Supplementary Appendix

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Supplementary Methods

Validation Study Populations

The Swedish Mammography Cohort (SMC) was established in 1987-1990, when 66,651 Swedish females in Uppsala and Västmanland Counties were enrolled in a mammography screening program (74% of general female population in the study area in central Sweden) that included completion of an initial questionnaire assessing medical, lifestyle and dietary information[1,2]. An expanded survey was sent to participants in 1997 (70% response rate) that updated this information and also assessed physical activity and smoking habits. The 1997 questionnaire was also administered to men in Västmanland and Örebro Counties that same year, establishing the Cohort of Swedish Men (CoSM, n=45,906) with a response rate of approximately 49%[2,3].

The European Prospective Investigation into Cancer and Nutrition (EPIC) cohort was established in 1992-1999, when 521,324 participants were enrolled from 23 different centers across Spain, Italy, France, the United Kingdom, Greece, Germany, the Netherlands, Denmark, Sweden, and Norway[4,5]. Participants completed a combination of lifestyle and dietary/food frequency questionnaires, and anthropomorphic data was gathered either by participant report or direct measurement by trained staff. For our study, the Greek cohort was excluded (n=28,572) as were several centers/countries for which IBD information is not available: Norway (n=37,200), Asturias in Spain (n=8,542), and Naples and Milan in Italy (n=17,141). Finally, Umea was excluded as physical activity in METs was not available (n=25,725).

After exclusions, there were 37,275; 40,810; and 404,144 participants from each of the SMC, CoSM, and EPIC cohorts, respectively, with EPIC participants from Spain, Italy, France, United Kingdom, Germany, the Netherlands, Denmark, and Southern Sweden included in this study.

IBD Ascertainment

In our primary cohorts (NHS, NHSII, and HPFS), date of IBD diagnosis was used as date of index colonoscopy and histopathology results as determined during medical record review. We did not include participants who denied record review or whose diagnoses were unable to be confirmed (n=1209).

For SMC and CoSM, IBD was ascertained through linkage with the Swedish Patient Register and presence of at least two encounters that used an IBD-diagnosis code, through end of follow-up in 2017. The positive predictive value of this definition has been previously reported as 93% (95% CI: 87-97) for any IBD, 79% (66-88) for UC and 72% (60-82) for CD[6]. In the EPIC cohort, one or more of the following was used for disease confirmation through 2009: linkage with national or regional registries, follow-up questionnaires, and/or medical records reviewed by 1-2 physicians[7].

Rheumatoid Arthritis (RA), Colorectal Cancer (CRC), and Cardiovascular Disease (CVD) Ascertainment

RA cases were first self-reported on biennial questionnaires in NHS and NHSII cohorts. Participants who reported a diagnosis of RA were then sent a 6-question connective tissue disease screening questionnaire (CSQ) assessing symptoms of RA, as well as permission to request and review medical records. A positive CSQ screen was considered as 2 or more symptoms of connective tissue disease. We excluded those who denied a history of RA, were diagnosed with RA prior to baseline, denied permission for record review, or had a negative CSQ screen. Two rheumatologists blinded to exposure information then reviewed medical records. Cases were confirmed according to American College of Rheumatology criteria for RA and date of diagnosis was defined as date of first RA symptom.

Diagnoses of CRC were ascertained as in previously described methods[8]. Briefly, participants were queried on biennial questionnaires regarding new cancer diagnoses, and permission was requested to obtain and review medical records. Study physicians blinded to exposure information then reviewed records and pathology to confirm diagnoses. Additionally, for participants who died from colorectal cancer, next of kin, National Death Index, death certificates, and medical records were used to confirm the diagnosis in participants who had not reported their diagnosis on biennial questionnaires.

Finally, CVD was defined as a combined endpoint of coronary heart disease (CHD), coronary revascularization (including coronary bypass (CABG) or angioplasty), or stroke as has previously been described[9]. Briefly, participants self-reported a history of myocardial infarction (MI), angina, CABG, transient ischemic attack (TIA) or stroke on biennial questionnaires. Permission to obtain medical records was requested and reviewed by physicians. Non-fatal MI was diagnosed according to World Health Organization and the updated European Society of Cardiology and American College of Cardiology criteria[10,11]. CABG was self-reported. Non-fatal stroke was diagnosed according to Nation Survey of Stroke criteria[12]. Fatal CHD or stroke were identified by next of kin or by search of the National Death Index and confirmed on death certificates, medical records during hospitalization, or autopsy records.

