Supplementary Methods

Supplementary Methods: Detailed exclusion criteria for NIH-AARP

A total of 566,398 respondents completed the baseline questionnaire and provided informed consent. We excluded from analysis participants who responded by proxy (N = 15,760), had a self-reported (N = 49,318) or Surveillance, Epidemiology, and End Results (SEER) registry ascertained (N = 2,007) CRC or other cancer diagnosis before study entry, had self-reported end-stage renal disease (N = 997), had death-only ascertainment of CRC (N = 912) or other cancers (N = 4,017), had implausible total energy intakes (< 500 or > 6,000 kcal/day; N = 6,240) estimated from the Diet History Questionnaire (DHQ), skipped > 15% of the DHQ questions (N = 4,346), had missing self-reported height/weight (N = 11,009) or height/weight > 3 interquartile ranges outside the 75th and 25th percentiles (N = 818; (1)), or had other missing lifestyle questions (N = 7,509). The final analytic sample size was 453,465.

Supplementary Methods: Outcome Ascertainment

We defined incident CRC cases according to *International Classification of Diseases for Oncology* codes C180-C189, C199, C209, and C260.

Supplementary Methods: Description of the DIS and LIS

Briefly, the 19 and four components of the DIS and LIS, respectively, were determined and grouped *a priori*, based on prior literature, biological plausibility, and ease of re-creating them using a variety of FFQs used in major epidemiologic studies, using Block 98 FFQ (2) and lifestyle questionnaire responses (Table S1) in a diverse subset (N = 639) of participants in the previously-described REasons for Geographic and Racial Differences in Stroke Study

(REGARDS) cohort (3,4). REGARDS is a national, on-going prospective cohort study that recruited 30,239 male, female, white, and black participants ≥ 45 years old from the 48 contiguous states of the United States, intiated January 2003 – October 2007, with oversampling of black and Southeastern US residents. We excluded from the analytic sample participants with circulating CRP concentrations > 10 mg/dL, extreme outlying values for other inflammation biomarker concentrations, implausible energy intakes (< 500 or > 6,000 kcal/day), > 10% missing FFQ items, ≥ 2 comorbidities, end-stage renal disease, and age ≥ 75 years.

Weights for the DIS and LIS components were calculated in REGARDS based on their multivariable-adjusted strengths of associations with an inflammation biomarker score. To create the biomarker score, for each participant, plasma inflammation biomarker concentrations were transformed by the natural logarithm, normalized, and then summed (high-sensitivity C-reactive protein (hsCRP), interleukin (IL)-6, IL-8, and IL-10 [the latter with a negative sign]). Next, each DIS component (all continuous) was standardized, by sex, to a mean of 0 and standard deviation of 1.0; indicator variables were created for the LIS components (all categorical). Then, associations of the DIS and LIS components with the biomarker score were estimated using multivariable linear regression. The β-coefficients from the score component-biomarker score associations were taken as the components' weights. When the DIS scoring procedures and weights were applied in three different external populations in which different Willett FFQ versions were used, the DIS was more strongly directly associated with circulating biomarkers of inflammation than was the DII or EDIP (5). The estimated associations of the DIS and LIS with inflammation biomarkers were similar across sex and race (5).

Supplementary Methods: Calculating the DIS and LIS in the NIH-AARP Diet and Health Study

In NIH-AARP, we standardized each food group and the supplement score, by sex, to a mean of 0 and standard deviation of 1.0 based on the baseline distribution among all participants; i.e.,

$$\frac{X - \mu}{\sigma}$$

where μ denotes the study population mean, σ denotes the study population standard deviation, and *X* denotes the participant's intake.

For the LIS, baseline smoking status was categorized as 'current' or 'former and never'. Baseline body mass index (BMI) was categorized as normal (18.5 – 24.99 kg/m2), overweight (25 – 29.99 kg/m2), or obese (BMI ≥ 30 kg/m2). Baseline heavy alcohol consumption for men and women was defined as > 2 or > 1 drinks/day, respectively; moderate consumption was defined as individuals consuming alcohol in less than these amounts. For physical activity, we categorized participants as those who did not or rarely exercised, exercised 1 – 2 times/week, or exercised ≥ 3 times/wk.

