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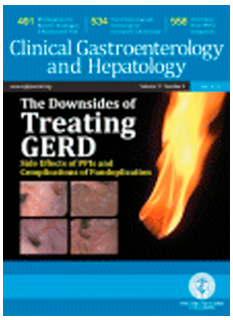

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PII: S1542-3565(19)31266-2
DOI: https://doi.org/10.1016/j.cgh.2019.11.011
Reference: YJCGH 56851

To appear in: *Clinical Gastroenterology and Hepatology*
Accepted Date: 4 November 2019

Please cite this article as: Ma W, Jovani M, Nguyen LH, Tabung FK, Song M, Liu P-H, Cao Y, Tam I, Wu K, Giovannucci EL, Strate LL, Chan AT, Association Between Inflammatory Diets, Circulating Markers of Inflammation, and Risk of Diverticulitis, *Clinical Gastroenterology and Hepatology* (2019), doi: https://doi.org/10.1016/j.cgh.2019.11.011.

Association Between Inflammatory Diets, Circulating Markers of Inflammation, and Risk of Diverticulitis

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Running title: Inflammation and diverticulitis

Author contributions: Study concept and design: WM, LLS, ATC; acquisition of data: KW, ELG, LLS, ATC; statistical analysis: WM; interpretation of data: all authors; drafting of the manuscript: WM, LLS, ATC; critical revision of the manuscript for important intellectual content: all authors.

Funding: This work was supported by grants U01 CA167552, R01 DK101495, R00 CA207736, and K24 DK098311 from the National Institutes of Health. The funders had no role in study design, data collection and analysis, interpretation of data, writing of the report, and decision to submit the paper for publication.

Acknowledgements: We would like to thank the participants and staff of the Health Professionals Follow-Up Study for their valuable contributions.

Declaration of interests: Dr. Andrew T. Chan previously served as a consultant for Janssen Pharmaceuticals, Pfizer Inc., and Bayer Pharma AG for work unrelated to the topic. The remaining authors have no conflicts of interest to disclose.

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Tables and figures: 4 tables; **Supplemental tables:** 3

ABSTRACT

Background & Aims: Lifestyle and dietary risk factors for diverticulitis have also been associated with chronic inflammation. We performed a prospective study of associations among inflammatory potential of diets, circulating markers of inflammation, and the incidence of diverticulitis.

Methods: We followed 46,418 men, initially free of diverticulitis, from 1986 through 2014 in the Health Professionals Follow-Up Study. We collected data on empirical dietary inflammatory pattern scores, which indicate inflammatory potential of diets, and determined their association with risk of incident diverticulitis using Cox proportional hazards regression. We used blood samples provided by 18,225 participants from 1993 through 1995 to conduct a nested case–control study; we used conditional logistic regression to evaluate pre-diagnostic plasma levels of markers of inflammation, including C-reactive protein (CRP), interleukin 6 (IL6) , and TNF receptor superfamily member 1B (TNFRSF1B), in 310 diverticulitis cases and 310 matched diverticulitis-free individuals (controls).

Results: We documented 1110 cases of incident diverticulitis over 992,589 person-years of follow up. Compared with participants in the lowest quintile of empirical dietary inflammatory pattern scores, men in the highest quintile had a multivariable-adjusted hazard ratio for diverticulitis of 1.31 (95% CI, 1.07–1.60; P_{trend}=.01). The association did not differ significantly by strata of body mass index or vigorous activity (*P* for interaction>.05 for each). In the nested case–control study, plasma levels of CRP and IL6 were associated with risk of diverticulitis. When we compared extreme quintiles, the multivariable-adjusted relative risk for diverticulitis was 1.85 for CRP (95% CI, 1.04–3.30) and 2.04 for IL6 (95% CI, 1.09–3.84).

Conclusions: In a large prospective cohort of men, we found that the inflammatory potential of diet and pre-diagnostic plasma levels of markers of inflammation were associated with incident diverticulitis.

Keywords: EDIP; diverticular disease; colon; food

INTRODUCTION

The prevalence of diverticulosis reaches 60% by age 70.[1] Diverticulitis is inflammation of diverticulosis that may progress to serious complications and recurrence. It is one of the most common gastrointestinal indications for hospitalization and outpatient clinic visits in the US, and also among the leading causes of health care spending for gastrointestinal diseases.[2] Despite the tremendous clinical and economic burden, there is no proven medical treatment for diverticulitis. Several randomized controlled trials have challenged the need for routine antibiotic treatment for uncomplicated diverticulitis.[3, 4] Elective colon resection, which treatment of complicated diverticulitis and recurrence largely relies on, is associated with over 10% risk of major complications and does not eliminate the possibility of recurrent events.[5] Thus, a greater understanding of the etiological mechanisms is a high priority to inform evidence-based, preventative interventions for this understudied disease.

The etiopathogenesis of diverticulitis remains incompletely understood.[6] Traditional but largely unproven theories suggest that diverticulitis results from mechanical trauma and obstruction of a diverticulum with subsequent ischemia, microperforation, and infection.[7] However, recent evidence indicates that chronic inflammation and alterations in the gut microbiome may be key factors predisposing to the development of diverticulitis.[6, 8] Low-grade chronic, systemic inflammation has been associated with risk of several chronic diseases, including cardiovascular disease,[9] cancers,[10, 11] and inflammatory bowel disease.[12] A growing body of evidence has identified modifiable lifestyle and dietary risk factors for diverticulitis, such as obesity,[13, 14] smoking,[15] physical inactivity,[16, 17] and low fiber intake,[18-20] which are closely linked to chronic inflammation.[21-24] Several studies have also shown that individuals with diverticulitis are at increased risk of subsequent cardiovascular disease,[25, 26] suggesting common etiopathogenetic mechanisms. In addition, patients with diverticular disease demonstrated low-grade inflammatory features including chronic mucosal inflammation and depletion

of gut microbiota members with anti-inflammatory properties.[27, 28] Case series suggest that elevations of circulating inflammatory markers may aid in the diagnosis of diverticulitis.[29-31] However, no study has prospectively examined the role of chronic inflammation in the pathogenesis of diverticulitis.

