although this association was not observed with total iron intake (P_{trend}=0.33), or intake of red or processed meat (Table 2).

In contrast to the associations with CD, neither western nor prudent dietary patterns, or the consumption of specific food groups during high school were associated with risk of UC (Table 3).

DISCUSSION

In a large cohort of women with prospective ascertainment of high school and adult diet followed for incident CD and UC, we observed a lower incidence of CD among women with a high prudent diet score during high school. Specifically, during high school, greater dietary intake of fiber and fish, two major components of a prudent diet, was associated with reduced risk of CD independent of habitual adult intake. In contrast, a Western dietary pattern during high school was not associated with increased risk of CD. Neither prudent or Western dietary patterns nor specific food groups were associated with risk of UC. Our findings support the hypothesis that a prudent diet, and in particular, intake during early adulthood, is independently associated with lower risk of CD.

In our study, a high prudent dietary pattern score during high school was associated with a reduced incidence of Crohn's disease. Specifically within this dietary pattern, three main dietary constituents were found to modify risk of CD, all of them supported by considerable biologic plausibility. Dietary intake of fiber has been consistently demonstrated to be inversely associated with risk of IBD though only few have utilized a prospective cohort design, minimizing the potential for 'reverse causality' by reduction of dietary fiber intake due to pre-diagnosis symptoms[9–11, 16, 17]. In a case-control study of children with CD, Amre *et al*. identified an inverse association with consumption of fruits, vegetables, or overall dietary fiber[9]. Similarly, a dietary pattern consisting of high intake of vegetables, fruits, olive oil, fish, grains and nuts was also inversely associated with lower risk of CD[10]. These findings are consistent with our study demonstrating an association with a higher prudent diet score, and trend towards independent associations with total fiber as well as intake of vegetables. The persistence of this association even after accounting for adult diet suggests that adolescent dietary exposures may durably and independently modify risk of IBD apart from adult diet.

There are several mechanisms through which dietary fiber may play a role in the development of CD. First, a long-term diet high in fiber, fruits, vegetables and simple carbohydrates is associated with a gut enterotype that is rich in *Prevotella* and low in *Bacteroides*[5]. Prior data has demonstrated reduced bacterial protein signals from *Prevotella* in CD cases compared to healthy controls[39] and more abundant occurrence of *Prevotella* in biopsies from healthy controls compared to CD[40]. Patients with a predominance of *Prevotella* at intestinal resection also have a lower risk of post-operative recurrence[41]. A second possible mechanism of action of dietary fiber is through its effect on maintenance of barrier integrity. In an elegant series of studies, Roberts *et al*. demonstrated that soluble fiber from plantains reduced translocation of intestinal pathogens, and in particular *Escherichia coli* (*E coli*), across Peyer's patches and colonic lymphoid follicles[7, 42]. A third mechanism is through direct immune effects of ligands present in sources of fiber; for example dietary indole-3-carbinol found in cruciferous vegetables may stimulate the aryl hydrocarbon receptor (AhR) [8].

Dietary fish intake during high school also inversely correlated with risk of CD in our study, consistent with a few prior case-control studies of pediatric and adult onset CD[43, 44]. In contrast, clinical trials of fish oil for the maintenance of remission in CD have not

demonstrated efficacy[45] and other small case-control studies reported an increased risk of UC with fish consumption[46]. Such conflicting results highlight potential biases in case-control studies and the need for rigorous cohort studies controlling for relevant confounders. Additionally, discrepancy between epidemiologic studies and clinical trials may be owe to certain factors that could have varying roles in disease onset and maintenance or remission, or may have clinical efficacy in established disease at doses different than studied in clinical trials. Moreover, our data suggest that early dietary exposures may be important predictors of subsequent risk of CD. Short-term clinical trials of fish oil are not able to specifically examine such a prolonged latency of effect.