Supplementary Methods: Statistical Analyses

Prior to conducting the Cox proportional hazards regression, we assessed the proportional hazards assumption by calculating Martingale and Schoenfeld residuals, testing time-dependent covariates, and inspecting log(-log) survival curves for each variable in the model. Variables that violated the proportional hazards assumptions were included in the SAS *STRATA* statement in all models and are listed in the table footnotes. We ruled out multicollinearity considering a condition index ≥ 30 and a variance decomposition proportion ≥ 0.5 as evidence of multicollinearity.

Potential confounders were based on biological plausibility, previous literature on their associations with CRC, inflammation, or dietary and lifestyle exposures, and causal diagrams. Covariates considered for all models included age, sex, race, education, marital status, comorbidities (self-reported gallbladder disease, heart disease, emphysema, or diabetes mellitus), hormone replacement therapy use (among women), family history of CRC in a first degree relative, self-reported history of colon polyps, and total energy intake. Covariates considered for the DIS models also included individual covariates for smoking status, BMI, alcohol intake, and physical activity since they are strong CRC risk factors with hypothesized contributions to colorectal carcinogenesis through inflammation plus other independent pro- or anti-carcinogenic pathways. Covariates considered for the LIS models included former smoking status since the LIS only includes current smoking at baseline as a component, and former tobacco smoking is also associated with CRC risk. LIS models also included the equally-weighted DIS, since the 19 DIS components individually are weak CRC risk factors, to account for the components inflammation plus other colorectal carcinogenic-related effects, and to reduce model size (including the score components individually or collectively in the equally-weighted dietary inflammation score yielded no substantial differences in our estimated LIS-CRC association estimated HRs). We also considered adjustment for regular aspirin and other NSAID use in the subset of the cohort that completed RFQs 6 months from baseline, and adjustment for colonoscopy screening over follow-up in the subset that completed follow-up questionnaires from 2004 – 2005; however, adjustment for these covariates did not materially change the estimated DIS/LIS-CRC associations.

We also investigated potential effect modification by conducting separate analyses for the DIS and LIS within categories of age (< / ≥ 65 years), sex and hormone replacement therapy use (among women), race (white, black, or other), baseline comorbidity (yes/no), family history of CRC in a first degree relative (yes/no), and for the DIS, baseline smoking status (never, former, or current), BMI (normal, overweight, or obese), baseline alcohol intake (non-drinker, moderate drinker, or heavy drinker), and baseline physical activity (exercises never or rarely, 1 – 3 times/week, ≥ 3 times/week). In a subset of the cohort that completed RFQs 6 months from their baseline questionnaire, we conducted analyses within strata of regular aspirin or other NSAID use (≥ once/week). In the subset that completed follow-up questionnaires from 2004 – 2005, we excluded participants who were diagnosed with CRC or were otherwise censored prior to 2004, and conducted analyses within strata of time since their last colonoscopy during follow up (never, < 5 years ago, ≥ 5 years ago). We assessed effect modification by comparing the stratum-specific estimates and by calculating Wald test p-values for model interaction terms.

To test statistically for heterogeneity by CRC site, we conducted a case-only analysis using multivariable logistic regression. The dependent variable was the CRC subtype (i.e., colon, left colon, right colon, and rectum/rectosigmoid cancer) with rectum/rectosigmoid cancer as the referent group. The independent variables were the DIS and LIS modeled continuously, with the same covariates as in the Cox proportional hazards models plus person-time (years of follow-up). We took the *P*-value for the continuous DIS and LIS to be the $P_{\text{heterogeneity}}$.

Supplementary Methods: Sensitivity Analyses, Expanded with Rationales

To assess the sensitivity of the associations to various considerations, we repeated the analyses with the following variations. First, to explore potential differences in inflammation-related vs. total contributions of the aggregated score components to risk, we constructed equally-weighted DIS and LIS versions by assigning positive or negative equal weights to dietary/lifestyle components we hypothesized *a priori* to be pro-inflammatory or anti-inflammatory, respectively. Second, to rule out a substantial influence of the the supplement score component in our DIS, we calculated a DIS without Supplementary micronutrients and assessed its association with CRC. Third, we calculated a reverse-direction Healthy Eating Index-2015 (reverse HEI-2015; i.e., so a higher score would be higher risk) (6), and the empirical dietary inflammatory pattern (EDIP), as described by Tabung et al. (7), and investigated their associations with CRC. Fourth, we investigated associations of each individual lifestyle component with CRC. Fifth, we excluded individuals who died or were diagnosed with CRC within two years from baseline to rule out spurious effects on risk estimates by participants with an undiagnosed CRC or morbid illness that may have affected their long-term diets or lifestyles at the time of questionnaire completion.