To address this question, we prospectively examined the inflammatory potential of the diet and circulating biomarkers associated with chronic inflammation in relation to incident diverticulitis in a large cohort of men in the Health Professionals Follow-Up Study (HPFS).

METHODS

Prospective Cohort Study

*Study Population***.** The HPFS is a cohort of 51,529 male health professionals aged 40 to 75 years at enrollment in 1986.[32] Participants have been mailed questionnaires every two years since inception collecting information on demographics, lifestyle factors, medical history, and disease outcomes, with a follow-up rate greater than 90% of available person-time. Diet was assessed through administration of a validated 131-item semi-quantitative food frequency questionnaire (FFQ) every 4 years. We excluded participants who reported a diagnosis of diverticulitis, cancer, or inflammatory bowel disease prior to baseline in 1986, those who had incomplete information for dietary data, and those who reported implausible total energy intake (< 800 or > 4200 kcal/day). After exclusions, a total 46,418 men were included in the primary analysis. The study was approved by Institutional Review Board of Harvard T.H. Chan School of Public Health. Return of the questionnaires was considered to imply written informed consent.

*Assessment of Empirical Dietary Inflammatory Pattern Score and Covariates***.** The development of the empirical dietary inflammatory pattern (EDIP) score has been previously described.[33-35] In brief, using data collected from 5,230 women in the Nurses' Health Study, 39 predefined food groups were entered into reduced-rank regression models followed by stepwise linear regression analyses to identify

a dietary pattern most predictive of 3 plasma markers of inflammation: C-reactive protein (CRP), Interleukin 6 (IL6) and TNF receptor superfamily member 1B (TNFRSF1B). The EDIP score is the weighted sum of 18 food groups (processed meat, red meat, organ meat, fish, other vegetables, refined grains, high-energy beverages, low-energy beverages, tomatoes, beer, wine, tea, coffee, dark yellow vegetables, green leafy vegetables, snacks, fruit juice, and pizza) and assesses the inflammatory potential of diet with higher values indicating greater dietary inflammatory potential **(Supplemental Table 1)**.[33] The EDIP score has been validated in independent samples of men and women using dietary and inflammatory biomarker data from the HPFS (n=2,632) and Nurses' Health Study II (n=1,002).[33] We calculated EDIP score for each participant in each 4-year questionnaire cycle from 1986 to 2010 based on FFQ data. Missing values for a given FFQ were carried forward from prior available assessments. We adjusted EDIP scores for total energy intake using the residual method.[36] Assessment of covariates are described in **Supplemental Methods**.

Nested Case-control Study

Study Population. From 1993-1995, 18,225 participants in the HPFS returned a blood sample. Among these participants free from inflammatory bowel disease and gastrointestinal cancer, we identified 310 incident cases of diverticulitis during follow-up through 2012. We randomly selected one diverticulitis-free control for each case matched on age at time of blood draw, month and year of blood draw, and fasting status.

Measurement of Markers of Inflammation. We used a highly sensitive immunoturbidimetric assay on the Roche Cobas 6000 system (Roche Diagnostics) to measure CRP and enzyme-linked immunosorbent assays (R&D Systems) to measure IL6 and TNFRSF1B, as previously described.[11] Samples from cases and their matched controls were analyzed in the same batch. Quality control samples were randomly interspersed among the case-control samples. Personnel were blinded to quality

control and case-control status. The intra-assay correlation coefficients of variation from blinded quality control samples were 4.2% for CRP, 12.1% for IL6, and 8.1% for TNFRSF1B.

Ascertainment of Diverticulitis

Beginning in 1990, participants who reported newly diagnosed diverticulitis on the biennial study questionnaires were sent supplementary questionnaires that ascertained the date of diagnosis, presenting symptoms, diagnostic procedures, and treatment for each reported event. Diverticulitis was defined as abdominal pain attributed to diverticular disease and one of the following criteria: diverticular complications including perforation, abscess, fistula, or obstruction; hospitalization, antibiotic therapy, or surgery resulting from diverticulitis; pain categorized as severe or acute; or abdominal pain presenting with fever, requiring medical therapy or radiologic evaluation with an abdominal computed tomography. Beginning in 2006, we revised our supplementary questionnaire to further assess uncomplicated diverticulitis, diverticular complications including abscesses, fistula formation, perforation, obstruction, diverticular bleeding, and asymptomatic diverticulosis. The validity of self-reported diverticulitis in HPFS has been assessed previously[14, 37] with 84% of diverticulitis cases confirmed by chart review.

Statistical Analysis

For the cohort study, we calculated person-time from the date of the first FFQ completion until the date of diagnosis of diverticulitis, death, last follow-up questionnaire, or the end of the study period (January 31, 2014), whichever came first. We categorized participants into quintiles according to their EDIP score. To assess linear trend, we assigned the median EDIP value to each category and modeled this as a continuous variable. We used Cox proportional hazards regression models stratified by age and questionnaire cycle with time-varying exposure and covariates to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for EDIP scores in relation to diverticulitis risk, with the lowest EDIP quintile as the reference group. Subgroup analyses were performed by lifestyle risk factors for diverticulitis

including BMI and vigorous activity. *P* values for interaction were calculated by evaluating the significance of the cross-product term of EDIP quintile as ordinal variable and stratified covariates.

For the nested case-control study, participants were categorized into quintiles based on the distribution of plasma levels of inflammatory biomarkers among controls. To evaluate the association of inflammatory biomarker levels and diverticulitis risk, we performed conditional logistic regression with conditioning on matching factors and potential confounding factors. We also evaluated BMI as a potential effect modifier using unconditional logistic regression because it preserved more power for testing interactions in matched studies.