A potential mechanism to explain the inverse association between fish and CD is through marine ω3 PUFA content in fish[15, 47–50]. Dietary ω3 PUFA may inhibit, through competitive mechanisms, formation of pro-inflammatory leukotrienes and prostaglandins through the arachidonic pathway and also inhibit adaptive immune responses through the peroxisome proliferator-activated receptor pathway[50]. Additionally, ω3 PUFA may inhibit vascular adhesion, migration and angiogenesis[50]. In contrast to a few prior studies suggesting an inverse association between ω3 PUFA intake and risk of UC[12, 15], in the present study, we did not identify any association between high school fish intake or total PUFA intake and risk of UC. There are a few possible reasons for this. First, the effect of intake during high school compared to habitual intake during adult life may be different and the relative contribution (and consequently biological effect) in the context of other constituents in the diet of individual dietary factors may vary. Of note, most of the prior studies demonstrating an inverse association with fish intake and CD were conducted in the pediatric population,[9, 10] and assessed diet during school years, while the studies that failed to identify an association were generally examining adult diet. As shown in Table 1, there is considerable difference between macronutrient consumption during adulthood when compared to during high school, and in particular much greater consumption of animal proteins and fats. Second, genetic variations in polymorphisms involved in metabolism of ω3 and ω6 PUFA may influence an individual's likelihood of protective benefit from their intake[51]. In an elegant study by Costea *et al*., a higher ω6/ω3 ratio was associated with decreased risk of CD only among those who carried specific variants of cytochrome P450 4F3 (CYP4F3) and fatty acid desaturase (FADS2) genes[51].

Other dietary factors that demonstrated non-statistically significant independent trends with greater risk of CD included heme-intake iron during high school and high intake of animal fat or protein. Biologic plausibility supports these associations as well. Adherent invasive *E coli*, putatively associated with CD pathogenesis are enriched in iron acquisition pathways compared to non-pathogenic *E coli*[51] and mice fed an iron supplemented diet demonstrate enhanced colonic interleukin-6 (IL-6) and IL-11 release, and Stat3 phosphorlyation and more severe colonic inflammation[52]. An added mechanism could be an increase in iron-mediated oxidative stress by facilitating production of hydroxyl radicals through the Fenton reaction[53, 54]. However, the effect of intestinal iron on colitis has not always been consistent with human studies demonstrating no adverse clinical effect of iron supplementation for treatment of anemia in CD and UC[55], and rat models demonstrating an expansion of the

protective butyrate producing gut microbiota and lack of worsening of histological activity[56].

In contrast to the inverse association with prudent diet, the lack of a direct significant association with western dietary patterns suggested epidemiologically by rising incidence of IBD in developing countries adopting an increasingly western lifestyle could have a few explanations. First, our study may have lacked the statistical power to identify more subtle effects of western diet. Second, the changing incidence of IBD in previously low incidence countries could equally or to a greater extent be due to reduced consumption of traditional prudent diets as increasing intake of western style diets. Third, our findings suggest modest associations may exist with individual dietary macronutrients (for example, animal fat, heme-iron from animal protein) rather than a broad western dietary pattern. Finally, association between increasing incidence of IBD with 'westernization' of lifestyle may be mediated by non-dietary factors such as psychosocial stress, physical activity, or other health behaviors.

There are several strengths to our study. To our knowledge, ours is the first study prospectively examining high school diet as a risk factor for CD and UC. Prior case-control studies have been susceptible to bias introduced by differential recall of diet between cases and controls as well as potential modification of diet due to pre-diagnosis symptoms. Assuming a usual age of high school graduation of 18 years, participants reported usual diet ranging from 11 to 46 years prior to diagnosis of IBD. Consequently, we do not expect differential recall due to such confounding to influence our results. We were also able to adjust for usual diet intake during adulthood, thereby facilitating our ability to evaluate the independent influence of high school dietary intake on risk.