References for Supplementary Methods

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Supplementary Tables

Supplementary Table 1. Components of the dietary (DIS) and lifestyle (LIS) inflammation scores and their rationales for inclusion

Components	Rationales for inclusion
LIS components*	
Overweight BMI	Adipose tissue synthesizes and releases pro-inflammatory adipokines, such as PA-1 and TNF-α (1,2)
Obese BMI	Mechanisms similar to those described above
Heavy drinker	Heavy alcohol intake results in oxidative stress via oxidation of ethanol to acetaldehyde (3,4)
Moderate drinker	A metabolite of ethanol is acetate, which can acutely lower pro-inflammatory free fatty acid concentrations; moderate alcohol intake increases serum adiponectin concentrations (an anti-inflammatory inflammation biomarker) (5) and inhibits IL-6 production and activity (6)
Moderately physically active	Physical activity improves systemic plasma antioxidant capacity (increases adaptive responses to oxidative stress), increases concentrations of anti-inflammatory cytokines, and lowers vascular wall inflammation (2,7)
Heavily physically active	Mechanisms similar to those described above
Current smoker	Toxins injure tissues, upregulating cytokines and acute phase reactants (8)
DIS components*	
Leafy greens and cruciferous vegetables	Contain variety of potent antioxidants (e.g., β-carotene, folacin, magnesium, calcium, glucosinolates, isothiocyanates, lutein, and indoles); contain flavonoids and polyphenols, which activate the transcription factor, Nrf2, which plays a key role in cellular protection against oxidative stress and inflammation (9,10, 19,11–18)
Tomatoes	Contain β-carotene, vitamin C, and lycopene, the latter of which is a potent singlet oxygen quencher and one of the most powerful antioxidants among the natural carotenoids (20–23)
Apples and berries	Contain flavonoids (e.g., anthocyanins, quercetin, and phenolic acids) that suppress pro-inflammatory cytokine production and are powerful antioxidants; potentially increase postprandial plasma antioxidant capacity (24–26)
Deep yellow or orange vegetables and fruit	Contain pro-vitamin A carotenoids (e.g., β-carotene and α-carotene), which have a conjugated double-bond structure making them strong antioxidants (27)
Other fruits and real fruit juices	Contain antioxidants (e.g., flavonoids, such as hesperidin, naringenin, neohesperidin, limonene, vitamin C, β-cryptoxanthin, plant sterols, salicylates, naringin, nobelitin, and narirutin) with similar mechanisms to those described above (13,28–35)
Other vegetables	Contain antioxidants and polyphenols with similar mechanisms to those described above