More details are provided in **Supplemental Methods**. All statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC), and 2-sided *P* values of < 0.05 were considered statistically significant.

RESULTS

Prospective Cohort Study

At baseline, participants consuming a diet with higher inflammatory potential reported higher BMI but lower physical activity (**Table 1**). They were more likely to use acetaminophen and less likely to be using multivitamins or aspirin. They also tended to consume less dietary fiber but more red meat.

We documented a total of 1,110 incident cases of diverticulitis over 992,589 person-years of follow-up. In age-adjusted analyses, compared to men in the lowest quintile of EDIP score, those in the highest quintile had a 30% elevated risk of diverticulitis (HR: 1.30; 95% CI: 1.08-1.56; *P*-trend = 0.009; **Table 2**). Further adjustment for other lifestyle factors did not materially change the association (HR: 1.31; 95% CI: 1.07-1.60; *P*-trend = 0.01). As a sensitivity analysis, we additionally adjusted for intake of dietary fiber which has been associated with a reduced risk of diverticulitis[19, 20] and red meat which has been associated with an increased risk[38]. Both also contribute to the EDIP score. Corresponding HR

comparing men in the highest EDIP quintile to those in the lowest quintile was 1.23 (95% CI: 1.00-1.50; *P*-trend = 0.07), suggesting that the association between EDIP score and diverticulitis might be partly attributable to fiber and red meat intake. When we further controlled for the Western dietary pattern, which has been positively associated with risk of diverticulitis,[39] the association for EDIP score remained significant (HR comparing the highest vs. lowest quintile: 1.27; 95% CI: 1.04-1.55; *P*-trend = 0.02).

The associations between dietary inflammatory potential and diverticulitis did not differ significantly in subgroups defined by BMI (< 25 kg/m^2 vs. ≥ 25 kg/m^2) or vigorous activity (no vs. yes) (*P* for interaction > 0.05 for each; **Table 3**).

Nested Case-control Study

Participants in the nested case-control study were on average 59 years old at the time of blood draw (**Supplemental Table 2**). The median time between blood collection and diagnosis of diverticulitis was 7.9 years. Men who developed diverticulitis during follow-up had lower levels of physical activity. They were more likely to use aspirin, other NSAIDs, or acetaminophen and had higher plasma levels of inflammatory markers including CRP, IL6, and TNFRSF1B.

People with the highest pre-diagnostic, plasma levels of CRP and IL6 had increased risk of diverticulitis compared to those with the lowest levels (**Table 4**). With adjustment for matching factors and potential confounders, men in the highest quintile had a relative risk for diverticulitis of 1.85 (95% CI, 1.04-3.30) for CRP and 2.04 (95% CI, 1.09, 3.84) for IL6, compared to those in the lowest quintile. We observed a suggestive linear trend for IL6 (*P*-trend = 0.06) but not for CRP (*P*-trend = 0.16). Analysis using restricted cubic spline did not support the possibility of a non-linear relationship. TNFRSF1B was not significantly associated with risk of diverticulitis with a HR of 1.50 (95% CI, 0.87-2.56; *P*-trend = 0.07) comparing men in the highest vs. those in the lowest TNFRSF1B quintile. Further

adjustment for EDIP score at the time of blood collection did not materially change the results. In stratified analyses by BMI (**Supplemental Table 3**), we found no significant interaction (*P* for interaction > 0.73 for each). We did not find evidence that the associations between the biomarkers and diverticulitis differed by the time interval between blood collection and diagnosis of diverticulitis (P for interaction > 0.59 for each).

DISCUSSION

In a large prospective cohort of men, we observed a significant association between chronic inflammation, represented by inflammatory potential of diet and plasma levels of CRP and IL6, and subsequent risk of diverticulitis. The associations were seen predominantly by comparing the extreme categories. The positive association between the inflammatory potential of diet and risk of diverticulitis was not significantly modified by BMI or vigorous activity. To our knowledge, this is the first prospective study to examine the role of chronic inflammation in diverticulitis from an epidemiological perspective.

Previous findings from our group and others have linked several dietary factors[19, 20, 38, 39] to risk of diverticulitis. Despite these epidemiological observations, the underlying pathophysiology of diverticulitis remains largely unclear. In traditional theories, diverticulitis results from obstruction of a diverticulum with subsequent ischemia, microperforation, and subsequent inflammation.[7] Recent models of diverticulitis pathogenesis involve chronic inflammation and alterations in the gut microbiome.[6, 8] Studies have shown that CRP levels > 50 mg/L assessed at the time of symptoms strongly support the diagnosis of acute diverticulitis.[29-31, 40] However, the role of long-term exposure to low-grade, chronic inflammation prior to the onset of symptoms in disease etiopathogenesis has not been directly tested. In our prospective analysis, the association between the EDIP score that characterizes the inflammatory potential of dietary intake and risk of incident diverticulitis suggests that chronic, systemic inflammation

is a potential mechanism that underlies the dietary effects on diverticulitis development. This is further supported by consistent findings for circulating levels of CRP and IL6. These results greatly expand our fundamental understanding of diverticulitis development.

A higher inflammatory potential of diet has been associated with other inflammatory conditions such as cardiovascular disease, colorectal cancer, as well as mortality.[34, 41, 42] The magnitude of association between the EDIP score and diverticulitis was comparable to that reported in other studies. Diet plays a major role in regulating intestinal homeostasis by altering microbial composition, diversity, and richness. Accumulating evidence has indicated that certain dietary components, such as low fiber and high fat, lead to dysbiosis by decreasing the abundance of beneficial bacteria and promoting the growth of harmful bacteria, contributing to increased gut permeability and intestinal inflammation.[43, 44] A prior study in our cohorts showed that inflammatory diets, based on EDIP score, were associated with increased risk of F nucleatum–positive colorectal carcinomas, but not carcinomas that did not contain these bacteria,[35] supporting interactive roles of diet-related inflammation and the gut microbiota in colorectal diseases. Future investigations are warranted to determine the role of gut microbiota in mediating the increased risk of diverticulitis associated with diet-induced inflammation.