Assessment of non-dietary factors

NHS, NHSII and HPFS cohorts

Non-dietary factors were ascertained from baseline and biennial questionnaires. Those with missing baseline dietary and lifestyle factors were excluded as described in the Methods. Missing data on follow up questionnaires were imputed using the last value from prior questionnaire. Body mass index (BMI) was calculated in kilograms of weight divided by meter squared baseline height, using updated weight every 2-years. Participants reported time spent in various physical activities per week, which was then converted to metabolic equivalent-hours (MET-hours) per week using expected METs per exercise[13–15], and cumulative-averaged to represent long-term patterns. Physical activity was categorized in quintiles of MET-hours/week. Smoking status was determined as previously described[16], using current and past smoking habits reported on baseline and subsequent questionnaires, and categorized as never, past, or current. Assessment of non-steroidal anti-inflammatory drug (NSAID) use has been previously reported[17]. Briefly, participants were asked about frequency and quantity of NSAID use on follow-up questionnaires. Regular NSAID use was defined as twice or more weekly use, and missing NSAID data was set to non-regular use. Family history of IBD in a first-degree relative was documented in 2012 in NHS and HPFS and in 2013 for NHSII. History of and date of appendectomy was asked in 1992 (NHS), 1995 (NHSII) and 1986 (HPFS). Family history of IBD and appendectomy were categorized as "yes/no," with missing data set to "no". Oral contraceptives were not included due to pooled cohorting of both males and females. Longitudinal antibiotic use was not available and was thus excluded from this analysis. For use in sensitivity analysis, family history of RA or systemic lupus erythematosus (SLE) in a first-degree relative was assessed in NHS in 2008, while in NHSII family history of RA in a first-degree relative was assessed in 2013. Family history of a first-degree relative with colorectal cancer was specifically asked and updated in NHS (2004, 2008), NHSII (2005, 2009) and HPFS (1996, 2008, 2012). Family history of a first degree relative with myocardial infarction and/or stroke were specifically queried in NHS (1996, 2008), NHSII (1993, 1997, 2001, 2005), and HPFS (1986).

Replication cohorts (SMC, CoSM, EPIC)

In validation studies, baseline data was used as longitudinal data was not uniformly available across all cohorts. In all cohorts, information on BMI and smoking were available at baseline. When using baseline

data, both past and current smoking status conferred increased risk for UC, potentially due to lack of a time-varying exposure. To account for this, UC-MRS was adapted such that the "low-risk" criterion for smoking was defined as never-smoking only. For physical activity, in SMC and CoSM, we included walking, cycling, or other exercise as physical activity[1,3,15]. In the EPIC cohort, physical activity (occupational, walking, cycling, gardening, housework, physical exercise, climbing stairs) was reported on standardized questionnaires for: France, Italy, Spain, the United Kingdom, the Netherlands, Greece, and Germany[4]. Denmark and Sweden, which joined the cohort later, developed independent scales of assessment that were then recoded to standardize physical activity to the original survey tool. For all cohorts, time spent in activities was multiplied by expected METs to achieve MET-hours per week, then modeled in quintiles[14]. Family history of IBD, history of appendectomy, and NSAID use were not uniformly available and thus were not included in derivation of lifestyle scores.

Assessment of dietary factors:

NHS, NHSII and HPFS cohorts

Participants were sent semi-quantitative food-frequency questionnaires (SFFQs) every 4 years and were asked to report food intake patterns over the previous year. The SFFQ assessed frequency of intake of standard-sized food items, ranging from never or less than once a month to 6 or more times per day. The Harvard Food Composition Database was used to calculate nutrient-level intake data from SFFQ data [18]. Derivation of nutrient intake data using SFFQ has previously been shown to correlate with 7-day dietary records and 24-hour dietary recalls [19,20]. To reduce the effect of extraneous variation in nutrient reporting, all nutrient values were adjusted to total energy intake using the residuals method[21,22]. We used cumulative average of daily servings to better represent long-term patterns of dietary intake[23], and modeled dietary variables in quintiles.

Red meat was defined as pork, beef or lamb products, including processed meat. As we chose to include processed red meat in our red meat definition, we did not include a separate score for degree of food processing in our risk scores to avoid overlap between variables.

Replication cohorts (SMC, CoSM, EPIC)

Dietary and nutrient data were assessed at baseline. For the SMC and CoSM cohorts, participants reported how frequently they consumed age-sized portions (servings) of common food items, ranging from never to 3 or more time per day. Nutrient values were then calculated based on the expected content of foods. The reproducibility and validity of this method for nutrient values has been previously established[2]. In the EPIC cohort, one of several methods was used to assess dietary intake across the various centers and countries, including quantitative dietary questionnaires (either self-reported or face to face interviews), SFFQs, and combined dietary methods (a combination of SFFQ and 7- or 14-day dietary recall)[4]. The use of SFFQ for this cohort has previously been validated against 24-hour recall questionnaires and nutrient biomarkers[24]. Ultimately, all servings and nutrient data from each of these methods was converted to grams per day to standardize reporting across these centers before central pooling of data. For use in our analysis, we converted grams per day to servings per day for fruit & vegetables and red meat intake using expected portion sizes reported in prior studies (one serving fruit and vegetables = 80 grams[25,26], one serving red meat = 90 grams [27,28]). All dietary factors were modeled in quintiles.

Statistical analysis

The Cox proportionality assumption was tested for by creating interaction terms between follow-up time and each of CD-MRS and UC-MRS and comparison the models with these interaction terms with the main models (without interaction terms) using the log likelihood ratio test. We observed no evidence for

an interaction between follow-up time and MRS for either CD (P=0.83) or UC (P=0.08), suggesting that the proportional hazards assumption was valid.