Legumes	Contain folacin, iron, isoflavones, protein, vitamin B6, and have a high antioxidant capacity; rich in fiber, which is associated with beneficial alterations to the gut microbiota, reducing immune response in the gut (12,36,37)
Fish	Contain Ω-3 fatty acids, which compete with pro-inflammatory Ω-6 fatty acids by synthesizing eicosanoids and suppress the capacity of monocytes to synthesize IL-1β and TNF-α (38–40)
Poultry	Inversely associated with inflammation markers (41); contain low amounts of saturated fat (42); contain l-arginine, which improves endothelium-dependent dilation (precursor of the endogenous vasodilator nitric oxide) and decreases platelet aggregation and monocyte adhesion (12)
Red and organ meats	Contain heme iron, which increases the bioavailability of iron, which in turn increases oxidative stress; contain Ω-6 fatty acids, which increase oxidative stress through free radical production and are converted to arachidonic acid which stimulates expression of IL-1β and TNF-α in monocytes, and IL-6 and IL-8 in endothelial cells (43–45); contain saturated fats that mimic lipopolysaccharide, a pro-inflammatory stimulant, in the gut, and increase cytotoxic, pro-oxidant, and pro-inflammatory bile acids in the colon (43,46)
Processed meats	Contain heme iron, higher saturated fat contents, Ω-6 fatty acids (see above), and additives, such as nitrites, with suspected pro-inflammatory properties (41,47)
Added sugars	Sparse in nutrients; induce postprandial hyperglycemia, which act as stressful stimuli through subsequent repeated mild postprandial hypoglycemia (48) and reduce nitric oxide availability (plays role in regulation of inflammatory response (49)); elevate pro-inflammatory free fatty acid levels (40); produce oxidative stress through oxidation of membrane lipids, proteins, lipoproteins, and DNA (50)
High-fat dairy	Contains calcium, which binds bile acids and free fatty acids, decreasing oxidative damage in the gut; dairy fat contains fatty acids with potential inflammation-reducing properties, such as CLA, cis- and trans-palmitoleic acid, butyric acid, phytanic acid, and alpha-linolenic acid (51–53)
Low-fat dairy	Similar mechanisms to high-fat dairy (see above), with lower fat content
Coffee and tea	Tea contains flavonoids and antioxidants (e.g., epicatechin and quercetin) (54); coffee contains phytochemicals and antioxidants, such as javamide; both coffee and tea contain varying amounts of caffeine which inhibit secretion of IL-1β induced by adenine and N4-acetylcytidine (36,55)
Nuts	Contain Ω-3 fatty acids (38, 40,56,57) and l-arginine (12) (mechanisms similar to those described above in ‘Fish’ and ‘Poultry’)
Other fats	Contain Ω-6 fatty acids and saturated fats (see ‘red and organ meats’ above)

Refined grains and starchy vegetables	Some processed grains contain emulsifiers, which potentially break down mucin in the gut leading to inflammation (58); and induce hyperglycemia (mechanisms described similar to those described above in 'Added Sugars')
Supplement score[†]	Comprises micro-nutrients, minerals, and vitamins solely from supplement intakes, some with similar mechanisms to those described above (e.g., iron as pro-oxidant, vitamins A, C, and E as antioxidants)

Abbreviations: BMI, body mass index; CLA, conjugated linoleic acids; DIS, dietary inflammation score; hsCRP, high-sensitivity C-reactive protein; IL, interleukin; LIS, lifestyle inflammation score; METs, metabolic equivalents of task; Nrf2, Nuclear factor-erythroid 2 (NF-E2)-related factor 2; NSAID, nonsteroidal anti-inflammatory drug; PA1, plasminogen activator inhibitor–1; TNF, tumor necrosis factor

* Weights are β coefficients from multivariable linear regression models conducted in a subset of the REGARDS cohort study (n = 639), and represent the average change in an inflammation biomarker score (sum of z-scores for circulating hsCRP, IL-6, IL-8, and IL-10 [the latter with a negative sign]) concentrations per one standard deviation increase in a dietary component or the presence of lifestyle component. Covariates in the final model to develop the weights included: age, sex, race (Black or White), education (high school graduate or less vs. some college or more), region (stroke belt, stroke buckle, or other region in the US), a comorbidity score (comprises a history of cancer, heart disease, diabetes mellitus, or chronic kidney disease), hormone replacement therapy (among women), total energy intake (kcal/day), season of baseline interview (Spring, Summer, Fall, or Winter), and regular use of aspirin, other non-steroidal anti-inflammatory drugs or lipid-lowering medications (≥ twice/wk); and all the dietary/lifestyle components in the DIS and LIS. For the NIH-AARP study, all dietary components were standardized based on their sex-specific distributions in the analytic cohort at baseline, and all lifestyle components were dummy variables.

† All vitamin and mineral supplement intakes measured (from multivitamin/mineral and individual supplements) were ranked into quantiles of intake and assigned a value of 0 (low or no intake), 1, or 2 (highest intake) for hypothesized anti-inflammatory supplements (e.g., vitamin E), and 0 (low or no intake), -1, or -2 (highest intake) for hypothesized pro-inflammatory supplements (e.g., iron)

Supplementary Table 2. Associations of the dietary (DIS) and lifestyle (LIS) inflammation scores* with incident colorectal cancer by selected characteristics; the NIH-AARP Diet and Health Study (NIH-AARP; n = 453,465), 1995 – 2011

