



Lifestyle Factors for the Prevention of Inflammatory Bowel Disease

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Author Contributions

EWL and HK were involved in the study concept and design. EWL, SSMC, KEB, PL, ANA, MMB, JMR, ATC, HK participated in acquisition of data. EWL, SSMC, MS, NH, AC and HK were involved in statistical analysis. All authors participated in interpretation of data. EWL and HK performed drafting of the manuscript. All authors participated in critical revision of the manuscript. Authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned have been explained.

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Abstract

Objective: To estimate the proportion of cases of Crohn's disease (CD) and ulcerative colitis (UC) that could be prevented by modifiable lifestyle factors.

Design: In a prospective cohort study of US adults from the Nurses' Health Study (NHS; n=72,290), NHSII (n=93,909), and Health Professionals Follow-up Study (HPFS; n=41,871), we created modifiable risk scores (MRS; 0–6) for CD and UC based on established lifestyle risk factors, and healthy lifestyle scores (HLS; 0–9) derived from American healthy lifestyle recommendations. We calculated the population attributable risk by comparing the incidence of CD and UC between low (CD-MRS 1, UC-MRS 2, HLS 7) and high-risk groups. We externally validated our findings in three European cohorts: the Swedish Mammography Cohort (n=37,275), Cohort of Swedish Men (n=40,810), and European Prospective Investigation into Cancer and Nutrition (n=404,144).

Results: Over 5,117,021 person-years of follow-up (NHS, HPFS: 1986–2016; NHSII: 1991–2017), we documented 346 CD and 456 UC cases. Adherence to a low MRS could have prevented 42.9% (95% CI 12.2 to 66.1%) of CD and 44.4% (95% CI 9.0 to 69.8%) of UC cases. Similarly, adherence to a healthy lifestyle could have prevented 61.1% (95% CI 16.8 to 84.9%) of CD and 42.2% (95% CI 1.7 to 70.9%) of UC cases. In our validation cohorts, adherence to a low MRS and healthy lifestyle could have respectively prevented 43.9–51.2% and 48.8–60.4% of CD cases, and 20.6–27.8% and 46.8–56.3% of UC cases.

Conclusions: Across six US and European cohorts, a substantial burden of IBD risk may be preventable through lifestyle modification.

INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory bowel diseases (IBD) that affect an estimated 3.1 million adults in the US¹ and another 1.3 million in Europe². Globally, the incidence of IBD is increasing, particularly in newly industrialized countries³. IBD is associated with significant societal cost, with an estimated annual healthcare cost of \$23,000 per-person in the US⁴. Thus, strategies to prevent IBD could substantially decrease morbidity associated with disease and healthcare costs. However, to date, no strategies exist to prevent the development of IBD.

One approach to prevent chronic diseases is via modification of lifestyle risk factors. Indeed, previous observational studies have identified several lifestyle factors to be associated with IBD⁵, but whether modification of these lifestyle factors could be an attractive prevention strategy is unknown. Thus, in this study, we created modifiable risk scores (MRS) based on established risk factors for IBD and estimated the proportion of IBD cases that could have been prevented using population attributable risk (PAR). As some of the established risk factors such as smoking and body mass index (BMI) have opposite associations with CD and UC^{6,7}, we also estimated the proportion of cases that could be prevented by adhering to an overall healthy lifestyle, as recommended by the US Department of Health and Human Services (HHS), the US Department of Agriculture (USDA), and the American Heart Association (AHA).

METHODS

Study population

Our primary cohort included participants from three prospective cohorts: the Nurses' Health Study (NHS), NHSII, and Health Professionals Follow-up Study (HPFS). Briefly, the NHS enrolled 121,700 female nurses (30–55 years) across 11 US states in 1976, while the NHSII cohort, established in 1989, followed a younger cohort of 116,429 female nurses (25–42 years) from 15 US states⁸. The HPFS cohort enrolled 51,529 male physicians (40–75 years) across all 50 states in 1986⁹. Participants completed baseline and biennial questionnaires that assessed lifestyle factors, anthropomorphic data, and medical history. Dietary information was collected every four years via semi-quantitative food frequency questionnaires (SFFQ) beginning in 1986 for NHS and HPFS and 1991 for NHSII (defined as baseline). Follow-up rates for these cohorts have consistently exceeded 85%^{8,9}.

We excluded participants who had missing baseline SFFQ or implausible daily caloric intake (<600 or >3500 kcal/day for women, <800 or >4200 kcal/day for men; n=67,671 (23%)), those who only completed baseline questionnaire (n=8,177 (2.8%)), those with a diagnosis of IBD at baseline (n=144 (0.05%)), and missing or implausible BMI (BMI <10 kg/m²; n=1,468 (0.5%)). The study protocol was approved by the Institutional Review Boards of the Brigham and Women's Hospital and the Harvard T.H. Chan School of Public Health (#2001P001128).

We also used three large European cohorts to externally replicate our results: the Swedish Mammography Cohort (SMC; n=37,275), the Cohort of Swedish Men (CoSM; n=40,810),

and the European Prospective Investigation into Cancer and Nutrition (EPIC; n=404,144; Supplementary Appendix). Briefly, the SMC and CoSM are parallel cohorts of females (40–74 years) and males (45–79 years)¹⁰, respectively, in Sweden, while the EPIC cohort is composed of both males and females (35–70 years) across 10 European countries¹¹. Detailed medical, lifestyle, and dietary information were collected at baseline (1997 for SMC and CoSM, 1992–1999 for EPIC) via self-administered questionnaires in all cohorts (Supplementary Appendix).

Patient and Public Involvement

Patient or the public were not involved in the design or interpretation of this study.