Sensitivity analyses

We constructed MRS using weighted criteria to account for known linear relationships between risk factors and IBD risk. For fruit and vegetables, physical activity, fiber, and n3:n6 PUFAs, lowest quintile of intake was assigned a maximum value of 5 points, followed by 2nd quintile: 4 points, 3rd quintile: 3 points, 2nd quintile: 2 points, and highest quintile of intake: 1 point. Conversely, red meat intake was scored 5 points for highest quintile intake, down to 1 point for lowest quintile. Regular NSAID use was given 5 points, with 1 point for non-use. For smoking status, never-smokers received 1 point, past-smokers 3 points, and current smokers 5 points for CD, while for UC, past smokers received 5 points, never smokers received 3 points, and current smokers received 1 point. For BMI, 1 point was assigned to BMI <30 kg/m^2 and 5 points to BMI ≥30 kg/m^2 for CD, and vice-versa for UC. Similar to primary analysis, weighted CD-MRS summed scores for smoking, NSAID use, BMI, physical activity, fruit & vegetable intake, and fiber intake, while weighted UC-MRS was totaled based on scores from smoking, NSAID use, BMI, fruit & vegetable intake, n3:n6 PUFA intake, and red meat intake (final MRS range 6-30 for each).

Healthy lifestyle scores

Healthy lifestyle criteria were created using standardized health recommendations from the US Department of Health and Human Services and US Department of Agriculture (USDA) Dietary Guidelines for Americans, and the American Heart Association (AHA) Guidelines for Healthy Living[29–31]. We defined healthy physical activity as ≥7.5 MET-hours per week based on recommendations for 150 minutes per week of moderate (MET=3) physical activity[31]. Never-smoking and 18.5 ≤ BMI < 25 kg/m^2 were considered healthy[29,30]. Healthy dietary patterns were chosen to reflect a Mediterranean style diet, which is supported by both the AHA and USDA guidelines. Though recommended intake for fruit and vegetables varies between the USDA and AHA guidelines, we chose to use the higher threshold of ≥ 8 servings/day recommended by the AHA given the overall higher intake of fruits and vegetables in our cohort. We chose a minimum of 25 grams/day of fiber intake as "healthy" based on the minimum amount of intake recommended for US females [32]. Using a standard serving size for meat of 3 oz[29] and a recommended maximum meat intake of 1.8 oz daily[32], we defined healthy red meat intake as <0.5 servings/day. Based on a recommendation for 8 oz fish per week and a standard serving size of 3.5-4 oz fish per serving, we defined healthy fish (including shellfish) intake as a minimum of 2 servings per week. Using a standard serving size (1 oz equivalents) of 0.5 oz for nuts and seeds and 1 tablespoon for nut butters[29,30], and a recommended minimum intake of 0.5 oz equivalents per day of nuts, seeds, and nut butters[32], we defined healthy nut and seed intake as a minimum of 0.5 servings/day. We did not consider beans/legumes as a separate category, as beans/peas/lentils as vegetables were included in our daily servings of vegetables assessed, and recommended intake of protein from beans/legumes are not explicitly defined in these guidelines. Finally, healthy alcohol use was defined as a maximum of 1 drink per day for women or 2 per day for men[29,30], with a standard serving size defined as 14 g alcohol content per drink, or 12 fluid oz of beer (1 glass, can, or bottle), 4-5 fluid oz wine, or 1.5 fluid oz (1 shot or drink) distilled spirits[30]. Missing dietary data was set to baseline cohort-specific median. Baseline data were used to be consistent across primary and validation cohorts. A reference group of 7-9 was used for healthy lifestyle scores and scores of 0-1 were grouped due to a small percentage of scores equal to 0.

Assessing residual confounding using the E-value

To assess for residual confounding, we applied the E-value method to our primary analysis to estimate the minimum strength of association that an unmeasured confounder would need to have on both the exposure and outcome to fully explain the observed aHR (95% CIs). As our outcome was relatively rare, we employed the following formula as described by VanderWeele et al[33]:

E-value for HR = HR + sqrt{HR×(HR− 1)}
E-value for LL (for a HR > 1) = LL+ sqrt{LL×(LL− 1)}

Where HR = the adjusted hazard ratio for CD- and UC-MRS with CD and UC, respectively, conditional on age, family history of IBD, and history of appendectomy; and LL = the lower limit of the confidence interval for these aHRs. We applied this to the binary CD- and UC-MRS used in the primary PAR analysis, as well as to individual levels of the CD- and UC-MRS.

Supplementary Results

Inclusion of a term for processed meat in MRS

We included a term for processed meat in the construction of CD-MRS (range 0-7) and replaced the term for red meat with processed meat when calculating UC-MRS (range 0-6), similar to our primary analysis. Compared to those with a CD-MRS of 0-1, those with a CD-MRS of 2, 3, 4, 5, 6, and 7 had an aHR (95% CI) of: 1.03 (0.46-2.29), 1.18 (0.57-2.42), 1.59 (0.80-3.15), 1.86 (0.94-3.68), 2.12 (1.03-4.35) and 4.04 (1.69-9.67) for CD, respectively (P_{trend}<0.0001). Adherence to low CD-MRS (0-1) could have prevented 37.7% (-7.2-69.9%) cases of CD (PAR). Similarly, compared to those with a UC-MRS of 0-2, those with a UC-MRS of 3, 4, 5, and 6 had an aHR (95% CI) of: 1.60 (0.84-3.07), 2.14 (1.16-3.94), 2.11 (1.15-3.89), and 2.92 (1.50-5.65) for UC, respectively (P_{trend}=0.0007). Adherence to low UC-MRS (0-2) could have prevented 49.0% (14.4-73.0%) of UC cases (PAR).