Circulating CRP, IL6, and TNF-α mediate the inflammatory response and are frequently used as biomarkers for chronic inflammation.[10, 45] TNFRSF1B is considered a reliable surrogate marker for TNF-α since it is more stable in stored frozen biospecimens.[11, 46] Despite a nominally significant trend, we did not find significantly elevated risk of diverticulitis in the highest quintile of TNFRSF1B compared to the lowest quintile. As the upstream regulator of CRP and IL6,[47] part of the effect of TNFRSF1B might have been accounted for by its downstream mediators. Thus, CRP and IL6 may be superior markers of the pro-inflammatory milieu that predisposes to development of diverticulitis. The potentially divergent roles of CRP, IL6, and TNFRSF1B have been reported in studies of other

inflammatory diseases.[46, 48] For example, elevated levels of CRP and IL6, but not TNFRSF1B, were associated with an increased risk of diabetes in postmenopausal women,[46] whereas in a meta-analysis of prospective studies, only circulating CRP showed a significant association with risk of ovarian cancer.[48]

The current study has several important strengths. The use of circulating levels of markers of inflammation as well as a complementary food-based EDIP score that is associated with levels of inflammatory biomarkers enhances the robustness of our findings. The prospectively and repeatedly collected, detailed information on diet and lifestyle factors reduces the potential for residual confounding and recall bias. Plasma samples were drawn prior to diagnosis of diverticulitis, which minimizes the likelihood of reverse causation related to elevation of the inflammatory markers by diverticulitis itself.

This study also has limitations. First, we obtained only one baseline measure of circulating markers of inflammation. However, others have shown that these markers are generally stable among the same individual with frozen blood samples in the long-term.[49] Moreover, intraindividual variation in levels over time would tend to attenuate our observed associations.[50] Second, our study population was comprised entirely of men. Thus, additional studies are needed to generalize our findings to women.

In conclusion, a diet with higher inflammatory potential and higher circulating markers of inflammation were associated with increased risk of diverticulitis, supporting the importance of low-grade chronic inflammation as a mechanistic pathway for the disease. Our results suggest that an overall anti-inflammatory dietary pattern, including high intake of green leafy vegetables, dark-yellow vegetables, coffee, and tea, and low consumption of red meat, processed meat, refined grain, and sugary beverages, may be a reasonable recommendation to reduce the risk of developing diverticulitis.

REFERENCES

1. Peery AF, Barrett PR, Park D, et al. A high-fiber diet does not protect against asymptomatic diverticulosis. Gastroenterology. 2012;142(2):266-72 e1.

2. Peery AF, Crockett SD, Murphy CC, et al. Burden and Cost of Gastrointestinal, Liver, and Pancreatic Diseases in the United States: Update 2018. Gastroenterology. 2018.

3. Chabok A, Pahlman L, Hjern F, et al. Randomized clinical trial of antibiotics in acute uncomplicated diverticulitis. Br J Surg. 2012;99(4):532-9.

4. Daniels L, Unlu C, de Korte N, et al. Randomized clinical trial of observational versus antibiotic treatment for a first episode of CT-proven uncomplicated acute diverticulitis. Br J Surg. 2017;104(1):52-61.

5. Stollman N, Smalley W, Hirano I, et al. American Gastroenterological Association Institute Guideline on the Management of Acute Diverticulitis. Gastroenterology. 2015;149(7):1944-9.

6. Strate LL, Morris AM. Epidemiology, Pathophysiology, and Treatment of Diverticulitis. Gastroenterology. 2019.

7. Humes DJ, Spiller RC. Review article: The pathogenesis and management of acute colonic diverticulitis. Aliment Pharmacol Ther. 2014;39(4):359-70.

8. Ceresoli M, Lo Bianco G, Gianotti L, et al. Inflammation management in acute diverticulitis: current perspectives. J Inflamm Res. 2018;11:239-46.

9. Emerging Risk Factors C, Kaptoge S, Di Angelantonio E, et al. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. Lancet. 2010;375(9709):132-40.

10. Heikkila K, Harris R, Lowe G, et al. Associations of circulating C-reactive protein and interleukin-6 with cancer risk: findings from two prospective cohorts and a meta-analysis. Cancer Causes Control. 2009;20(1):15-26.

11. Chan AT, Ogino S, Giovannucci EL, et al. Inflammatory markers are associated with risk of colorectal cancer and chemopreventive response to anti-inflammatory drugs. Gastroenterology. 2011;140(3):799-808, quiz e11.

12. Lochhead P, Khalili H, Ananthakrishnan AN, et al. Association Between Circulating Levels of C-Reactive Protein and Interleukin-6 and Risk of Inflammatory Bowel Disease. Clin Gastroenterol Hepatol. 2016;14(6):818-24 e6.

13. Ma W, Jovani M, Liu PH, et al. Association Between Obesity and Weight Change and Risk of Diverticulitis in Women. Gastroenterology. 2018.

14. Strate LL, Liu YL, Aldoori WH, et al. Obesity increases the risks of diverticulitis and diverticular bleeding. Gastroenterology. 2009;136(1):115-22 e1.

15. Humes DJ, Ludvigsson JF, Jarvholm B. Smoking and the Risk of Hospitalization for Symptomatic Diverticular Disease: A Population-Based Cohort Study from Sweden. Dis Colon Rectum. 2016;59(2):110-4.

16. Strate LL, Liu YL, Aldoori WH, et al. Physical activity decreases diverticular complications. Am J Gastroenterol. 2009;104(5):1221-30.

17. Williams PT. Incident diverticular disease is inversely related to vigorous physical activity. Med Sci Sports Exerc. 2009;41(5):1042-7.