Ascertainment of IBD diagnosis

Ascertainment of IBD diagnoses in NHS, NHSII and HPFS has been previously described in detail¹². Briefly, participants first self-reported diagnoses of either CD or UC in biennial questionnaires. Supplementary questionnaires were then mailed requesting detailed information on IBD diagnoses and permission to review medical records. Records were then reviewed by two gastroenterologists blinded to exposure information. IBD cases were confirmed by endoscopic and histopathology findings and date of diagnosis defined as date of index endoscopy or surgery and pathology results. IBD cases in the validation cohorts were ascertained either through medical record review or validated definitions used in patient registers (Supplementary Appendix).

Assessment of lifestyle risk factors and other covariates

Briefly, non-dietary factors including BMI, family history of IBD, history of appendectomy (self-reported), physical activity, smoking status, and non-steroidal anti-inflammatory drug (NSAID) use were assessed from baseline and follow-up questionnaires. Dietary factors, including daily servings of fruit and vegetables and red meat, fiber intake in grams (g), and ratio of n3:n6 polyunsaturated fatty acid (PUFA) intake were ascertained using frequency of intake reported on every 4-year SFFQ and the Harvard Food Composition Database to calculate nutrient-level data¹³. BMI, smoking status, and NSAID use were updated every 2 years while physical activity and dietary variables were cumulative-averaged over the follow up time to better represent long-term patterns¹⁴. In external cohorts, covariates were ascertained at baseline only. Further details for the variables assessed in the primary and external cohorts are described in the Supplementary Appendix.

Statistical Analysis

We constructed MRS for each of CD and UC (CD-MRS and UC-MRS) based on established modifiable risk factors, including BMI^{6,15}, smoking status⁷, NSAID use¹⁶, physical activity¹⁷, and daily consumption of fruit and vegetables¹⁸, fiber^{19,20}, n3:n6 PUFAs²¹, and red meat^{22,23}. The directed acyclic graph for the proposed relationship between risk factors and outcomes is shown in Figure S1 (created using DAGitty v3.0)²⁴. We defined low-risk criteria for each factor based on observed associations from prior literature, some of which had opposite relationships with CD and UC (Table 1)⁵. For example, never-smoking and non-obese BMI were considered low-risk for CD, while current-smoking and obese BMI

were considered low-risk for UC^{6,7,15}. For each participant, we assigned 1 point to each factor not meeting its low-risk criterion (0 otherwise) and summed each category for a total MRS of 0 to 6 points, so that higher scores reflected a greater number of disease-specific risk factors. The low-risk group (reference) was defined as a score 0–1, or 0–2 when there were too few cases of CD and UC (defined by non-convergence of the models) in the 0–1 group.

Additionally, we note that adherence to low-risk factors did not necessarily represent healthy habits, particularly for UC, where current smoking and obese BMI are protective. Thus, we additionally constructed healthy lifestyle scores (HLS), to assess adherence to healthy lifestyle recommendations by the US HHS and USDA Dietary Guidelines for Americans, and the AHA Guidelines for Healthy Living^{25–27} (Supplementary Appendix). Healthy criteria were defined as BMI 18.5 to <25 kg/m²; never smoking; physical activity 7.5 metabolic equivalent of task (MET)-hours/week; intakes of fruit and vegetables 8 servings/day, red meat <0.5 servings/day, fiber 25 g/day, fish 2 servings/week, nuts/seeds 0.5 servings/day; and alcohol consumption 1 drink (14g)/day (females) or 2 drinks (28g)/day (males; Table S1). We assigned 1 point for each healthy criterion met, and calculated HLS by summing across all categories (range 0–9), such that higher scores reflected healthier lifestyle. The healthy group (reference) was defined as a score of 7–9, as insufficient number of participants met 8 or 9 criteria, and the unhealthy group was defined as a score < 7.

We calculated person-time from date of return of baseline questionnaire to first of: date of IBD diagnosis, death, date of last returned biennial questionnaire, or end of follow-up (2016 for NHS, HPFS; 2017 for NHSII). We used Cox proportional hazards models to estimate multivariable-adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) for CD and UC according to CD- and UC-MRS, respectively, as well as HLS. Models were stratified by age, time-period (2-year intervals), and cohort (NHS, NHSII, or HPFS), and were additionally adjusted for appendectomy and family history of IBD⁵.

In analyses that used NHS, NHSII and HPFS data only, all covariates except family history of IBD were modeled as time-varying. However, because EPIC only collected dietary and lifestyle data at baseline, analyses that compared NHS, NHSIII and HPFS data with the external cohorts were done using baseline data only.

We calculated the population attributable risk (PAR) for CD and UC to estimate the proportion of cases that could have been prevented through lifestyle modification, assuming a causal relationship. We used a binary term to compare (1) high- versus low-risk groups and (2) unhealthy versus healthy groups, as has been previously described^{28,29}. For PAR calculations, exposure prevalence and aHRs were derived separately for each of the pooled NHS, NHSII and HPFS cohorts, pooled SMC and CoSM cohorts, and EPIC cohort. In this way, PAR could be interpreted as the proportion of cases in each cohort that could have been prevented if all individuals had been in the (1) low-risk group or (2) healthy group, assuming a causal relationship exists.

We conducted several exploratory and sensitivity analyses. First, we examined whether the relationship between MRS and IBD differed according to sex. Second, because the

binary variables in MRS calculation could not account for incremental changes in IBD risk, we derived weighted-MRS scores (range 6–30) using refined categories of lifestyle factors, and used individuals in the lowest 15% of scores as the reference (Supplementary Appendix). Third, we estimated partial PAR for individual modifiable risk factors²⁸. Fourth, because of the previously reported association between processed meat intake and risk of IBD³⁰, we repeated our primary analysis, replacing red meat intake with processed meat intake for calculation of UC-MRS and including a term for processed meat in derivation of CD-MRS. Finally, to demonstrate that our scores are relatively specific to IBD, we performed a falsification analysis to determine the relationship between our MRS and rheumatoid arthritis (RA), a similar immune-mediated disease (Supplementary Appendix). We chose RA because it shares multiple risk factors with CD^{31,32}, but has an inverse relationship with several factors used in the UC-MRS, such as BMI and smoking. In this way, we expect *a priori* that the PAR for RA according to CD-MRS might yield comparable results as in our primary analysis for CD, but that the PAR for RA according to UC-MRS should be substantially lower or zero. To further test the specificity of our scores for IBD, we performed additional falsification analyses for two non-immune mediated diseases, colorectal cancer (CRC) and cardiovascular disease (CVD; Supplementary Appendix).