Falsification Analyses

Compared to those with a CD-MRS of 0-1, the aHR (95%CI) for RA of those with a CD-MRS of 2, 3, 4, 5, and 6 was 1.09 (0.82-0.45), 1.02 (0.79-1.33), 1.24 (0.96-1.60), 1.59 (1.20-2.11), and 1.77 (1.13-2.77), respectively (P_{trend} <0.0001). Compared to those with a UC-MRS of 0-2, the aHR (95%CI) for RA of those with a UC-MRS of 3, 4, 5, and 6 was 0.80 (0.58-1.80), 0.88 (0.67-1.17), 0.91 (0.69-1.20), and 1.15 (0.82-1.60), respectively (P_{trend}=0.12). Adherence to low CD-MRS (0-1) could have prevented 32.3% (0.4-58.3%) of RA. Conversely, because a UC-MRS > 2 (when compared to a reference of 0-2) was associated with an aHR < 1, PAR for adherence to low UC-MRS (0-2) could not be calculated. In other words, adherence to low UC-MRS could not prevent RA in our cohorts.

Compared to those with a CD-MRS of 0-1, the aHR (95%CI) for CRC of those with a CD-MRS of 2, 3, 4, 5, and 6 was 1.15 (0.98-1.35), 1.09 (0.94-1.26), 1.36 (1.18-1.57), 1.44 (1.22-1.71), and 1.47 (1.06-2.03), respectively (P_{trend} = <0.0001). Adherence to low CD-MRS (0-1) could have prevented 13.3% (2.3-23.9%) of CRC. Compared to those with a UC-MRS of 0-2, the aHR (95%CI) for CRC of those with a UC-MRS of 3, 4, 5, and 6 was 1.11 (0.92-0.34), 1.12 (0.93-1.33), 1.12 (0.94-1.33), and 0.89 (0.71-1.12), respectively (P_{trend} = 0.60). Adherence to low UC-MRS (0-2) was associated with higher risk for CRC compared to the UC-MRS > 2 group, and therefore PAR for adherence to low UC-MRS could not be calculated. In other words, adherence to low UC-MRS could not prevent CRC in our cohorts.

In the CVD analysis, compared to those with a CD-MRS of 0-1, the aHR (95%CI) for CVD of those with a CD-MRS of 2, 3, 4, 5, and 6 was 1.05 (0.98-0.13), 1.10 (1.03-1.17), 1.25 (1.18-1.33), 1.54 (1.43-1.65),

and 1.68 (1.47-1.92), respectively (P_{trend} = < 0.0001). Adherence to low CD-MRS (0-1) could have prevented 14.0% (9.6-18.5%) of CVD. Compared to those with a UC-MRS of 0-2, the aHR (95%CI) for CVD of those with a UC-MRS of 3, 4, 5, and 6 was 0.93 (0.86-1.00), 0.88 (0.82-0.95), 0.79 (0.74-0.85), and 0.80 (0.73-0.87), respectively (P_{trend} = < 0.0001). Adherence to low UC-MRS (0-2) was associated with higher risk for CVD compared to the UC-MRS > 2 group, and therefore PAR for adherence to low UC-MRS could not be calculated. In other words, adherence to low UC-MRS could not prevent CVD in our cohorts.

Table S1. Definitions for healthy criteria used in construction of Healthy Lifestyle Scores (HLS).

Modifiable Risk Factor	Healthy Criterion
BMI	18.5 $kg/m^2 \leq$ BMI < 25 kg/m^2
Smoking status	Never smoking
Physical activity	≥ 7.5 MET-hours/week
Fruit & vegetables	≥ 8 servings/day
Fiber	≥ 25 grams/day
Red meat intake	< 0.5 servings/day
Fish intake	≥ 2 servings/week
Nuts & Seeds	≥ 0.5 serving/day
Alcohol[a]	Females: ≤ 1 drink/day Males: ≤ 2 drinks/day

BMI Body mass index. **MET** Metabolic equivalent of task. [a] One drink is equivalent to 14g of alcohol.