18. Aldoori WH, Giovannucci EL, Rimm EB, et al. A prospective study of diet and the risk of symptomatic diverticular disease in men. Am J Clin Nutr. 1994;60(5):757-64.

19. Crowe FL, Balkwill A, Cairns BJ, et al. Source of dietary fibre and diverticular disease incidence: a prospective study of UK women. Gut. 2014;63(9):1450-6.

20. Ma W, Nguyen LH, Song M, et al. Intake of Dietary Fiber, Fruits, and Vegetables and Risk of Diverticulitis. Am J Gastroenterol. 2019.

21. Imayama I, Ulrich CM, Alfano CM, et al. Effects of a caloric restriction weight loss diet and exercise on inflammatory biomarkers in overweight/obese postmenopausal women: a randomized controlled trial. Cancer Res. 2012;72(9):2314-26.

22. Kasapis C, Thompson PD. The effects of physical activity on serum C-reactive protein and inflammatory markers: a systematic review. J Am Coll Cardiol. 2005;45(10):1563-9.

23. Ma Y, Hebert JR, Li W, et al. Association between dietary fiber and markers of systemic inflammation in the Women's Health Initiative Observational Study. Nutrition. 2008;24(10):941-9.

24. Shiels MS, Katki HA, Freedman ND, et al. Cigarette smoking and variations in systemic immune and inflammation markers. J Natl Cancer Inst. 2014;106(11).

25. Strate LL, Erichsen R, Horvath-Puho E, et al. Diverticular disease is associated with increased risk of subsequent arterial and venous thromboembolic events. Clin Gastroenterol Hepatol. 2014;12(10):1695-701 e1.

26. Lin JN, Lin CL, Yang CH, et al. Increased Risk of Acute Coronary Syndrome in Patients With Diverticular Disease: A Nationwide Population-Based Study. Medicine (Baltimore). 2015;94(45):e2020.

27. Horgan AF, McConnell EJ, Wolff BG, et al. Atypical diverticular disease: surgical results. Dis Colon Rectum. 2001;44(9):1315-8. Epub 2001/10/05.

28. Barbara G, Scaioli E, Barbaro MR, et al. Gut microbiota, metabolome and immune signatures in patients with uncomplicated diverticular disease. Gut. 2017;66(7):1252-61. Epub 2016/09/14.

29. Lameris W, van Randen A, van Gulik TM, et al. A clinical decision rule to establish the diagnosis of acute diverticulitis at the emergency department. Dis Colon Rectum. 2010;53(6):896-904.

30. Andeweg CS, Knobben L, Hendriks JC, et al. How to diagnose acute left-sided colonic diverticulitis: proposal for a clinical scoring system. Ann Surg. 2011;253(5):940-6.

31. Tursi A, Elisei W, Brandimarte G, et al. Predictive value of serologic markers of degree of histologic damage in acute uncomplicated colonic diverticulitis. J Clin Gastroenterol. 2010;44(10):702-6.

32. Rimm EB, Giovannucci EL, Willett WC, et al. Prospective study of alcohol consumption and risk of coronary disease in men. Lancet. 1991;338(8765):464-8.

33. Tabung FK, Smith-Warner SA, Chavarro JE, et al. Development and Validation of an Empirical Dietary Inflammatory Index. J Nutr. 2016;146(8):1560-70.

34. Tabung FK, Liu L, Wang W, et al. Association of Dietary Inflammatory Potential With Colorectal Cancer Risk in Men and Women. JAMA Oncol. 2018;4(3):366-73.

35. Liu L, Tabung FK, Zhang X, et al. Diets That Promote Colon Inflammation Associate With Risk of Colorectal Carcinomas That Contain Fusobacterium nucleatum. Clin Gastroenterol Hepatol. 2018;16(10):1622-31 e3.

36. Willett W, Stampfer MJ. Total energy intake: implications for epidemiologic analyses. Am J Epidemiol. 1986;124(1):17-27.

37. Strate LL, Liu YL, Syngal S, et al. Nut, corn, and popcorn consumption and the incidence of diverticular disease. JAMA. 2008;300(8):907-14.

38. Cao Y, Strate LL, Keeley BR, et al. Meat intake and risk of diverticulitis among men. Gut. 2017.

39. Strate LL, Keeley BR, Cao Y, et al. Western Dietary Pattern Increases, and Prudent Dietary Pattern Decreases, Risk of Incident Diverticulitis in a Prospective Cohort Study. Gastroenterology. 2017;152(5):1023-30 e2.

40. Tursi A. Biomarkers in diverticular diseases of the colon. Dig Dis. 2012;30(1):12-8.

41. Zhong X, Guo L, Zhang L, et al. Inflammatory potential of diet and risk of cardiovascular disease or mortality: A meta-analysis. Sci Rep. 2017;7(1):6367.

42. Shivappa N, Harris H, Wolk A, et al. Association between inflammatory potential of diet and mortality among women in the Swedish Mammography Cohort. Eur J Nutr. 2016;55(5):1891-900.

43. Schroeder BO, Birchenough GMH, Stahlman M, et al. Bifidobacteria or Fiber Protects against Diet-Induced Microbiota-Mediated Colonic Mucus Deterioration. Cell Host Microbe. 2018;23(1):27-40 e7.

44. Wan Y, Wang F, Yuan J, et al. Effects of dietary fat on gut microbiota and faecal metabolites, and their relationship with cardiometabolic risk factors: a 6-month randomised controlled-feeding trial. Gut. 2019.

45. Hussain SP, Harris CC. Inflammation and cancer: an ancient link with novel potentials. Int J Cancer. 2007;121(11):2373-80.

46. Liu S, Tinker L, Song Y, et al. A prospective study of inflammatory cytokines and diabetes mellitus in a multiethnic cohort of postmenopausal women. Arch Intern Med. 2007;167(15):1676-85.

47. Calabro P, Chang DW, Willerson JT, et al. Release of C-reactive protein in response to inflammatory cytokines by human adipocytes: linking obesity to vascular inflammation. J Am Coll Cardiol. 2005;46(6):1112-3.