Characteristics	No. cases	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P_{trend}	$P_{interaction}$ †
DIS, ‡								
Age, y								
< 65	5,567	1.00 (Referent)	1.01 (0.92, 1.10)	1.04 (0.95, 1.14)	1.06 (0.97, 1.16)	1.24 (1.14, 1.36)	<0.001	
≥ 65	4,769	1.00 (Referent)	1.01 (0.92, 1.12)	1.07 (0.98, 1.18)	1.17 (1.07, 1.29)	1.29 (1.18, 1.42)	<0.001	0.64
HRT use and sex								
Men	6,905	1.00 (Referent)	1.04 (0.96, 1.12)	1.07 (0.99, 1.15)	1.10 (1.02, 1.19)	1.29 (1.19, 1.39)	<0.001	
Women on HRT	1,197	1.00 (Referent)	0.93 (0.78, 1.12)	1.01 (0.85, 1.22)	1.03 (0.85, 1.24)	1.25 (1.03, 1.51)	0.02	
Women not on HRT	2,234	1.00 (Referent)	0.98 (0.85, 1.13)	1.05 (0.91, 1.21)	1.19 (1.04, 1.37)	1.21 (1.05, 1.39)	0.001	0.33
Race								
White	9,546	1.00 (Referent)	1.01 (0.94, 1.08)	1.05 (0.98, 1.12)	1.10 (1.03, 1.17)	1.26 (1.18, 1.35)	<0.001	
Black	396	1.00 (Referent)	1.11 (0.70, 1.76)	1.23 (0.78, 1.92)	1.44 (0.94, 2.19)	1.31 (0.87, 1.97)	0.14	
Other	394	1.00 (Referent)	0.93 (0.63, 1.38)	1.00 (0.69, 1.45)	1.36 (0.95, 1.96)	1.05 (0.72, 1.52)	0.34	0.28
Comorbidity‖								
No	7,047	1.00 (Referent)	1.05 (0.97, 1.13)	1.08 (1.00, 1.16)	1.14 (1.06, 1.24)	1.28 (1.19, 1.39)	<0.001	
Yes	3,289	1.00 (Referent)	0.94 (0.83, 1.05)	1.02 (0.91, 1.15)	1.05 (0.94, 1.18)	1.21 (1.08, 1.36)	<0.001	0.36
Family history of CRC¶								
No	8,868	1.00 (Referent)	1.01 (0.94, 1.08)	1.06 (0.99, 1.13)	1.12 (1.05, 1.20)	1.26 (1.18, 1.35)	<0.001	
Yes	1,019	1.00 (Referent)	1.00 (0.82, 1.23)	0.95 (0.77, 1.16)	1.00 (0.81, 1.23)	1.22 (0.99, 1.50)	0.08	0.78
Tobacco use								
Non-smoker	3,251	1.00 (Referent)	0.96 (0.86, 1.08)	1.03 (0.92, 1.15)	1.07 (0.96, 1.20)	1.20 (1.07, 1.34)	<0.001	
Former smoker	5,792	1.00 (Referent)	1.06 (0.98, 1.16)	1.09 (1.00, 1.19)	1.16 (1.07, 1.27)	1.37 (1.26, 1.49)	<0.001	
Current smoker	1,293	1.00 (Referent)	0.86 (0.68, 1.09)	0.93 (0.74, 1.16)	0.90 (0.73, 1.11)	0.98 (0.80, 1.19)	0.70	0.28
BMI, kg/m_2								
18.5 – 24.99	3,181	1.00 (Referent)	1.07 (0.95, 1.19)	0.99 (0.88, 1.11)	1.11 (0.99, 1.25)	1.29 (1.15, 1.45)	<0.001	
25 – 29.99	4,619	1.00 (Referent)	0.92 (0.84, 1.02)	1.07 (0.98, 1.18)	1.13 (1.03, 1.24)	1.25 (1.14, 1.37)	<0.001	
≥ 30	2,515	1.00 (Referent)	1.13 (0.98, 1.29)	1.11 (0.97, 1.27)	1.09 (0.95, 1.25)	1.26 (1.11, 1.44)	0.002	0.26
Alcohol use#								
Non-drinker	2,408	1.00 (Referent)	1.07 (0.92, 1.24)	1.00 (0.87, 1.16)	1.15 (1.00, 1.33)	1.30 (1.13, 1.49)	<0.001	
Moderate drinker	6,907	1.00 (Referent)	1.01 (0.93, 1.09)	1.08 (1.00, 1.17)	1.08 (1.00, 1.17)	1.23 (1.14, 1.34)	<0.001	
Heavy drinker	1,021	1.00 (Referent)	1.00 (0.80, 1.25)	1.00 (0.80, 1.25)	1.30 (1.05, 1.61)	1.48 (1.20, 1.83)	<0.001	0.21
Physical activity								
Rarely or never exercises	2,069	1.00 (Referent)	0.82 (0.68, 0.98)	0.93 (0.79, 1.11)	0.96 (0.81, 1.13)	1.09 (0.93, 1.28)	0.01	
Exercises 1 – 2 times/wk	3,717	1.00 (Referent)	1.01 (0.90, 1.14)	0.99 (0.89, 1.11)	1.08 (0.97, 1.21)	1.20 (1.07, 1.34)	<0.001	
Exercises ≥ 3 times/wk	4,550	1.00 (Referent)	1.06 (0.97, 1.16)	1.11 (1.01, 1.22)	1.17 (1.06, 1.28)	1.35 (1.22, 1.48)	<0.001	0.27