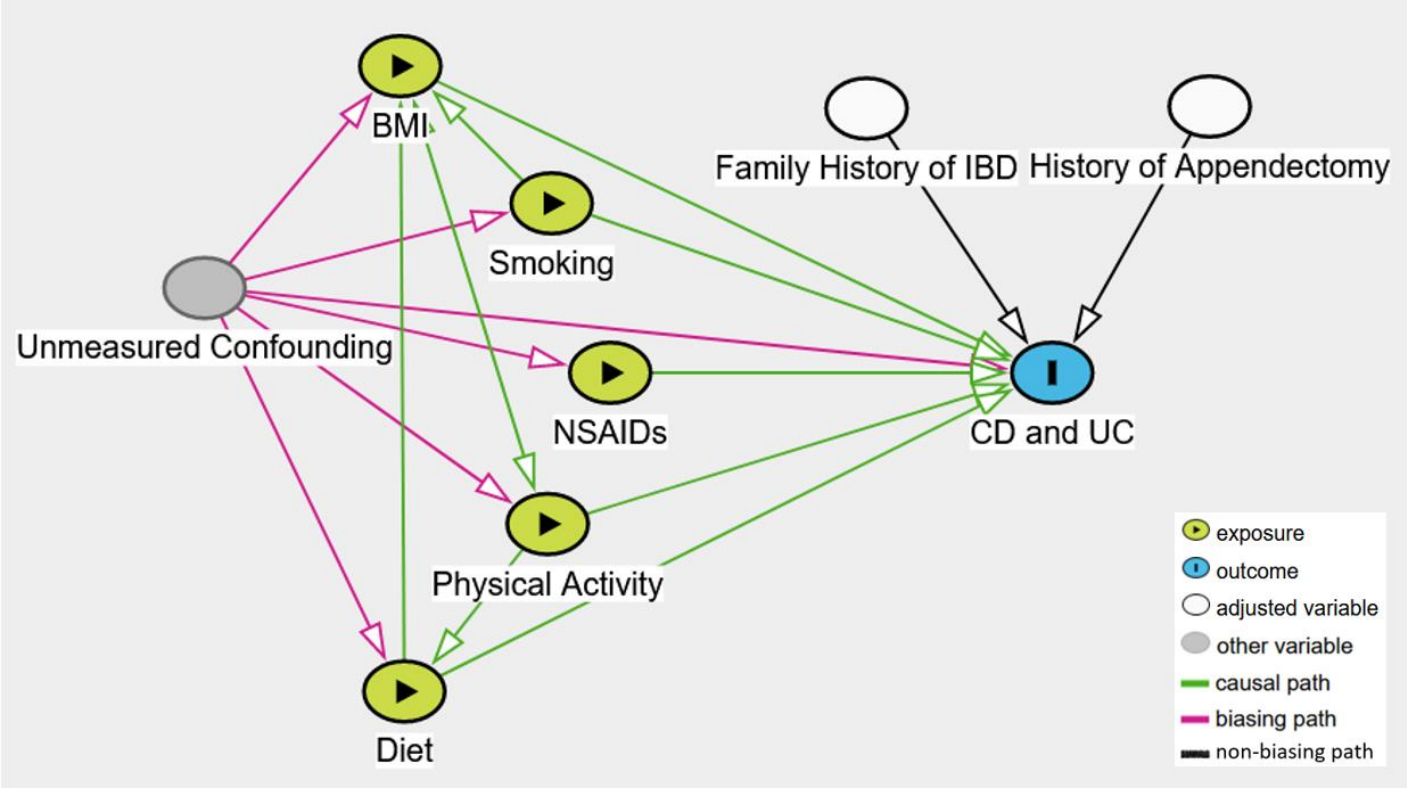

Figure S1. Directed acyclic graph (DAG) for proposed relationships between risk factors, outcomes, and potential confounders. **CD** Crohn's disease. **NSAID** Non-steroidal anti-inflammatory drug. **UC** Ulcerative colitis.

Table S2. Baseline characteristics of pooled primary cohort according to modifiable risk score (MRS).

	CD-MRS		UC-MRS	
	MRS 0-1 (n=18,110)	**MRS 6 (n=1,207)**	**MRS 0-2 [a] (n=10,083)**	**MRS 6 (n=8,567)**
Age [b] (years)	45.95 (11.4)	42.87 (9.4)	47.6 (10.8)	40.2 (9.3)
Sex (% female)	79	84	85	75
Body mass index (kg/m^2)	23.5 (3.1)	35.04 (4.8)	26.9 (6.2)	24.2 (2.9)
Physical activity (MET-hrs/wk)	41.0 (38.0)	7.2 (7.3)	27.3 (33.8)	16.8 (21.0)
Smoking status				
- Never (%)	85	0	39	63
- Past (%)	12	65	26	37
- Current (%)	3	35	35	0
Regular NSAID use [c] (%)	12	55	15	61
History of appendectomy (%)	17	29	20	23
Family history of IBD (%)	4	4	4	4
Fruits (servings/day)	2.9 (1.7)	1.0 (0.8)	2.6 (1.8)	1.2 (0.8)
Vegetables (servings/day)	6.6 (2.9)	2.9 (1.3)	6.7 (3.3)	2.9 (1.2)
Fiber (grams/day)	27.1 (6.5)	15.5 (3.4)	25.1 (8.2)	17.1 (4.5)
Red meat (servings/day)	0.5 (0.5)	0.9 (0.6)	0.3 (0.4)	0.8 (0.5)
n3:n6 PUFA ratio	0.15 (0.05)	0.12 (0.03)	0.18 (0.06)	0.11 (0.02)

[a] Reference level for UC set to 0-2 given low number of scores 0-1. [b] All values other than age are standardized to the age distribution of the study population. Values are mean (standard deviation) unless stated otherwise. Values of polytomous variables may not sum to 100% due to rounding. [c] NSAIDs use in year 1986 for NHS and 1991 for NHSII (regular use equals ≥2x/week). **CD** Crohn's disease. **IBD** Inflammatory bowel disease. **MET** Metabolic equivalent of task. **MRS** Modifiable Risk Score. **NSAID** Non-steroidal anti-inflammatory drug. **PUFA** Polyunsaturated fatty acid. **UC** Ulcerative colitis.

Table S3. Risk and PAR of CD and UC according to CD-MRS and UC-MRS, stratified by sex.