Statistical calculations were performed in SAS version 9.4 (SAS Institute Inc, Cary, NC) and STATA 16.1/MP (StataCorp LLC), and statistical significance was defined as $p < 0.05$ using two-tailed tests. The proportional hazards assumption was tested by testing for significance of interaction terms between follow-up time and CD- and UC-MRS (CD: $P=0.83$, UC: $P=0.08$; Supplementary Appendix). Residual confounding for the primary analysis was assessed using the E-value method (Supplementary Appendix)³³.

RESULTS

In our primary cohort, a total of 208,070 participants were included after exclusions (NHS: $n=72,290$, NHSII: $n=93,909$, and HPFS: $n=41,871$). During 5,117,021 person-years of follow-up, we ascertained 346 CD and 456 UC cases, with an incidence rate of 7 cases of CD and 9 cases of UC per 100,000 person-years. Baseline characteristics for the pooled primary cohort are shown in Table S2.

Compared to participants with a CD-MRS of 0–1, the aHR (95%CI) of those with a CD-MRS of 6 was 4.15 (1.95–8.84; Figure 1). Similarly, compared to those with a UC-MRS of 0–2, the aHR (95%CI) of those with a UC-MRS of 6 was 2.78 (1.47–5.25). Risk of CD and UC increased with each one-point increase in CD-MRS ($P_{\text{trend}} < 0.0001$) and UC-MRS ($P_{\text{trend}} = 0.008$), respectively. Our findings were similar for both females and males (all $P_{\text{interaction}} > 0.19$; Table S3). When using binary scores, those with a CD-MRS ≥ 2 had an aHR (95% CI) of 1.85 (1.12–3.06; $p=0.02$) for CD when compared to those with a score of 0–1. Similarly, those with a UC-MRS ≥ 3 had an aHR (95% CI) of 1.92 (1.08–3.40; $p=0.03$) for UC when compared to those with a score of 0–2.

We estimated that adherence to low CD-MRS (0–1) and UC-MRS (0–2) could have prevented 42.9% (12.2–66.1%) of CD and 44.4% (9.0–69.8%) of UC, respectively (PAR; Figure 1). These findings were similar when incorporating processed meat intake in

derivation of CD-MRS and UC-MRS (Supplementary Appendix). In a sensitivity analysis using weighted-criteria to define MRS, adherence to low CD-MRS and UC-MRS (lowest 15% of scores) could have prevented 41.0% (17.5–60.0%) of CD and 27.7% (7.5–45.7%) of UC (Table S4).

Falsification analysis yielded anticipated results (Supplementary Appendix). Adherence to low CD-MRS (0–1) could have prevented 32.3% (0.4–58.3%) of RA, 13.3% (2.3–23.9%) of CRC, and 14.0% (9.6–18.5%) of CVD. Conversely, adherence to low UC-MRS (0–2) was associated with higher risk of RA, CRC, and CVD compared to the UC-MRS > 2 group, and therefore PAR for adherence to a low UC-MRS could not be calculated. In other words, adherence to low UC-MRS could not prevent RA, CRC, or CVD in our cohorts (Supplementary Appendix).

We also confirmed our primary findings using baseline data. In the pooled NHS, NHSII and HPFS cohort, baseline CD-MRS and UC-MRS remained significantly associated with increased risk of CD and UC, respectively (both $P_{\text{trend}} < 0.003$; Figures 2–3). For CD, adherence to low baseline CD-MRS (0–1) could have prevented 36.5% (5.3–61.3%) of CD, while adherence to low baseline UC-MRS (0–2) could have prevented 35.9% (11.2–56.5%) of UC.

Our findings were similar in the external cohorts. For CD, low baseline CD-MRS (0–1) could have prevented 43.9% (–7.4–76.8%) and 51.2% (0.01–80.9%) of CD in the pooled SMC and CoSM cohort and EPIC, respectively. Similarly, for UC, low baseline UC-MRS (0–2) could have prevented 20.6% (–14.5–51.0%) and 27.8% (0.001–51.6%) of UC in the pooled SMC and CoSM cohort and EPIC, respectively.

We also calculated the proportion of IBD cases that could have been prevented by adherence to American healthy lifestyle guidelines. In the pooled NHS, NHSII and HPFS cohort, baseline HLS was associated with decreased risk of CD and UC ($P_{\text{trend}} < 0.004$ and 0.02 , respectively; Table 2). Adherence to a healthy lifestyle (HLS 7–9) could have prevented 61.1% (16.8–84.9%) of CD and 42.2% (1.7–70.9%) of UC cases. These results were consistent in external cohorts (Table 2). Adherence to a healthy lifestyle could have prevented 48.8% (–37.4–89.8%) and 60.4% (4.1–87.6%) of CD in the pooled SMC and CoSM cohort and EPIC, respectively, and 56.3% (1.3–85.1%), and 46.8% (9.7–72.5%) of UC in the pooled SMC and CoSM cohort and EPIC, respectively.

Additionally, we explored the contribution of individual lifestyle factors and risk of CD and UC in our primary cohorts (Tables S5–S6). Low fiber intake conferred the largest PAR for CD (27.9%) followed by past or current smoking (14.4%), and low physical activity (12.9%; Table S7). Low fruit and vegetable intake contributed the largest PAR for UC (20.1%), followed by past smoking (18.0%) and low n3:n6 PUFA (11.0%; Table S7). In comparison, family history of IBD conferred a PAR of 12.2% (8.0–16.2%) for CD and 8.8% (5.4–12.1%) for UC.