Take aspirin ≥ once/wk**								
No	3,913	1.00 (Referent)	1.06 (0.95, 1.18)	1.07 (0.96, 1.20)	1.23 (1.11, 1.37)	1.34 (1.21, 1.49)	<0.001	
Yes	2,541	1.00 (Referent)	1.06 (0.93, 1.20)	1.19 (1.05, 1.35)	1.12 (0.98, 1.28)	1.35 (1.18, 1.54)	<0.001	0.27
Take NSAID ≥ once/wk**								
No	5,238	1.00 (Referent)	1.04 (0.95, 1.14)	1.09 (0.99, 1.19)	1.18 (1.08, 1.29)	1.35 (1.23, 1.48)	<0.001	
Yes	1,204	1.00 (Referent)	1.07 (0.88, 1.31)	1.30 (1.08, 1.58)	1.27 (1.04, 1.54)	1.30 (1.06, 1.59)	0.003	0.18
Had a colonoscopy††								
Never had one	920	1.00 (Referent)	1.15 (0.90, 1.46)	1.18 (0.93, 1.50)	1.24 (0.98, 1.56)	1.23 (0.98, 1.56)	0.08	
< 5 years ago	3,713	1.00 (Referent)	1.02 (0.92, 1.14)	1.04 (0.94, 1.16)	1.17 (1.05, 1.30)	1.32 (1.18, 1.47)	<0.001	
≥ 5 years ago	485	1.00 (Referent)	0.75 (0.54, 1.03)	0.85 (0.62, 1.17)	1.07 (0.78, 1.45)	1.43 (1.05, 1.93)	0.003	0.24
LIS, ‡‡								
Age, y								
< 65	5,567	1.00 (Referent)	1.21 (1.10, 1.33)	1.29 (1.18, 1.41)	1.34 (1.22, 1.46)	1.50 (1.37, 1.64)	<0.001	
≥ 65	4,769	1.00 (Referent)	1.05 (0.96, 1.15)	1.14 (1.04, 1.25)	1.11 (1.01, 1.22)	1.28 (1.16, 1.41)	<0.001	0.07
HRT use and sex								
Men	6,905	1.00 (Referent)	1.15 (1.06, 1.24)	1.29 (1.19, 1.39)	1.26 (1.16, 1.36)	1.49 (1.37, 1.62)	<0.001	
Women on HRT	1,197	1.00 (Referent)	1.11 (0.92, 1.34)	1.21 (1.03, 1.44)	1.40 (1.17, 1.67)	1.39 (1.16, 1.67)	<0.001	
Women not on HRT	2,234	1.00 (Referent)	1.10 (0.95, 1.27)	0.99 (0.86, 1.14)	1.04 (0.91, 1.19)	1.13 (0.99, 1.29)	0.23	0.001
Race								
White	9,546	1.00 (Referent)	1.13 (1.06, 1.21)	1.22 (1.15, 1.31)	1.24 (1.16, 1.32)	1.40 (1.31, 1.50)	<0.001	
Black	396	1.00 (Referent)	1.10 (0.73, 1.65)	0.99 (0.66, 1.50)	1.05 (0.71, 1.53)	1.22 (0.84, 1.78)	0.25	
Other	394	1.00 (Referent)	0.96 (0.70, 1.31)	1.11 (0.82, 1.50)	0.95 (0.69, 1.32)	1.23 (0.88, 1.71)	0.39	0.70
Comorbidity‖								
No	7,047	1.00 (Referent)	1.15 (1.06, 1.24)	1.21 (1.13, 1.31)	1.25 (1.16, 1.35)	1.44 (1.33, 1.56)	<0.001	
Yes	3,289	1.00 (Referent)	1.05 (0.93, 1.20)	1.19 (1.05, 1.35)	1.13 (1.00, 1.27)	1.26 (1.12, 1.42)	<0.001	0.18
Family history of CRC¶								
No	8,868	1.00 (Referent)	1.12 (1.05, 1.21)	1.19 (1.11, 1.28)	1.21 (1.13, 1.29)	1.38 (1.29, 1.49)	<0.001	
Yes	1,019	1.00 (Referent)	1.03 (0.83, 1.26)	1.22 (1.00, 1.49)	1.19 (0.98, 1.45)	1.30 (1.05, 1.60)	<0.001	0.43
Take aspirin ≥ once/wk**								
No	3,913	1.00 (Referent)	1.07 (0.97, 1.19)	1.19 (1.08, 1.32)	1.17 (1.05, 1.29)	1.29 (1.16, 1.43)	<0.001	
Yes	2,541	1.00 (Referent)	1.23 (1.08, 1.40)	1.32 (1.16, 1.51)	1.34 (1.18, 1.53)	1.42 (1.24, 1.63)	<0.001	0.40
Takes NSAID ≥ once/wk**								
No	5,238	1.00 (Referent)	1.11 (1.01, 1.21)	1.22 (1.12, 1.33)	1.24 (1.13, 1.35)	1.38 (1.26, 1.51)	<0.001	
Yes	1,204	1.00 (Referent)	1.24 (1.02, 1.51)	1.32 (1.09, 1.60)	1.26 (1.04, 1.52)	1.29 (1.06, 1.57)	<0.001	0.32
Had a colonoscopy††								
Never had one	920	1.00 (Referent)	1.22 (0.97, 1.53)	1.36 (1.09, 1.70)	1.42 (1.15, 1.76)	1.35 (1.07, 1.70)	<0.001	