We acknowledge a few limitations to our study. Our cohort consisted only of women and was predominantly white. While few prior studies have suggested racial differences in environmental influences on risk of IBD, it is important to replicate the associations with diet and other environmental factors identified from Caucasian populations in other populations that are racially and ethnically diverse, and from different geographic locations including migrant populations[57–59]. The population was younger and differed in distribution of some covariates than in our previously reported studies that included both the full cohort of NHS II and older women included in the Nurses Health Study (NHS I). However, the incidence of IBD in our cohort is comparable to other population based studies, supporting generalizability of our findings. Second, the median age of diagnosis of CD or UC was 45 years, although our study also included women between the ages of 29 – 64 years. Consequently, our findings may be less generalizable to a cohort with pediatric onset disease though our findings are generally consistent with those previously reported in pediatric cohorts. Third, all participants in our cohorts were nurses and may have health behaviors that may differ from the general population; however, the incidence of IBD in our cohort is comparable to other population-based studies[60] and the environmental factors previously identified in our cohorts have been replicated in diverse populations[61, 62]. As in all observational analyses, we cannot exclude the possibility of residual confounding. However, our findings remained robust after adjustment for widely accepted risk factors for IBD including several lifestyle factors. The number of cases within each quartile was small

precluding detailed subgroup analyses. As well, some of the associations that showed borderline significant trends may be demonstrated more robustly in larger cohorts. A post-hoc power calculation revealed a power of 80% to detect an odds ratio of 0.38 for prudent diet in CD and 0.43 for UC. We also lacked information on other potential risk factors including socioeconomic status, family history, and prior exposure to antibiotics. However, that all the participants were female registered nurses provides some homogeneity in socioeconomic status. Additionally, for other risk factors to be confounders, they would need to be associated with both disease as well as dietary exposure, with the latter association being unlikely for family history of IBD or antibiotic usage. Additionally, only a small proportion of patients with IBD have a positive family history, and prior work has not shown that environmental risk factors differ in their association based on genetic predisposition. Our study also focused on high school diet using a validated questionnaire; it is plausible that dietary intake earlier in childhood may also be important in the pathogenesis of IBD; however, such diets are less reliably assessed by self-report than during adolescence.

In conclusion, we observed an inverse association between a prudent dietary pattern and in particular intake of fiber, vegetables, and fish and risk of CD independent of intake during adult life. None of the high school dietary factors modified risk of UC. Our findings support the hypothesis that adolescent diet may play a role in the pathogenesis of CD. Continued studies into the mechanisms underlying the association between dietary factors and risk of CD are important to further our understanding of these complex diseases.

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References

1. Molodecky NA, Soon IS, Rabi DM, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology. 2012; 142:46–54. e42. quiz e30. [PubMed: 22001864]
2. Abraham C, Cho JH. Inflammatory bowel disease. N Engl J Med. 2009; 361:2066–78. [PubMed: 19923578]
3. Khor B, Gardet A, Xavier RJ. Genetics and pathogenesis of inflammatory bowel disease. Nature. 2011; 474:307–17. [PubMed: 21677747]
4. Lee D, Albenberg L, Compher C, et al. Diet in the Pathogenesis and Treatment of Inflammatory Bowel Diseases. Gastroenterology. 2015
5. Wu GD, Chen J, Hoffmann C, et al. Linking long-term dietary patterns with gut microbial enterotypes. Science. 2011; 334:105–8. [PubMed: 21885731]
6. Devkota S, Wang Y, Musch MW, et al. Dietary-fat-induced taurocholic acid promotes pathobiont expansion and colitis in Il10-/- mice. Nature. 2012; 487:104–8. [PubMed: 22722865]
7. Roberts CL, Keita AV, Duncan SH, et al. Translocation of Crohn's disease Escherichia coli across M-cells: contrasting effects of soluble plant fibres and emulsifiers. Gut. 2010; 59:1331–9. [PubMed: 20813719]