48. Zeng F, Wei H, Yeoh E, et al. Inflammatory Markers of CRP, IL6, TNFalpha, and Soluble TNFR2 and the Risk of Ovarian Cancer: A Meta-analysis of Prospective Studies. Cancer Epidemiol Biomarkers Prev. 2016;25(8):1231-9.

49. Hardikar S, Song X, Kratz M, et al. Intraindividual variability over time in plasma biomarkers of inflammation and effects of long-term storage. Cancer Causes Control. 2014;25(8):969-76.

50. Platz EA, Sutcliffe S, De Marzo AM, et al. Intra-individual variation in serum C-reactive protein over 4 years: an implication for epidemiologic studies. Cancer Causes Control. 2010;21(6):847-51.

Table 1. Baseline age-adjusted characteristics of participants according to quintiles of inflammatory potential of diet score in Health Professionals Follow-up Study (1986)*

	Quintiles of inflammatory potential of diet score				
	1	2	3	4	5
Age, years	52.7 (9.1)	53.9 (9.6)	54.3 (9.8)	54.6 (10.0)	53.8 (10.0)
White, %	97.4	97.1	96.0	94.9	93.2
Body mass index, kg/m^2	25.3 (3.1)	25.3 (3.1)	25.3 (3.1)	25.5 (3.2)	26.0 (3.8)
Alcohol, g/d	22.0 (21.0)	12.3 (13.9)	9.4 (12.3)	7.5 (11.1)	6.3 (11.5)
Physical activity, MET-h/week	20.8 (26.9)	19.9 (26.4)	18.6 (26.1)	18.2 (25.4)	17.1 (25.4)
Past smoker, %	49.3	44.5	41.3	37.9	36.4
Current smoker, %	11.7	9.6	9.1	8.4	8.9
Multivitamin use, %	64.0	63.8	62.6	62.3	58.9
Aspirin use, %	31.0	29.7	29.1	28.3	28.7
Other NSAID use, %	5.6	5.4	5.2	5.4	5.5
Acetaminophen use, %	5.2	5.2	5.4	5.6	6.7
Physical examination for symptoms or routine screening, %	51.5	51.2	51.2	50.9	48.0
Total energy intake, kcal/d	2108 (622)	1934 (580)	1893 (586)	1884 (599)	2097 (660)
Total fiber intake, g/d	21.1 (7.5)	21.5 (6.9)	21.6 (7.1)	21.2 (6.8)	20.2 (7.0)
Red meat intake, serving/d	1.0 (0.7)	1.0 (0.7)	1.0 (0.7)	1.1 (0.8)	1.5 (1.0)

* Values are means (SD) or percentages and are standardized to the age distribution of the study population, with the exception of age itself. Inflammatory potential of diet score was adjusted for total energy using the residual method. Lower scores indicate anti-inflammatory diets whereas higher scores indicate proinflammatory diets.

Table 2. Inflammatory potential of diet and risk of diverticulitis in HPFS*

	Quintiles of inflammatory potential of diet score					P for trend
	1	2	3	4	5	
No. of cases	200	220	213	222	255	
Person-years	199675	199527	194922	199371	199095	
Model 1, HR (95% CI)	1.0 (ref)	1.10 (0.91, 1.34)	1.12 (0.92, 1.36)	1.12 (0.92, 1.35)	1.30 (1.08, 1.56)	0.009
Model 2, HR (95% CI)	1.0 (ref)	1.12 (0.92, 1.36)	1.18 (0.96, 1.44)	1.15 (0.94, 1.41)	1.31 (1.07, 1.60)	0.01

* Inflammatory potential of diet score was adjusted for total energy using the residual method. Higher EDIP scores indicating pro-inflammatory dietary patterns whereas lower scores indicate anti-inflammatory dietary patterns.

Model 1 was adjusted for age (continuous, years).

Model 2 was further adjusted for body mass index (<22.5, 22.5-24.9, 25.0-27.4, 27.5-29.9, 30.0-34.9, ≥35.0 kg/m^2), vigorous activity (0, 0.1-3.4, 3.5-10.4, 10.5-28.4, ≥28.5 MET-h/week), smoking status (never smoker, past smoker, current smoker (1-14, 15-24, ≥25 cigarettes/d)), alcohol consumption (0, 0-4.9, 5.0-9.9, 10.0-14.9, 15.0-29.9, ≥30 g/d), aspirin use (yes/no), acetaminophen use (yes/no), use of other NSAIDs (yes/no), multivitamin use (yes/no), and physical examination for symptoms or routine screening (yes/no).

Table 3. Inflammatory potential of diet and risk of diverticulitis in HPFS according to lifestyle characteristics*

	Quintiles of inflammatory potential of diet score						P for interaction
	1	2	3	4	5	P for trend	
Body mass index							0.68
< 25 kg/m^2 (n=400†), HR (95% CI)	1.0 (ref)	1.00 (0.73, 1.36)	1.16 (0.84, 1.60)	1.01 (0.73, 1.41)	1.32 (0.96, 1.84)	0.12	
≥ 25 kg/m^2 (n=708), HR (95% CI)	1.0 (ref)	1.21 (0.94, 1.56)	1.20 (0.93, 1.56)	1.27 (0.99, 1.64)	1.34 (1.04, 1.72)	0.03	
Vigorous activity							0.25
No (n=523), HR (95% CI)	1.0 (ref)	1.22 (0.91, 1.64)	1.23 (0.91, 1.65)	1.27 (0.95, 1.70)	1.26 (0.94, 1.69)	0.13	
Yes (n=587), HR (95% CI)	1.0 (ref)	1.06 (0.81, 1.38)	1.14 (0.87, 1.50)	1.07 (0.81, 1.41)	1.39 (1.06, 1.82)	0.03	