Finally, we used the E-value method to assess for residual confounding in the relationship between binary MRS scores and IBD used in our primary PAR analysis (Table S8). To explain an aHR of 1.85 for CD with a CD-MRS = 2, an unmeasured confounder would

need to have a risk ratio of 3.10 with each of the CD-MRS exposure and CD outcome, after controlling for the measured confounders, to fully explain away the observed relationship. Similarly, the observed aHR of 1.92 for UC with a UC-MRS ≥ 3 would need to be explained by an unmeasured confounder that was associated with a 3.25-fold risk with each of the UC-MRS exposure and UC outcome, after controlling for measured confounders. Weaker confounding could otherwise not explain away the observed relationships³³.

DISCUSSION

In three large prospective US cohorts, we demonstrate that modifiable lifestyle factors could substantially decrease the burden of IBD. We found that 43% of CD and 44% of UC cases could have been prevented by adhering to low-risk modifiable lifestyle factors, assuming a causal relationship exists. Moreover, adherence to American healthy lifestyle recommendations could have prevented 61% of CD cases and 42% of UC cases. These findings were consistent across three European cohorts. In comparison, in our primary cohorts, family history of IBD had a modest PAR of 12% for CD and 9% for UC.

Few studies have examined the total contribution of lifestyle factors on IBD development at a population level. In an Italian cohort, smoking, oral contraceptive use, and lack of breast feeding accounted for roughly 30% of the attributable risk for IBD³⁴, while Brant et al estimated that current tobacco use conferred a 47% attributable risk for CD³⁵. To our knowledge, our study represents the first to comprehensively assess the contribution of modifiable lifestyle and dietary factors to the risk of CD and UC. Nonetheless, our estimates are similar to those published for other immune-mediated diseases. For example, in two prior studies, modification of lifestyle risk factors could have prevented 41% of RA³⁶ and 48% of psoriasis cases³⁷. Further, similar to our study, family history had only a modest contribution to risk of RA and psoriasis (~20% each).

Importantly, our data suggest that adherence to an overall healthy lifestyle may prevent a modest proportion of cases of CD and UC. While unhealthy factors such as obesity and smoking have been inversely associated with risk of UC^{6,38}, we saw that their contribution was outweighed by the total effect of healthy living. That is, more UC cases could have been prevented by adherence to a healthy lifestyle (42–56%) as compared to adherence to ‘traditional’ UC risk factors assessed by our UC-MRS scores (21–44%). Thus, current guidelines for healthy living, which are primarily recommended to reduce cardiovascular disease risk, may have additional benefits for prevention of other immune-mediated diseases such as IBD.

A key assumption of our findings is that the relationship between lifestyle factors and IBD development is causal. Though this has yet to be established, several lines of evidence support the critical role of environmental and lifestyle factors in development of IBD. First, in genome-wide association studies, genetic factors account for less than 15% of the total variance of IBD³⁹. Similarly, in monozygotic twins, concordance for disease is estimated to be around only 15% for UC and 30% for CD^{40,41}. Second, the high incidence of IBD in industrialized societies and sharp rise of IBD in developing countries also suggest that Westernization of diet and environment influences disease development³. Further,

in immigrants who move from low- to high-incidence countries, risk for IBD is higher in second-versus first-generation immigrants⁴². Finally, the dietary and lifestyle factors considered here have also been linked with systemic inflammation, microbial dysbiosis, and gut permeability, providing mechanistic plausibility for a causal relationship^{43–46}. Thus, although family history of IBD was the single strongest risk factor for IBD in our cohorts (aHR (95% CI) = 4.53 (3.38–6.07) for CD and 3.24 (2.45–4.29) for UC), the collective impact of environmental factors on IBD development is likely greater.

Though there are currently no known disease prevention strategies for CD and UC, dietary and lifestyle modifications may change the immunologic and microbiologic milieu necessary for disease development and therefore could serve as a strategy for IBD prevention. This may be of particular relevance to high-risk groups, such as first-degree relatives of IBD patients, who have an estimated 2–17% risk of developing the disease over their lifetime⁴⁷. Similar strategies have been applied in other immune-mediated diseases, including type I diabetes⁴⁸ and in unaffected first-degree relatives of those with RA⁴⁹.

Our study has several strengths. Exposure data were collected prospectively, minimizing the risk of recall or selection bias. Diet and physical activity variables were cumulatively averaged to account for long-term patterns. We used validated methods to assess lifestyle factors across all cohorts^{50,51}, and updated them over time to minimize exposure misclassification. Compared to prior studies, we considered a comprehensive list of modifiable lifestyle factors in the quantification of PAR, and avoided use of non-modifiable factors, pre-clinical markers of disease, and surrogates for proximal disease exposures in our MRS⁵². Further, falsification analysis demonstrated that our scores are relatively specific for IBD. For example, though associations and PAR estimates were similar for RA, a chronic immune-mediated disease with shared risk factors for CD, the corresponding PARs, and therefore preventable cases, were lower in CRC and CVD in spite of similar direction of association. This is largely due to differences in strength of associations and prevalence of risk factors, and presence of other modifiable risk factors such as alcohol and medications or supplements which are strongly associated with these other conditions^{29,53}. We also note that the follow up period in our cohorts coincided with a significant rise in the incidence of IBD in the western countries, allowing us to examine relevant secular changes in lifestyle and dietary behaviors³. In our primary cohorts and EPIC, cases of IBD were confirmed through blinded, medical record review by two gastroenterologists, minimizing outcome misclassification bias. Additionally, while several PAR values had wide CIs, potentially due to a limited number of cases or a high standard error introduced by a broad exposure definition⁵², the large majority did not cross 0%, increasing confidence in potential importance of dietary and lifestyle modifications in preventing CD and UC. Finally, our findings were largely reproducible in three European prospective cohorts, confirming external validity.