8. Monteleone I, MacDonald TT, Pallone F, et al. The aryl hydrocarbon receptor in inflammatory bowel disease: linking the environment to disease pathogenesis. Curr Opin Gastroenterol. 2012; 28:310–3. [PubMed: 22450895]
9. Amre DK, D'Souza S, Morgan K, et al. Imbalances in dietary consumption of fatty acids, vegetables, and fruits are associated with risk for Crohn's disease in children. Am J Gastroenterol. 2007; 102:2016–25. [PubMed: 17617201]
10. D'Souza S, Levy E, Mack D, et al. Dietary patterns and risk for Crohn's disease in children. Inflamm Bowel Dis. 2008; 14:367–73. [PubMed: 18092347]
11. Ananthakrishnan AN, Khalili H, Konijeti GG, et al. A prospective study of long-term intake of dietary fiber and risk of Crohn's disease and ulcerative colitis. Gastroenterology. 2013; 145:970–7. [PubMed: 23912083]
12. Ananthakrishnan AN, Khalili H, Konijeti GG, et al. Long-term intake of dietary fat and risk of ulcerative colitis and Crohn's disease. Gut. 2014; 63:776–84. [PubMed: 23828881]
13. de Silva PS, Olsen A, Christensen J, et al. An association between dietary arachidonic acid, measured in adipose tissue, and ulcerative colitis. Gastroenterology. 2010; 139:1912–7. [PubMed: 20950616]
14. Hart AR, Luben R, Olsen A, et al. Diet in the aetiology of ulcerative colitis: a European prospective cohort study. Digestion. 2008; 77:57–64. [PubMed: 18349539]
15. John S, Luben R, Shrestha SS, et al. Dietary n-3 polyunsaturated fatty acids and the aetiology of ulcerative colitis: a UK prospective cohort study. Eur J Gastroenterol Hepatol. 2010; 22:602–6. [PubMed: 20216220]
16. Chapman-Kiddell CA, Davies PS, Gillen L, et al. Role of diet in the development of inflammatory bowel disease. Inflamm Bowel Dis. 2010; 16:137–51. [PubMed: 19462428]
17. 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; 106:563–73. [PubMed: 21468064]
18. Nimptsch K, Bernstein AM, Giovannucci E, et al. Dietary intakes of red meat, poultry, and fish during high school and risk of colorectal adenomas in women. Am J Epidemiol. 2013; 178:172–83. [PubMed: 23785116]
19. Nimptsch K, Malik VS, Fung TT, et al. Dietary patterns during high school and risk of colorectal adenoma in a cohort of middle-aged women. Int J Cancer. 2014; 134:2458–67. [PubMed: 24493161]
20. Francino MP. Early development of the gut microbiota and immune health. Pathogens. 2014; 3:769–90. [PubMed: 25438024]
21. Colditz GA, Manson JE, Hankinson SE. The Nurses' Health Study: 20-year contribution to the understanding of health among women. J Womens Health. 1997; 6:49–62. [PubMed: 9065374]
22. Malik VS, Fung TT, van Dam RM, et al. Dietary patterns during adolescence and risk of type 2 diabetes in middle-aged women. Diabetes Care. 2012; 35:12–8. [PubMed: 22074723]
23. Maruti SS, Feskanich D, Colditz GA, et al. Adult recall of adolescent diet: reproducibility and comparison with maternal reporting. Am J Epidemiol. 2005; 161:89–97. [PubMed: 15615919]
24. Maruti SS, Feskanich D, Rockett HR, et al. Validation of adolescent diet recalled by adults. Epidemiology. 2006; 17:226–9. [PubMed: 16477265]
25. Hu FB. Dietary pattern analysis: a new direction in nutritional epidemiology. Curr Opin Lipidol. 2002; 13:3–9. [PubMed: 11790957]
26. Willett WC, Reynolds RD, Cottrell-Hoehner S, et al. Validation of a semi-quantitative food frequency questionnaire: comparison with a 1-year diet record. J Am Diet Assoc. 1987; 87:43–7. [PubMed: 3794132]
27. Willett WC, Sampson L, Browne ML, et al. The use of a self-administered questionnaire to assess diet four years in the past. Am J Epidemiol. 1988; 127:188–99. [PubMed: 3337073]
28. Willett WC, Sampson L, Stampfer MJ, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. Am J Epidemiol. 1985; 122:51–65. [PubMed: 4014201]
29. Ananthakrishnan AN, Khalili H, Higuchi LM, et al. Higher predicted vitamin d status is associated with reduced risk of Crohn's disease. Gastroenterology. 2012; 142:482–9. [PubMed: 22155183]