* Inflammatory potential of diet score was adjusted for total energy using the residual method. Higher EDIP scores indicating pro-inflammatory dietary patterns whereas lower scores indicate anti-inflammatory dietary patterns.
Models were adjusted for age (continuous, years), body mass index (<22.5, 22.5-24.9, 25.0-27.4, 27.5-29.9, 30.0-34.9, ≥35.0 kg/m^2), vigorous activity (0, 0.1-3.4, 3.5-10.4, 10.5-28.4, ≥28.5 MET-h/week), smoking status (never smoker, past smoker, current smoker (1-14, 15-24, ≥25 cigarettes/d)), alcohol consumption (0, 0-4.9, 5.0-9.9, 10.0-14.9, 15.0-29.9, ≥30 g/d), aspirin use (yes/no), acetaminophen use (yes/no), use of other NSAIDs (yes/no), multivitamin use (yes/no), and physical examination for symptoms or routine screening (yes/no), with omission of the effect modifier of interest in the corresponding model.
† n indicates number of cases.

Table 4. Plasma levels of markers of inflammation and risk of diverticulitis in the nested case-control study of HPFS

	Quintiles of biomarker levels					P for trend
	1	2	3	4	5	
CRP (mg/L)						
Median	0.29	0.60	1.13	1.82	4.29	
Case/control	41/62	72/60	48/64	77/61	71/62	
Model 1, RR (95% CI)	1.0 (ref)	1.72 (1.03, 2.87)	1.08 (0.61, 1.91)	1.83 (1.10, 3.06)	1.66 (0.99, 2.81)	0.15
Model 2, RR (95% CI)	1.0 (ref)	1.92 (1.12, 3.29)	1.19 (0.65, 2.18)	2.12 (1.22, 3.68)	1.85 (1.04, 3.30)	0.16
IL6 (pg/mL)						
Median	0.46	0.62	0.81	1.17	1.98	
Case/control	47/61	57/62	72/62	54/62	79/62	
Model 1, RR (95% CI)	1.0 (ref)	1.31 (0.75, 2.30)	1.73 (0.99, 3.04)	1.29 (0.73, 2.28)	1.93 (1.08, 3.46)	0.08
Model 2, RR (95% CI)	1.0 (ref)	1.22 (0.67, 2.21)	1.82 (1.00, 3.32)	1.39 (0.76, 2.54)	2.04 (1.09, 3.84)	0.06
TNFRSF1B (pg/mL)						
Median	1706	1961	2237	2596	3177	
Case/control	60/61	52/62	55/62	56/62	86/62	
Model 1, RR (95% CI)	1.0 (ref)	0.84 (0.50, 1.42)	0.92 (0.53, 1.58)	0.92 (0.55, 1.57)	1.45 (0.87, 2.41)	0.06
Model 2, RR (95% CI)	1.0 (ref)	0.88 (0.51, 1.51)	0.96 (0.55, 1.69)	0.95 (0.55, 1.64)	1.50 (0.87, 2.56)	0.07

Model 1 was adjusted for matching factors (age at blood draw, month/year of blood draw, fasting status).
Model 2 was further adjusted for body mass index (continuous, kg/m^2), physical activity (continuous, MET-h/week), alcohol consumption (continuous, g/d), smoking status (never smoker, past smoker, current smoker), aspirin use (yes/no), acetaminophen use (yes/no), use of other NSAIDs (yes/no).

SUPPLEMENTAL METHODS

Assessment of Covariates

Information on body weight, smoking status, physical examination for symptoms or routine screening, and use of multivitamins, aspirin, other nonsteroidal anti-inflammatory drugs (NSAIDs), or acetaminophen was obtained at baseline and during follow-up through biennial questionnaires. Physical activity was assessed every 2-4 years using validated questionnaires.[1] We defined vigorous activity as those activities with MET-hours ≥ 6 including jogging, running, bicycling, swimming, tennis, squash or racquetball, rowing, and heavy outdoor work. For the cohort study, we allowed covariates to be time-varying by using the most recent information. For the nested case-control study, we used covariates assessed in the 1994 questionnaire that was most adjacent to blood collection.

Statistical Analysis

For the cohort study, we censored participants who reported a new diagnosis of gastrointestinal cancer or inflammatory bowel disease at the date of diagnosis. No violation of the proportional hazards assumption was observed (*P* for interaction > 0.05). Multivariable models were adjusted for body mass index (BMI), vigorous physical activity, smoking, alcohol consumption, use of aspirin, other NSAIDs, or acetaminophen, multivitamin use, and recent physical examination as a proxy for healthcare engagement.

For the nested case-control study, we performed conditional logistic regression with conditioning on matching factors (age, month/year of blood draw, and fasting status), and adjusting for potential confounding factors (BMI, physical activity, alcohol consumption, smoking status, aspirin use, acetaminophen use, and other NSAID use). We also examined the possibility of non-linear relation between biomarkers of inflammation and risk of diverticulitis non-parametrically with restricted cubic splines.[2] Tests for non-linearity used the likelihood ratio

test, comparing the model with only the linear term to the model with the linear and the cubic spline terms.