We also acknowledge several limitations. Mean age of IBD diagnosis (~45 years) for our cohort was higher than the typical age of onset of IBD, thus younger onset disease may be under-represented. Given the stronger genetic association with early-onset disease⁵⁴, our PAR figures may overestimate the potential for lifestyle modifications in preventing early-onset IBD. Nonetheless, this finding may remain relevant for older-onset disease, which

may be driven more heavily by environmental and lifestyle factors. Early lifestyle factors such as antibiotic exposure and breastfeeding, which have not been associated with IBD risk in these cohorts⁵⁵, environmental factors including pollution, and socioeconomic factors were also not considered as these may not be readily modifiable⁵². We also acknowledge that we did not have information on several other potentially modifiable factors such as stress in our cohorts. Thus, residual confounding may exist and affect the validity of PAR estimates if all confounders are not modeled^{28,52}. However, as most observed relationships between environmental and lifestyle factors and risk of IBD rarely exceed relative risk ratios of 3.00⁵, we feel the E-value analysis for residual confounding builds confidence in the validity of our results. We note that longitudinal data were not available for all cohorts thus time-varying exposures could not be used in our external cohorts. PAR is also affected by exposure prevalence, which may differ across non-Western countries, and therefore generalizability may be limited. Finally, because of our limited sample size, we could not independently explore the contribution of modifiable lifestyle factors to risk of IBD in high-risk individuals, defined as those with a first degree relative with IBD.

CONCLUSION:

Across six US and European cohorts, we confirmed that a substantial proportion of CD and UC risk may be preventable through modification of lifestyle risk factors, or adherence to a healthy lifestyle. Further prospective interventional studies are needed to determine whether lifestyle modification is effective for the primary prevention of IBD, particularly in high-risk population and younger-onset disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Sharing:

Further information including the procedures to obtain and access data from the Nurses' Health Studies and Health Professionals Follow-up Study is described at <https://www.nurseshealthstudy.org/researchers> (contact email: nhsaccess@channing.harvard.edu) and <https://sites.sph.harvard.edu/hpfs/for-collaborators/>.

Abbreviations:

BMI	Body mass index
CD	Crohn's disease
HPFS	Health Professionals Follow-up Study
IBD	Inflammatory bowel disease
NHS	Nurses' Health Study
NHSII	Nurses' Health Study II
NSAIDs	non-steroidal anti-inflammatory drugs
SFFQ	semi-quantitative food frequency questionnaire
UC	ulcerative colitis

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WHAT IS ALREADY KNOWN ON THIS TOPIC

- Several modifiable lifestyle and dietary risk factors have been identified for Crohn's disease (CD) and ulcerative colitis (UC), and are widely thought to contribute to disease pathogenesis.
- One approach to the prevention of chronic diseases is via modification of lifestyle and dietary factors.
- However, the extent by which adherence to low-risk factors or a healthy lifestyle could decrease the burden of CD and UC is unknown.

WHAT THIS STUDY ADDS

- In three prospective US cohorts, adherence to low-risk factors could have prevented 42.9% (95% CI 12.2 to 66.1%) of CD and 44.4% (95% CI 9.0 to 69.8%) of UC cases, while adherence to a healthy lifestyle could have prevented 61.1% (16.8 to 84.9%) of CD and 42.2% (1.7 to 70.9%) of UC cases. These findings were largely confirmed in three external European cohorts.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- Assuming a causal relationship exists, a substantial proportion of the burden of IBD may be preventable through lifestyle modification. Lifestyle modification may be an attractive strategy for future prevention strategies in IBD.