	Females					Males				
	Cases	**Person-Years**	**aHR (95% CI)**	**PAR (95% CI)**		**Cases**	**Person-Years**	**aHR (95% CI)**	**PAR (95% CI)**	**$P_{interaction}$**
CD-MRS					**CD-MRS**					
0-1	14	327,753	1.00 (ref)	43.0% (10.1-67.4%)	0-1	2	96,430	1.00 (ref)	43.4% (-44.6-88.7%)	0.79
2	30	601,991	1.21 (0.64-2.29)		2	5	170,556	1.38 (0.27-7.17)		
3	105	1,366,130	1.81 (1.03-3.16)		3	11	363,031	1.33 (0.29-6.05)		
4	99	1,261,718	1.85 (1.05-3.24)		4	16	324,865	2.37 (0.54-10.42)		
5+	59	515,414	2.74 (1.52-4.93)		5+	5	89,134	2.49 (0.47-13.09)		
P_{trend}	--	--	<0.0001		P_{trend}	--	--	0.09		
UC-MRS					**UC-MRS**					
0-2	11	197,213	1.00 (ref)	42.3% (4.1-69.7%)	0-2	1	43,822	1.00 (ref)	61.1% (-46.1-95.8%)	0.19
3	46	604,700	1.44 (0.74-2.78)		3	4	132,473	1.42 (0.15-12.92)		
4	139	1,377,580	1.92 (1.04-3.54)		4	19	317,409	2.69 (0.35-20.45)		
5	161	1,604,875	1.86 (1.01-3.44)		5	27	481,684	2.40 (0.32-17.98)		
6	38	288,640	2.45 (1.25-4.81)		6	10	68,626	6.03 (0.74-49.00)		
P_{trend}	--	--	0.006		P_{trend}	--	--	0.03		

Cox models adjusted for age (months), appendectomy (yes/no), and family history IBD (yes/no). PAR calculations adjusted for age (< 60, ≥ 60), appendectomy (yes/no) and family history IBD (yes/no). UC-MRS reference level set to 0-2 given low number of UC-MRS of 0-1. CD-MRS set to maximum value 5+ given n=0 for a CD-MRS of 6 in men. **aHR** Adjusted hazard ratio. **CD** Crohn's disease. **CI** Confidence interval. **MRS** Modifiable risk score. **PAR** Population attributable Risk. **UC** Ulcerative colitis.

Table S4. Risk of CD and UC using weighted CD-MRS and UC-MRS criteria.

	Cases	Person-Years	aHR (95% CI)	PAR (95% CI)
CD-MRS				
Low	27	691,467	1.00 (ref)	41.0% (17.5-60.0%)
High	319	4,425,554	1.78 (1.20-2.63)	
P-value			0.004	
UC-MRS				
Low	48	734,969	1.00 (ref)	27.7% (7.5-45.7%)
High	408	4,382,053	1.46 (1.08-1.97)	
P-value			0.01	

MRS score ranges 6-30 based on scaled criteria for known risk factors of CD and UC. Low MRS defined as lowest 15% compared to high MRS (remainder). 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 IBD (yes/no). PAR calculations adjusted for age (<40, 40 ≤ age <60, ≥ 60), cohort (NHS, NHSII, HPFS), appendectomy (yes/no) and family history IBD (yes/no). **aHR** Adjusted hazard ratio. **CD** Crohn's disease. **CI** Confidence interval. **MRS** Modifiable risk score. **PAR** Population attributable Risk. **UC** Ulcerative colitis.

Table S5. Risk of CD according to known risk factors for disease.

	Mean (sd) or %	Cases	Person-Years	aHR (95% CI)	P-value [a]
Smoking status					
Never smoking	55	164	2,829,085	1.00 (ref)	
Past smoking	30	131	1,832,503	1.26 (1.00-1.60)	0.05
Current smoking	15	51	455,432	1.85 (1.33-2.56)	0.0002
Regular NSAID use					
< 2 times/week	82	271	4,195,245	1.00 (ref)	
≥ 2 times/week	18	75	921,776	1.17 (0.90-1.52)	0.25
Appendectomy					
No	81	264	4,109,334	1.00 (ref)	
Yes	19	82	1,007,688	1.21 (0.93-1.56)	0.15
Family history of IBD					
None	96	291	4,905,946	1.00 (ref)	
Positive family history	4	55	211,075	4.53 (3.38-6.07)	<.0001
BMI					
BMI < 30 kg/m^2	80	260	4,089,944	1.00 (ref)	
BMI ≥ 30 kg/m^2	20	86	1,027,077	1.20 (0.93-1.55)	0.16
Physical activity (MET-hrs/wk)					
1st quintile	2.8 (1.8)	64	864,365	1.00 (ref)	
2nd quintile	7.9 (3.0)	88	1,030,065	1.19 (0.86-1.65)	
3rd quintile	14.5 (4.5)	73	1,080,409	0.97 (0.69-1.37)	
4th quintile	24.3 (6.8)	63	1,095,906	0.81 (0.57-1.16)	
5th quintile	52.2 (27.0)	58	1,046,277	0.81 (0.55-1.18)	0.04
Fruit & vegetable intake					
1st quintile	2.4 (0.7)	74	989,114	1.00 (ref)	
2nd quintile	3.8 (0.4)	76	1,028,130	1.05 (0.75-1.47)	
3rd quintile	5.0 (0.5)	70	1,037,979	0.96 (0.67-1.40)	
4th quintile	6.3 (0.6)	68	1,039,140	0.97 (0.65-1.45)	
5th quintile	9.4 (2.4)	58	1,022,659	0.97 (0.62-1.52)	0.78
Fiber intake (g/day)					
1st quintile	13.1 (2.0)	74	954,654	1.00 (ref)	
2nd quintile	16.5 (1.4)	66	1,037,921	0.88 (0.62-1.25)	
3rd quintile	18.9 (1.6)	83	1,057,753	1.14 (0.79-1.63)	
4th quintile	21.6 (2.0)	79	1,055,670	1.14 (0.77-1.70)	
5th quintile	27.4 (4.9)	44	1,011,023	0.67 (0.41-1.11)	0.61
Red meat intake (servings/day)					
1st quintile	0.2 (0.1)	62	963,342	1.00 (ref)	
2nd quintile	0.4 (0.1)	73	1,012,905	0.98 (0.69-1.38)	
3rd quintile	0.6 (0.1)	65	1,072,761	0.81 (0.56-1.16)	
4th quintile	0.8 (0.1)	73	1,055,649	0.89 (0.62-1.27)	
5th quintile	1.3 (0.4)	73	1,012,365	0.92 (0.63-1.33)	0.74