Supplemental Table 1. Components of the empirical dietary inflammatory pattern score and weights in the calculation

	Weights
Positive associations	
Processed meat	165.03
Red meat	140.19
Organ meat	144.61
Other fish	252.45
Other vegetables	136.14
Refined grains	81.21
High-energy beverages	156.85
Low-energy beverages	94.77
Tomatoes	167.92
Inverse associations	
Beer	-136.99
Wine	-249.70
Tea	-42.25
Coffee	-83.18
Dark yellow vegetables	-165.37
Leafy green vegetables	-190.29
Snacks	-45.08
Fruit juice	-58.95
Pizza	-1175.21

The food groups included and serving size per day were defined as follows: processed meat (1 piece or 1 slice processed meats, 2 slices bacon, or 1 hot dog), red meat [4–6 oz (113–170 g) beef, pork, or lamb, or 1 hamburger patty], organ meat [4 oz (113 g) beef, calf, or pork liver; 1 oz (28.3 g) chicken or turkey liver], other fish [3–5 oz (70–117 g) canned tuna, shrimp, lobster, scallops, fish, or other seafood other than dark-meat fish], other vegetables [4-inch (10.2-cm) stick celery, 1/2 cup fresh or cooked or 1 can mushrooms, 1/2 green pepper, 1 ear or 1/2 cup (90 g) frozen or canned corn, 1/2 cup (75 g) mixed vegetables, 1 eggplant, 1/2 cup (90 g) zucchini, 1/2 cup (16 g) alfalfa sprouts, or 1/4 cucumber], refined grains [1 slice white bread, 1 English muffin, 1 bagel or roll, 1 muffin or biscuit, 1 cup (250 g) white rice, 1 cup (140 g) pasta, or 1 serving of pancakes or waffles], high-energy beverages (1 glass, 1 bottle, or 1 can cola with sugar; other carbonated beverages with sugar; or fruit punch drinks), low-energy beverages (1 glass, 1 bottle, or 1 can low-energy cola; other low-energy carbonated beverages), tomatoes [1 fresh tomato, 1 small glass of tomato juice, or 1/2 cup (115 g) tomato sauce], beer (1 bottle, 1 glass, or 1 can), wine [4-oz (113-g) glass red or white wine], 1 cup tea (not herbal), 1 cup coffee, dark yellow vegetables [1/2 cup carrots, 1/2 cup yellow (winter) squash, or 1/2 cup (100 g) yams or sweet potatoes], leafy green vegetables (1/2 cup spinach, 1 serving of iceberg or head lettuce, or 1 serving of romaine or leaf lettuce), snacks [1 small bag or 1 oz (28.3 g) potato chips, corn chips, or popcorn; or 1 cracker], fruit juices (1 small glass apple juice or cider, orange juice, grapefruit juice, or other fruit juice), and 2 slices pizza.

Supplemental Table 2. Characteristics of study participants in the nested case-control study within HPFS at the time of blood draw

	Cases (n=309*)	Controls (n=309)
Age at blood draw, year	59.3 (8.1)	59.3 (8.1)
Body mass index, kg/m^2	25.8 (3.0)	26.1 (3.3)
Physical activity, MET-h/wk	29.5 (26.2)	34.5 (30.6)
Current smoker, %	3.2	3.9
Regular aspirin use, %	39.8	35.3
Regular NSAID use, %	17.5	12.9
Regular acetaminophen use, %	9.1	4.2
Alcohol consumption, g/day	11.0 (14.4)	11.3 (15.4)
Total fiber intake, g/day	21.9 (6.4)	23.3 (7.2)
Red meat intake, serving/day	1.1 (0.6)	1.1 (0.8)
Plasma biomarker concentrations, median (interquartile range)		
CRP, mg/L	1.34 (0.66-2.51)	1.13 (0.50-2.12)
IL6, pg/mL	0.87 (0.64-1.38)	0.81 (0.58-1.28)
TNFRSF1B, pg/mL	2342 (1954-2826)	2238 (1913-2699)

* One matched pair was excluded due to missingness in IL6 level.

Supplemental Table 3. Associations between plasma levels of markers of inflammation and risk of diverticulitis in HPFS according to body mass index using unconditional logistic regression model

	Quintiles of biomarker levels					P for interaction
	1	2	3	4	5	
CRP (mg/L)						0.76
BMI < 25kg/m^2, RR (95% CI)	1.0 (ref)	2.73 (1.31, 5.67)	1.81 (0.79, 4.11)	2.67 (1.23, 5.80)	1.67 (0.71, 3.93)	
BMI ≥ 25kg/m^2, RR (95% CI)	1.0 (ref)	1.35 (0.58, 3.16)	0.96 (0.41, 2.26)	1.66 (0.72, 3.81)	1.77 (0.76, 4.12)	
IL6 (pg/mL)						0.84
BMI < 25kg/m^2, RR (95% CI)	1.0 (ref)	0.99 (0.45, 2.19)	1.48 (0.66, 3.35)	1.03 (0.44, 2.42)	1.48 (0.64, 3.41)	
BMI ≥ 25kg/m^2, RR (95% CI)	1.0 (ref)	1.52 (0.70, 3.31)	2.18 (1.02, 4.66)	1.40 (0.65, 3.02)	2.33 (1.08, 4.99)	
TNFRSF1B (pg/mL)						0.73
BMI < 25kg/m^2, RR (95% CI)	1.0 (ref)	0.81 (0.37, 1.78)	0.60 (0.27, 1.31)	0.88 (0.38, 2.03)	1.09 (0.49, 2.42)	
BMI ≥ 25kg/m^2, RR (95% CI)	1.0 (ref)	0.87 (0.43, 1.78)	1.31 (0.63, 2.70)	0.87 (0.43, 1.77)	1.75 (0.87, 3.52)	

Models were adjusted for matching factors (age at blood draw, month/year of blood draw, fasting status), physical activity, alcohol consumption, smoking status, aspirin use, acetaminophen use, and use of other NSAIDs.

REFERENCES

1. Wolf AM, Hunter DJ, Colditz GA, et al. Reproducibility and validity of a self-administered physical activity questionnaire. Int J Epidemiol. 1994;23(5):991-9. Epub 1994/10/01.

2. Durrleman S, Simon R. Flexible regression models with cubic splines. Stat Med. 1989;8(5):551-61.

Need to Know

Background: Lifestyle and dietary risk factors for diverticulitis have also been associated with chronic inflammation.

Findings: In a large prospective cohort of men, we found that the inflammatory potential of diet and pre-diagnostic plasma levels of markers of inflammation were associated with incident diverticulitis.

Implications for patient care: Diverticulitis might be prevented or treated by modifications to diet to reduce foods that increase intestinal inflammation.