30. Higuchi LM, Khalili H, Chan AT, et al. A Prospective Study of Cigarette Smoking and the Risk of Inflammatory Bowel Disease in Women. American Journal of Gastroenterology. 2012 in press.
31. Khalili H, Higuchi LM, Ananthakrishnan AN, et al. Hormone Therapy Increases Risk of Ulcerative Colitis but not Crohn's Disease. Gastroenterology. 2012; 143:1199–206. [PubMed: 22841783]
32. Loftus CG, Loftus EV Jr, Harmsen WS, et al. Update on the incidence and prevalence of Crohn's disease and ulcerative colitis in Olmsted County, Minnesota, 1940–2000. Inflamm Bowel Dis. 2007; 13:254–61. [PubMed: 17206702]
33. Loftus EV Jr. Clinical epidemiology of inflammatory bowel disease: Incidence, prevalence, and environmental influences. Gastroenterology. 2004; 126:1504–17. [PubMed: 15168363]
34. Loftus EV Jr, Silverstein MD, Sandborn WJ, et al. Ulcerative colitis in Olmsted County, Minnesota, 1940–1993: incidence, prevalence, and survival. Gut. 2000; 46:336–43. [PubMed: 10673294]
35. Khalili H, Higuchi LM, Ananthakrishnan AN, et al. Oral contraceptives, reproductive factors and risk of inflammatory bowel disease. Gut. 2013; 62:1153–9. [PubMed: 22619368]
36. Ananthakrishnan AN, Higuchi LM, Huang ES, et al. Aspirin, Nonsteroidal Anti-inflammatory Drug Use, and Risk for Crohn Disease and Ulcerative Colitis: A Cohort Study. Ann Intern Med. 2012; 156:350–9. [PubMed: 22393130]
37. Khalili H, Ananthakrishnan AN, Konijeti GG, et al. Physical activity and risk of inflammatory bowel disease: prospective study from the Nurses' Health Study cohorts. BMJ. 2013; 347:f6633. [PubMed: 24231178]
38. Khalili H, Ananthakrishnan AN, Sauk J, et al. Dietary patterns and risk of crohn's disease and ulcerative colitis. Inflamm Bowel Dis. 2014; 20:S36–37.
39. Albenberg LG, Wu GD. Diet and the Intestinal Microbiome: Associations, Functions, and Implications for Health and Disease. Gastroenterology. 2014
40. Prindiville T, Cantrell M, Wilson KH. Ribosomal DNA sequence analysis of mucosa-associated bacteria in Crohn's disease. Inflamm Bowel Dis. 2004; 10:824–33. [PubMed: 15626901]
41. De Cruz P, Kang S, Wagner J, et al. Association between specific mucosa-associated microbiota in Crohn's disease at the time of resection and subsequent disease recurrence: A pilot study. J Gastroenterol Hepatol. 2015; 30:268–78. [PubMed: 25087692]
42. Roberts CL, Keita AV, Parsons BN, et al. Soluble plantain fibre blocks adhesion and M-cell translocation of intestinal pathogens. J Nutr Biochem. 2013; 24:97–103. [PubMed: 22818716]
43. Octoratou M, Merikas E, Malgarinos G, et al. A prospective study of pre-illness diet in newly diagnosed patients with Crohn's disease. Rev Med Chir Soc Med Nat Iasi. 2012; 116:40–9. [PubMed: 23077871]
44. Pugazhendhi S, Sahu MK, Subramanian V, et al. Environmental factors associated with Crohn's disease in India. Indian J Gastroenterol. 2011; 30:264–9. [PubMed: 22161539]
45. Feagan BG, Sandborn WJ, Mittmann U, et al. Omega-3 free fatty acids for the maintenance of remission in Crohn disease: the EPIC Randomized Controlled Trials. JAMA. 2008; 299:1690–7. [PubMed: 18398081]
46. Sakamoto N, Kono S, Wakai K, et al. Dietary risk factors for inflammatory bowel disease: a multicenter case-control study in Japan. Inflamm Bowel Dis. 2005; 11:154–63. [PubMed: 15677909]
47. Cabre E, Manosa M, Gassull MA. Omega-3 fatty acids and inflammatory bowel diseases - a systematic review. Br J Nutr. 2012; 107 (Suppl 2):S240–52. [PubMed: 22591898]
48. Larsson SC, Kumlin M, Ingelman-Sundberg M, et al. Dietary long-chain n-3 fatty acids for the prevention of cancer: a review of potential mechanisms. Am J Clin Nutr. 2004; 79:935–45. [PubMed: 15159222]
49. Uchiyama K, Nakamura M, Odahara S, et al. N-3 polyunsaturated fatty acid diet therapy for patients with inflammatory bowel disease. Inflamm Bowel Dis. 2010; 16:1696–707. [PubMed: 20222122]
50. Marion-Letellier R, Savoye G, Beck PL, et al. Polyunsaturated fatty acids in inflammatory bowel diseases: a reappraisal of effects and therapeutic approaches. Inflamm Bowel Dis. 2013; 19:650–61. [PubMed: 23328774]