Stratified by age (months), time-period (2-year intervals), and cohort (NHS, NHSII, or HPFS). Adjusted for BMI (< 30, or ≥ 30 kg/m^2); family history of IBD (yes/no); appendectomy (yes/no); physical activity (quintiles); smoking status (never, past, or current); regular NSAID use (yes/no); fruits, vegetables and red meat intake (quintiles servings/day), and fiber (quintiles g/day). [a] P-values for quintile data are P_{trend} values. **aHR** Adjusted hazard ratio. **BMI** Body mass index. **CD** Crohn's disease. **CI** Confidence interval. **IBD** Inflammatory bowel disease. **MET** Metabolic equivalent of task. **NSAID** Non-steroidal anti-inflammatory drug.

Table S6. Risk of UC according to known risk factors for disease.

	Mean (sd) or %	Cases	Person-Years	aHR (95% CI)	P-value [a]
Smoking status					
Current smoking	55	36	455,432	1.00 (ref)	
Never smoking	30	213	2,829,085	1.00 (0.70-1.43)	0.98
Past smoking	15	207	1,832,503	1.66 (1.16-2.38)	0.006
Regular NSAID use					
< 2 times/week	82	344	4,195,245	1.00 (ref)	
≥ 2 times/week	18	112	921,776	1.44 (1.15-1.79)	0.001
Appendectomy					
No	81	376	4,109,334	1.00 (ref)	
Yes	19	80	1,007,688	0.87 (0.68-1.12)	0.27
Family history of IBD					
None	96	398	4,905,946	1.00 (ref)	
Positive family history	4	58	211,075	3.24 (2.45-4.29)	<.0001
BMI					
BMI < 30 kg/m^2	80	367	4,089,944	1.00 (ref)	
BMI ≥ 30 kg/m^2	20	89	1,027,077	0.90 (0.71-1.14)	0.39
Physical activity (MET-hrs/wk)					
1st quintile	2.8 (1.8)	84	864,365	1.00 (ref)	
2nd quintile	7.9 (3.0)	83	1,030,065	0.87 (0.64-1.18)	
3rd quintile	14.5 (4.5)	98	1,080,409	0.99 (0.73-1.33)	
4th quintile	24.3 (6.8)	107	1,095,906	1.08 (0.80-1.45)	
5th quintile	52.2 (27.0)	84	1,046,277	0.92 (0.67-1.27)	0.81
Fruit & vegetable intake (servings/day)					
1st quintile	2.4 (0.7)	90	989,114	1.00 (ref)	
2nd quintile	3.8 (0.4)	119	1,028,130	1.31 (0.99-1.73)	
3rd quintile	5.0 (0.5)	76	1,037,979	0.83 (0.60-1.14)	
4th quintile	6.3 (0.6)	101	1,039,140	1.13 (0.83-1.53)	
5th quintile	9.4 (2.4)	70	1,022,659	0.82 (0.58-1.15)	0.15
Red meat intake (servings/day)					
1st quintile	0.2 (0.1)	83	963,342	1.00 (ref)	
2nd quintile	0.4 (0.1)	96	1,012,905	1.05 (0.78-1.41)	
3rd quintile	0.6 (0.1)	91	1,072,761	0.93 (0.68-1.26)	
4th quintile	0.8 (0.1)	97	1,055,649	0.99 (0.73-1.34)	
5th quintile	1.3 (0.4)	89	1,012,365	0.96 (0.70-1.31)	0.73
n3:n6 PUFA (ratio/day)					
1st quintile	0.09 (0.01)	101	960,831	1.00 (ref)	
2nd quintile	0.11 (0.01)	91	1,041,392	0.83 (0.63-1.11)	
3rd quintile	0.12 (0.01)	104	1,051,904	0.96 (0.72-1.27)	
4th quintile	0.14 (0.01)	79	1,050,103	0.73 (0.53-0.99)	
5th quintile	0.18 (0.04)	81	1,012,791	0.79 (0.57-1.09)	0.10

Stratified by age (months), time-period (2-year intervals), and cohort (NHS, NHSII, or HPFS). Adjusted for BMI (< 30, or ≥ 30 kg/m^2); family history of IBD (yes/no); appendectomy (yes/no); physical activity quintiles); smoking status (never, past, or current); regular NSAID use (yes/no); fruits, vegetables and red meat intake (quintiles servings/day), and n3:n6 PUFA (quintiles). [a] P-values for quintile data are P_{trend} values. **aHR** Adjusted hazard ratio. **BMI** Body mass index. **CI** Confidence interval. **IBD** Inflammatory bowel disease. **MET** Metabolic equivalent of task. **NSAID** Non-steroidal anti-inflammatory drug. **PUFA** Polyunsaturated fatty acid. **UC** Ulcerative colitis.