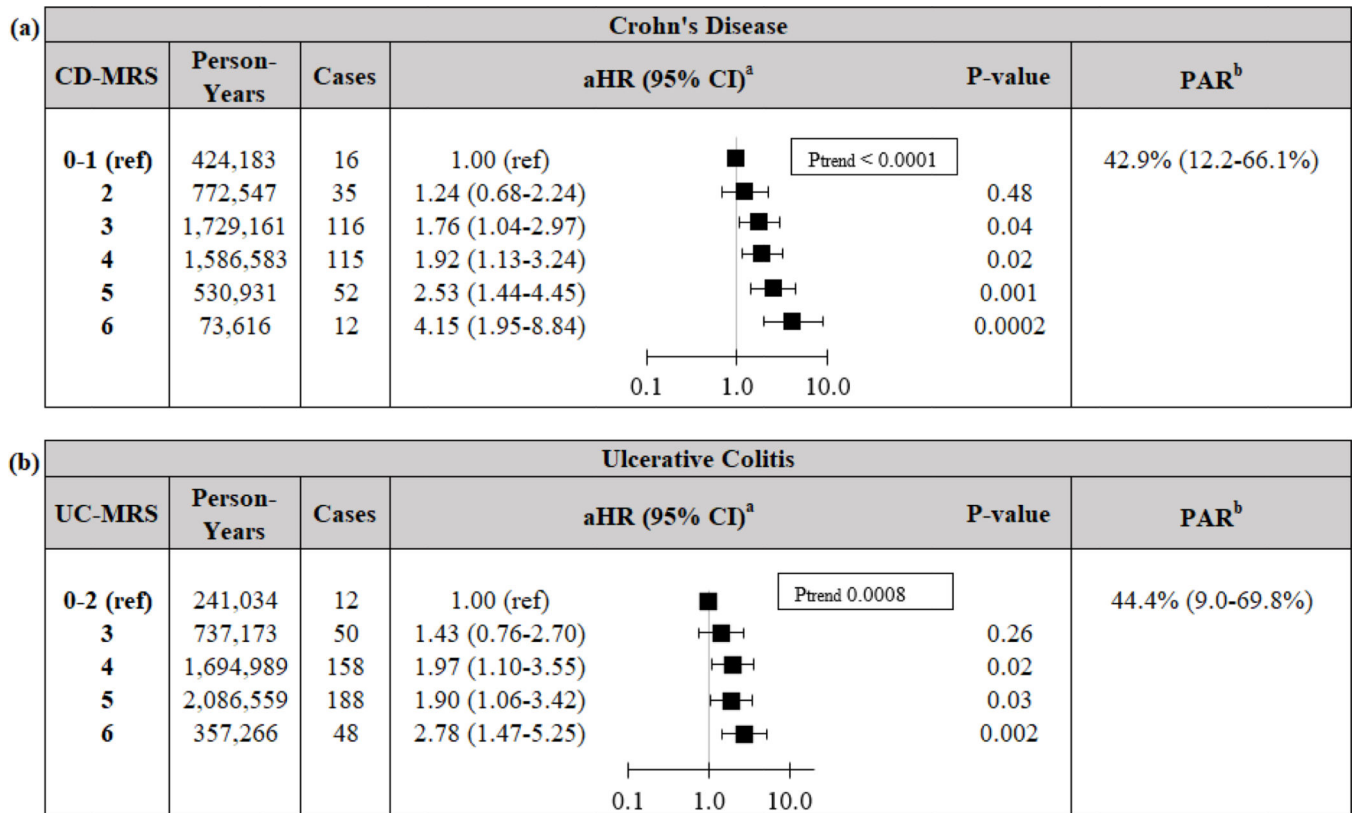
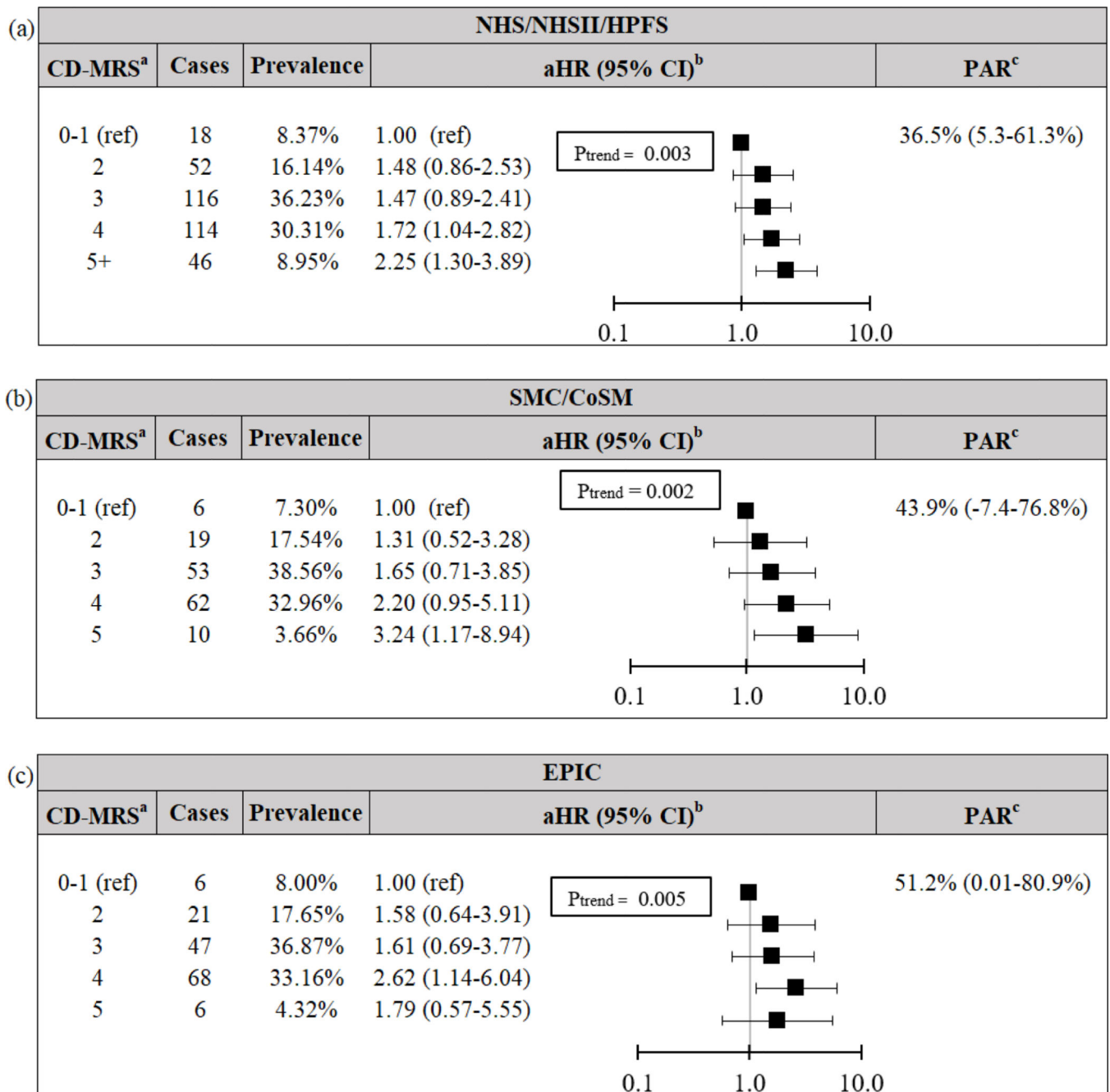


Figure 1.

Risk and PAR of (a) Crohn's disease and (b) ulcerative colitis according to modifiable risk scores. Reference level for UC set to 0–2 given low number of scores 0–1. ^a Cox models stratified by age (months), time-period (2-year intervals), and cohort (NHS, NHSII, or HPFS), and adjusted for appendectomy (yes/no), and family history of IBD (yes/no). ^b PAR for binary comparison between high-MRS (2+ risk factors for CD or 3+ risk factors for UC) and low-MRS (reference), adjusted for age (<40, 40–age <60, 60 years), cohort (NHS, NHSII, HPFS), appendectomy (yes/no) and family history of IBD (yes/no). **CD** Crohn's Disease. **CI** Confidence Interval. **aHR** Multivariable-adjusted Hazard Ratio. **MRS** Modifiable Risk Score. **PAR** Population Attributable Risk. **UC** Ulcerative Colitis.