51. Costea I, Mack DR, Lemaitre RN, et al. Interactions between the dietary polyunsaturated fatty acid ratio and genetic factors determine susceptibility to pediatric Crohn's disease. Gastroenterology. 2014; 146:929–31. [PubMed: 24406470]
52. Chua AC, Klopcic BR, Ho DS, et al. Dietary iron enhances colonic inflammation and IL-6/IL-11-Stat3 signaling promoting colonic tumor development in mice. PLoS One. 2013; 8:e78850. [PubMed: 24223168]
53. Reifen R, Matas Z, Zeidel L, et al. Iron supplementation may aggravate inflammatory status of colitis in a rat model. Dig Dis Sci. 2000; 45:394–7. [PubMed: 10711457]
54. Carrier J, Aghdassi E, Platt I, et al. Effect of oral iron supplementation on oxidative stress and colonic inflammation in rats with induced colitis. Aliment Pharmacol Ther. 2001; 15:1989–99. [PubMed: 11736731]
55. Dignass AU, Gasche C, Bettenworth D, et al. European Consensus on the Diagnosis and Management of Iron Deficiency and Anaemia in Inflammatory Bowel Diseases. J Crohns Colitis. 2014
56. Dostal A, Lacroix C, Pham VT, et al. Iron supplementation promotes gut microbiota metabolic activity but not colitis markers in human gut microbiota-associated rats. Br J Nutr. 2014; 111:2135–45. [PubMed: 24555487]
57. Ng SC, Tang W, Leong RW, et al. Environmental risk factors in inflammatory bowel disease: a population-based case-control study in Asia-Pacific. Gut. 2014
58. Burisch J, Pedersen N, Cukovic-Cavka S, et al. East-West gradient in the incidence of inflammatory bowel disease in Europe: the ECCO-EpiCom inception cohort. Gut. 2014; 63:588–97. [PubMed: 23604131]
59. Ko Y, Butcher R, Leong RW. Epidemiological studies of migration and environmental risk factors in the inflammatory bowel diseases. World J Gastroenterol. 2014; 20:1238–47. [PubMed: 24574798]
60. Khalili H, Huang ES, Ananthakrishnan AN, et al. Geographical variation and incidence of inflammatory bowel disease among US women. Gut. 2012; 61:1686–92. [PubMed: 22241842]
61. Higuchi LM, Khalili H, Chan AT, et al. A Prospective Study of Cigarette Smoking and the Risk of Inflammatory Bowel Disease in Women. American Journal of Gastroenterology. 2012; 107:1399–406. [PubMed: 22777340]
62. Mahid SS, Minor KS, Soto RE, et al. Smoking and inflammatory bowel disease: a meta-analysis. Mayo Clin Proc. 2006; 81:1462–71. [PubMed: 17120402]

Table 1

Characteristics of the study population at baseline[‡]