< 5 years ago	3,713	1.00 (Referent)	1.18 (1.06, 1.30)	1.25 (1.13, 1.39)	1.26 (1.13, 1.39)	1.35 (1.21, 1.51)	<0.001	
≥ 5 years ago	485	1.00 (Referent)	1.06 (0.80, 1.41)	1.16 (0.88, 1.52)	1.08 (0.81, 1.43)	1.13 (0.83, 1.54)	0.44	0.68

Abbreviations: BMI, body mass index; CI, confidence interval; CRC, colorectal cancer; DIS, dietary inflammation score; HEI, Healthy Eating Index; HR, hazard ratio; HRT, hormone replacement therapy; LIS, lifestyle inflammation score; NSAID, non-steroidal anti-inflammatory drug; NIH-AARP, National Institutes of Health-American Association for Retired Persons Diet and Health Study

* Inflammation scores constructed as described in the text and Table 1; a higher score reflects a higher balance of pro-inflammatory exposures

† From interaction term in the full Cox proportional hazards regression model, calculated using the Wald test

‡ Covariates in the DIS Cox proportional hazards models were: age at entry (continuous), sex, race (Black, White, or other), education (less than high school and high school graduate, some college, or college graduate or higher), marital status (married or non-married), heart disease or history of stroke at baseline (yes/no), diabetes mellitus at baseline (yes/no), emphysema at baseline (yes/no), gallstone or gallbladder disease at baseline (yes/no), current hormone replacement therapy use (among women), family history of colorectal cancer in a first degree relative, history of colon polyp, smoking (current, former, or never), body mass index (in kg/m2; continuous), alcohol intake (non-drinker, moderate-drinker, or heavy-drinker), physical activity level (exercises not at all or rarely, 1 – 2, or ≥ 3 times/wk), and total energy intake (kcal/day); history of CRC in a first degree relative, self-reported heart disease diagnosis, age at entry, sex, and BMI were included in the SAS *STRATA* statement

|| Self-reported heart disease, diabetes mellitus, gallstone or gallbladder disease, or emphysema at baseline