Table S7. Risk and PAR for Crohn's disease and ulcerative colitis according to individual risk factors.

	Reference level	Cases (ref)	Person-Years (ref)	aHR (95% CI)	P-value	PAR (95% CI)
Crohn's Disease [a]						
Family history	None	291	4,905,946	4.49 (3.35-6.01)	<0.0001	12.2% (8.0-16.2%)
Appendectomy	None	264	4,109,334	1.21 (0.93-1.56)	0.15	3.8% (-1.9-9.4%)
All Modifiable Risk Factors						
• BMI	<30 kg/m^2	260	4,089,944	1.18 (0.91-1.51)	0.21	4.3% (-2.3-10.7%)
• Past or current smoking	Never smokers	164	2,829,085	1.39 (1.12-1.73)	0.003	14.4% (1.5-26.9%)
• Regular NSAID use	<2x/week	271	4,195,245	1.16 (0.89-1.51)	0.27	3.2% (-2.4-8.8%)
• Physical activity [c]	Highest quintile	58	1,046,277	1.25 (0.86-1.81)	0.04	12.9% (-4.9-29.9%)
• Fruits & Vegetables [c]	Highest quintile	58	1,022,659	1.07 (0.69-1.64)	0.69	4.0% (-27.9-35.1%)
• Fiber [c]	Highest quintile	44	1,011,023	1.47 (0.93-2.34)	0.52	27.9% (-1.5-52.9%)
Ulcerative Colitis [b]						
Family history	None	398	4,905,946	3.24 (2.45-4.29)	<0.0001	8.8% (5.4-12.1%)
No Appendectomy	+Appendectomy	80	1,007,688	1.15 (0.90-1.47)	0.27	9.8% (-8.6-27.6%)
All Modifiable Risk Factors						
• BMI	≥30 kg/m^2	89	1,027,077	1.11 (0.87-1.41)	0.39	8.4% (-8.8-25.2%)
• Past smoking	Current smoking	36	455,432	1.66 (1.16-2.38)	0.006	18.0% (11.5-24.4%)
• Never smoking	Current smoking	36	455,432	1.00 (0.70-1.43)	0.98	N/A (HR ≤ 1)
• Regular NSAID use	<2x/week	344	4,195,245	1.44 (1.15-1.79)	0.001	7.1% (2.1-12.1%)
• Fruits & Vegetables [c]	Highest quintile	70	1,022,659	1.22 (0.87-1.73)	0.15	20.1% (-2.5-40.8%)
• Red meat [d]	Lowest quintile	83	963,342	0.96 (0.70-1.31)	0.73	2.9% (-12.4-18.1%)
• n3:n6 PUFA [c]	Highest quintile	81	1,012,791	1.27 (0.92-1.75)	0.10	11.0% (-4.8-26.4%)

All Cox models stratified by age (months), time-period (2-year intervals), and cohort (NHS, NHSII, or HPFS), and adjusted for BMI (<30, or ≥ 30 kg/m^2), family history of IBD (yes/no), appendectomy (yes/no), physical activity (quintiles MET-hrs/wk), smoking status (never, past, or current), regular NSAID use (yes/no), and fruits & vegetables (quintiles servings/day). [a]Additionally adjusted for fiber intake (quintiles g/day). [b]Additionally adjusted for red meat intake (quintiles servings/day) and n3:n6 PUFA (quintiles). [c]Protective factor; HR for lowest quintile and P_{trend} provided. [d]Risk factor; HR for highest quintile and P_{trend} provided. PAR calculations adjusted for age (<40, 40 ≤ age <60, ≥ 60 years), cohort (NHS, NHSII, HPFS), and other covariates as per Cox models. Indicator variables with HR<1 excluded from PAR analysis. **aHR** Multivariable-adjusted Hazard Ratio. **BMI** Body mass index. **CI** Confidence Interval. **NSAID** Non-steroidal anti-inflammatory drug. **PAR** Population Attributable Risk. **PUFA** Polyunsaturated fatty acid.

Table S8. E-values to assess minimum aHR that an unmeasured confounder would need to have with both the exposure and outcome to fully explain the observed relationships between CD- and UC-MRS and CD and UC, respectively.

CD-MRS	aHR	LL 95% CI	E-Value for aHR	E-Value for LL
CD-MRS 0-1	1.00	--	Ref	--
CD-MRS ≥ 2	1.85	1.12	3.10	1.49
CD-MRS = 2	1.24	0.68	1.79	1.00
CD-MRS = 3	1.76	1.04	2.92	1.24
CD-MRS = 4	1.92	1.13	3.25	1.51
CD-MRS = 5	2.53	1.44	4.50	2.24
CD-MRS = 6	4.15	1.95	7.77	3.31
UC-MRS				
UC-MRS 0-2	1.00	--	Ref	--
UC-MRS ≥ 3	1.92	1.08	3.25	1.37
UC-MRS = 3	1.43	0.76	2.21	1.00
UC-MRS = 4	1.97	1.10	3.35	1.43
UC-MRS = 5	1.90	1.06	3.21	1.31
UC-MRS = 6	2.78	1.47	5.00	2.30

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