	Prudent Diet Score (high school)		Western diet score (high school)	
	Quartile 1	**Quartile 4**	**Quartile 1**	**Quartile 4**
Age in years [Mean (SD)]	36.42(4.66)	36.57(4.68)	36.10(4.58)	36.96(4.71)
White Race (%)	98	96	96	98
Oral contraceptive use(%)				
Never	14	20	20	13
Ever	86	80	80	87
Smoking status(%)				
Never	65	69	73	61
Past	22	22	19	24
Current	13	9	8	15
Mean adult body mass index (SD)	24.57(5.37)	24.32(5.31)	23.79(4.88)	25.16(5.73)
Mean body mass index at age 18 (SD)	21.05(3.29)	21.27(3.28)	21.00(3.10)	21.42(3.53)
NSAID use (>− 2 tablets/week)(%)	17	16	14	17
High school diet				
Total Protein (g/day)	101.6 (14.3)	111.5 (15.6)	112.2(15.8)	102.0(13.7)
Total Carbohydrate (g/day)	302.4 (38.8)	325.0 (40.3)	328.3(39.5)	298.5(36.8)
Fat (g/day)	129.4 (12.7)	116.8 (14.0)	114.7(13.2)	131.1(12.2)
Fiber (g/day)	16.8 (3.1)	26.2 (5.7)	24.7(6.4)	18.6 (3.7)
Fish (g/day)	19.6 (15.8)	33.9 (29.2)	30.6(28.5)	23.2(19.0)
Vegetables (sv/day)	1.8 (0.8)	5.2 (2.1)	4.5(2.4)	2.4 (1.3)
Fruit (sv/day)	1.0 (0.6)	2.4 (1.3)	2.3 (1.3)	1.1(0.7)
Heme iron (mg/day)	1.7 (0.6)	1.7 (0.6)	1.7(0.6)	1.7(0.6)
Total iron (mg/day)	13.5 (2.5)	15.7 (2.8)	15.3 (3.0)	14.0(2.4)
Adult Diet				
Fiber (g/day)	16.5 (4.9)	20.8 (5.7)	20.3(5.8)	17.3 (5.0)
Fat (g/day)	65.5 (11.3)	59.6 (11.1)	59.0(10.8)	65. 9(11.5)
Carbohydrate (g/day)	221.0 (33.4)	231.6 (34.6)	234.1(33.5)	218.5(33.8)
Protein (g/day)	84.3 (15.1)	88.4 (15.9)	87.9(15.5)	85.4 (15.3)

SD – standard deviation; g/day – grams/day; sv/day – servings/day; NSAID - non-steroidal anti-inflammatory drug

[‡]Baseline characteristics were assessed at time of completion of the first adult diet food frequency questionnaire in 1991

Table 2

High School Diet and Risk of Crohn's disease[†]

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P(trend)
Dietary patterns					
Prudent pattern					
Cases / P-y	24/192,825	19/194,344	15/193,326	12/182,734	
HR (95% CI)	1.0	0.80 (0.43 – 1.47)	0.59 (0.30 – 1.14)	0.47 (0.23 – 0.98)	0.04
Western pattern					
Cases / P-y	23/195,674	16/195,872	19/195,870	12/175,813	
HR (95% CI)	1.0	0.68 (0.36 – 1.30)	0.78 (0.42 – 1.45)	0.51 (0.25 – 1.05)	0.10
Macronutrients					
Total Fiber	1.0	0.83 (0.45 – 1.53)	0.54 (0.27 – 1.09)	0.55 (0.27 – 1.12)	0.06
Total Carbohydrate	1.0	0.85 (0.46 – 1.58)	0.54 (0.27 – 1.11)	0.77 (0.40 – 1.48)	0.11
Total fat	1.0	1.09 (0.55 – 2.16)	0.95 (0.46 – 1.94)	1.37 (0.69 – 2.70)	0.43
Animal Fat	1.0	0.83 (0.38 – 1.78)	1.45 (0.71 – 2.96)	1.70 (0.82 – 3.54)	0.07
Total protein	1.0	0.97 (0.47 – 2.00)	1.58 (0.83 – 3.01)	0.95 (0.46 – 1.97)	0.78
Animal protein	1.0	2.07 (0.98 – 4.40)	1.84 (0.86 – 3.95)	1.69 (0.77 – 3.70)	0.32
Micronutrients and food groups					
Vegetables	1.0	0.59 (0.30 – 1.14)	0.83 (0.45 – 1.52)	0.50 (0.25 – 1.03)	0.11
Fruits	1.0	0.78 (0.41 – 1.47)	0.81 (0.42 – 1.55)	0.65 (0.32 – 1.32)	0.28
Total iron	1.0	1.16 (0.62 – 2.16)	0.63 (0.31 – 1.31)	0.70 (0.33 – 1.47)	0.19
Heme iron	1.0	1.10 (0.53 – 2.28)	1.03 (0.49 – 2.19)	1.62 (0.81 – 3.23)	0.14
PUFA	1.0	1.02 (0.52 – 1.99)	0.98 (0.49 – 1.93)	0.98 (0.50 – 1.92)	0.92
	< 10g/day	10–20g/day	20–30g/day	> 30g/day	
Fish	1.0	0.94 (0.51 – 1.74)	0.73 (0.37 – 1.45)	0.43 (0.21 – 0.90)	0.01