**Figure 2.**

Risk and PAR of Crohn's disease according to baseline modifiable risk score for (a) pooled NHS/NHSII/HPFS cohort, (b) pooled SMC/CoSM cohort, and (c) EPIC cohort. ^aNSAID data missing from external cohorts, thus maximum MRS = 5. ^bCox models adjusted for baseline age (years) and cohort. ^cPAR for 2+ risk factors compared to reference (0-1), adjusted for age (<40, 40-60, ≥60 years) and cohort. **CD** Crohn's Disease. **CI** Confidence Interval. **CoSM** Cohort of Swedish Men. **EPIC** European Prospective Investigation into Cancer and Nutrition. **HPFS** Health Professional's Follow-up Study. **aHR**

Multivariable-adjusted Hazard Ratio. **MRS** Modifiable Risk Score. **NHS** Nurses' Health Study. **PAR** Population Attributable Risk. **SMC** Swedish Mammography Cohort.

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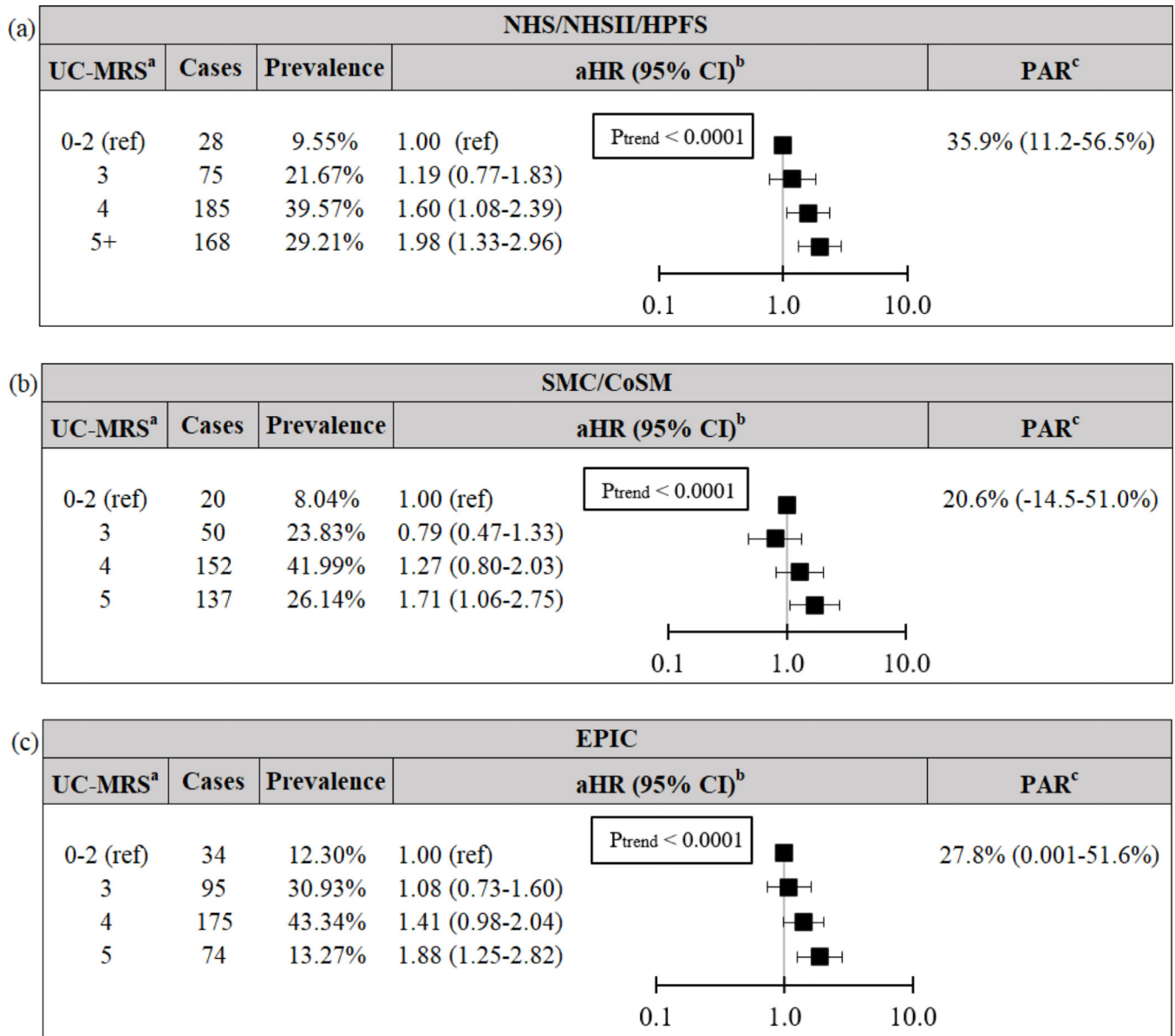


Figure 3.

Risk and PAR of ulcerative colitis according to baseline modifiable risk score for (a) pooled NHS/NHSII/HPFS cohort, (b) pooled SCM/CoSM cohort, and (c) EPIC cohort. ^aNSAID data missing from external cohorts, thus maximum MRS = 5. UC-MRS adapted such that “low-risk” criterion for smoking defined as never-smoking only. Given the low incidence of UC-MRS 0–1, reference level set to 0–2. ^bCox models adjusted for baseline age (years) and cohort. ^cPAR for 3+ risk factors compared to reference, adjusted for age (<40, 40–59, ≥60 years) and cohort. **CI** Confidence Interval. **CoSM** Cohort of Swedish Men. **EPIC** European Prospective Investigation into Cancer and Nutrition. **HPFS** Health Professional’s Follow-up Study. **aHR** Multivariable-adjusted Hazard Ratio. **MRS**

Modifiable Risk Score. **NHS** Nurses' Health Study. **PAR** Population Attributable Risk.
SMC Swedish Mammography Cohort. **UC** Ulcerative colitis.

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Table 1.

Associations between modifiable risk factors and Crohn's disease or ulcerative colitis, and definitions for 'low-risk' criteria used in calculation of modifiable risk scores (MRS).

Crohn's disease		Ulcerative Colitis	
Risk Factor	"Low-Risk" Criterion for MRS	Risk Factor	"Low-Risk" Criterion for MRS
BMI ^{6,15}	< 30 kg/m ²	BMI ⁶	30 kg/m ²
Smoking ⁷	Never smokers	Smoking ⁷	Current smokers
NSAIDs ¹⁶	< 2x/week	NSAIDs ¹⁶	< 2x/week
Physical activity ¹⁷	Highest quintile (MET-hrs/wk)	Fruit & vegetables ¹⁸	Highest quintile (servings/d)
Fruit & vegetables ¹⁸	Highest quintile (servings/d)	Red meat ^{22,23}	Lowest quintile (servings/d)
Fiber ^{19,20}	Highest quintile (grams/d)	n3:n6 PUFA ²¹	Highest quintile (servings/d)

BMI Body mass index. **MET** Metabolic equivalent of task. **NSAIDs** Non-steroidal anti-inflammatory drugs. **PUFA** Polyunsaturated fatty acid.

Table 2.

Preventable fraction of CD and UC cases due to American healthy lifestyle recommendations.

NHS/NHSII/HPFS				
Crohn's Disease				
Healthy lifestyle score ^a	Cases	Prevalence	aHR (95% CI) ^b	PAR (95% CI) ^c
7-9	5	4.24%	1.00 (ref)	61.1% (16.8 – 84.9%)
6	29	7.44%	3.13 (1.21–8.09)	
5	37	16.50%	1.67 (0.65–4.26)	
4	92	26.06%	2.58 (1.05–6.37)	
3	91	25.59%	2.57 (1.04–6.34)	
2	71	15.18%	3.42 (1.38–8.51)	
0-1	21	4.99%	3.01 (1.13–8.02)	
P _{trend}			0.004	
Ulcerative Colitis				
Healthy lifestyle score ^a	Cases	Prevalence	aHR (95% CI) ^b	PAR (95% CI) ^c
7-9	10	4.24%	1.00 (ref)	42.2% (1.7 – 70.9%)
6	30	7.44%	1.58 (0.77–3.23)	
5	71	16.50%	1.61 (0.83–3.13)	
4	109	26.06%	1.50 (0.78–2.87)	
3	132	25.59%	1.85 (0.97–3.53)	
2	72	15.18%	1.72 (0.88–3.34)	
0-1	32	4.99%	2.39 (1.17–4.87)	
P _{trend}			0.02	
SMC/CoSM				
Crohn's Disease				
Healthy lifestyle score ^a	Cases	Prevalence	aHR (95% CI) ^b	PAR (95% CI) ^c
7-9	2	2.62%	1.00 (ref)	48.8% (–37.4 – 89.8%)
6	16	10.19%	1.99 (0.46–8.66)	
5	34	23.32%	1.86 (0.45–7.74)	
4	36	30.88%	1.51 (0.36–6.27)	
3	39	22.31%	2.27 (0.55–9.41)	
2	19	8.79%	2.85 (0.66–12.23)	
0-1	4	1.89%	2.77 (0.51–15.14)	
P _{trend}			0.08	
Ulcerative Colitis				
Healthy lifestyle score ^a	Cases	Prevalence	aHR (95% CI) ^b	PAR (95% CI) ^c
7-9	4	2.62%	1.00 (ref)	56.3% (1.3 – 85.1%)
6	21	10.19%	1.27 (0.44–3.70)	

SMC/CoSM				
Crohn's Disease				
Healthy lifestyle score ^a	Cases	Prevalence	aHR (95% CI) ^b	PAR (95% CI) ^c
5	79	23.32%	2.10 (0.77–5.72)	
4	123	30.88%	2.52 (0.93–6.83)	
3	82	22.31%	2.35 (0.86–6.41)	
2	41	8.79%	3.03 (1.09–8.46)	
0–1	9	1.89%	3.05 (0.94–9.89)	
P _{trend}			0.0004	

EPIC				
Crohn's Disease				
Healthy lifestyle score ^a	Cases	Prevalence	aHR (95% CI) ^b	PAR (95% CI) ^c
7–9	4	6.50%	1.00 (ref)	60.4% (4.1 – 87.6%)
6	17	12.48%	2.13 (0.71 – 6.34)	
5	18	22.62%	1.21 (0.41 – 3.57)	
4	52	27.40%	2.82 (1.02 – 7.81)	
3	43	20.45%	3.09 (1.11 – 8.63)	
2	12	8.86%	1.97 (0.64 – 6.12)	
0–1	4	1.69%	3.43 (0.86 – 13.76)	
P _{trend}			0.005	
Ulcerative Colitis				
Healthy lifestyle score ^a	Cases	Prevalence	aHR (95% CI) ^b	PAR (95% CI) ^c
7–9	13	6.50%	1.00 (ref)	46.8% (9.7 – 72.5%)
6	29	12.48%	1.21 (0.62 – 2.38)	
5	65	22.62%	1.45 (0.78 – 2.68)	
4	123	27.40%	2.20 (1.22 – 3.98)	
3	103	20.45%	2.43 (1.34 – 4.42)	
2	44	8.86%	2.37 (1.25 – 4.48)	
0–1	7	1.69%	1.97 (0.78 – 4.99)	
P _{trend}			<0.001	

^aMaximum value set to 7+ given few participants with scores of 8–9 in primary cohort.

^bCox models adjusted for baseline age (years) and cohort (NHS, NHSII, HPFS, SMC, CoSM).

^cPAR for HLS 6 compared to reference category (7–9), adjusted for age (<40, 40–60, ≥60 years) and cohort. **CD** Crohn's Disease. **CI** Confidence Interval. **aHR** Multivariable-adjusted Hazard Ratio. **PAR** Population Attributable Risk. **UC** Ulcerative Colitis.