PUFA – polyunsaturated fatty acids

[†]Multivariable-adjusted for smoking, oral contraceptive use, menopausal status and post-menopausal hormone use, body mass index, non-steroidal anti-inflammatory drug use, physical activity, and adult dietary fiber and vitamin D intake.

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Table 3

High School Diet and Risk of Ulcerative colitis[†]

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P(trend)
Dietary patterns					
Prudent pattern					
Cases / P-y	24/192,825	33/194,344	32/193,326	14/182,734	
HR (95% CI)	1.0	1.41 (0.83 – 2.40)	1.36 (0.79 – 2.34)	0.60 (0.30 – 1.19)	0.08
Western pattern					
Cases / P-y	28/195,674	26/195,872	28/195,870	21/175,813	
HR (95% CI)	1.0	0.91 (0.53 – 1.55)	0.99 (0.58 – 1.69)	0.83 (0.46 – 1.47)	0.60
Macronutrients					
Fiber	1.0	0.88 (0.50 – 1.58)	1.23 (0.71 – 2.12)	1.06 (0.59 – 1.89)	0.65
Carbohydrate	1.0	1.11 (0.63 – 1.95)	0.90 (0.49 – 1.64)	1.38 (0.80 – 2.38)	0.30
Total fat	1.0	1.19 (0.68 – 2.07)	1.16 (0.65 – 2.05)	1.15 (0.64 – 2.05)	0.67
Animal fat	1.0	0.65 (0.36 – 1.18)	0.93 (0.53 – 1.62)	0.88 (0.49 – 1.59)	0.90
Total protein	1.0	0.80 (0.48 – 1.35)	0.53 (0.30 – 0.94)	0.74 (0.43 – 1.25)	0.13
Animal protein	1.0	1.12 (0.68 – 1.84)	0.62 (0.34 – 1.11)	0.76 (0.44 – 1.33)	0.14
Micronutrients and food groups					
Vegetables	1.0	1.18 (0.70 – 2.00)	1.09 (0.64 – 1.87)	0.74 (0.40 – 1.37)	0.33
Fruits	1.0	0.93 (0.52 – 1.67)	1.16 (0.66 – 2.04)	1.47 (0.84 – 2.57)	0.10
Total iron	1.0	1.19 (0.70 – 2.05)	0.95 (0.53 – 1.69)	0.92 (0.50 – 1.70)	0.62
Heme iron	1.0	1.05 (0.62 – 1.78)	0.83 (0.46 – 1.48)	0.82 (0.46 – 1.46)	0.39
PUFA	1.0	0.58 (0.32 – 1.04)	0.77 (0.45 – 1.32)	0.91 (0.54 – 1.52)	0.96
	< 10g/day	10–20g/day	20–30g/day	> 30g/day	
Fish	1.0	1.12 (0.63 – 1.98)	1.17 (0.65 – 2.10)	0.99 (0.55 – 1.77)	0.81

PUFA – polyunsaturated fatty acids

[†]Adjusted for smoking, oral contraceptive use, menopausal status and post-menopausal hormone use, body mass index, non-steroidal anti-inflammatory drug use, physical activity, and adult dietary fiber and vitamin D intake.