¶ In a first degree relative

Heavy drinker defined as > 1 drink/day for women and > 2 drinks/day drinks for men; moderate drinker defined as 1 drink/day for women, 1 – 2 drinks/day for men

** Aspirin/other NSAID use was ascertained in a subset of the baseline cohort that completed follow-up and risk factor questionnaires (N = 284,211 and N = 283,295, respectively)

†† Colonoscopy history was assessed in remaining baseline cohort members from 2004 – 2005; CRC cases diagnosed prior to 01/01/2004 were excluded from colonoscopy history stratification

‡‡ Covariates in the LIS Cox proportional hazards models were: age at entry (continuous), sex, race (Black, White, or other), education (less than high school and high school graduate, some college, or college graduate or higher), marital status (married or non-married), heart disease or history of stroke at baseline (yes/no), diabetes mellitus at baseline (yes/no), emphysema at baseline (yes/no), gallstone or gallbladder disease at baseline (yes/no), current hormone replacement therapy use (among women), family history of colorectal cancer in a first degree relative, history of colon polyp, total energy intake (kcal/day), former smoker (yes/no), and the equally-weighted DIS; history of CRC in a first degree relative, self-reported heart disease diagnosis, age at entry, and sex were included in the SAS *STRATA* statement

Supplementary Table 3. Associations of the equally-weighted DIS* and LIS* with incident colorectal cancer in the NIH-AARP Diet and Health Study (NIH-AARP; n = 453,465), 1995 – 2011

Quintiles	Overall		Men		Women	
	DIS-equal weight†	LIS-equal weight‡	DIS-equal weight†	LIS-equal weight‡	DIS-equal weight†	LIS-equal weight‡
	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)
1	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
2	1.04 (0.98, 1.11)	1.17 (1.09, 1.26)	1.05 (0.97, 1.14)	1.17 (1.07, 1.28)	1.02 (0.91, 1.14)	1.19 (1.04, 1.35)
3	1.14 (1.07, 1.22)	1.24 (1.15, 1.34)	1.17 (1.08, 1.27)	1.27 (1.16, 1.39)	1.08 (0.96, 1.21)	1.19 (1.05, 1.36)
4	1.19 (1.11, 1.27)	1.36 (1.26, 1.47)	1.19 (1.10, 1.29)	1.40 (1.27, 1.54)	1.17 (1.04, 1.31)	1.28 (1.13, 1.47)
5	1.35 (1.26, 1.44)	1.55 (1.43, 1.68)	1.38 (1.27, 1.49)	1.64 (1.48, 1.82)	1.28 (1.14, 1.43)	1.40 (1.23, 1.61)

Abbreviations: BMI, body mass index; CI, confidence interval; CRC, colorectal cancer; DIS, dietary inflammation score; HR, hazard ratio; LIS, lifestyle inflammation score; NIH-AARP, National Institutes of Health-American Association for Retired Persons Diet and Health Study

* Dietary and lifestyle components of the equally-weighted inflammation scores are the same as those in the weighted scores (see text and Table 1); weights for all dietary and lifestyle components were equally assigned *a priori* (all in the same direction as the weights in Table 1); higher scores indicate a higher balance of pro- versus anti-inflammatory exposures

† Covariates in the DIS-equal weight Cox proportional hazards models were: age at entry (continuous), sex, race (Black, White, or other), education (less than high school and high school graduate, some college, or college graduate or higher), marital status (married or non-married), heart disease or history of stroke at baseline (yes/no), diabetes mellitus at baseline (yes/no), emphysema at baseline (yes/no), gallstone or gallbladder disease at baseline (yes/no), current hormone replacement therapy use (among women), family history of colorectal cancer in a first degree relative, history of colon polyp, smoking (current, former, or never), body mass index (in kg/m^2; continuous), alcohol intake (non-drinker, moderate-drinker, or heavy-drinker), physical activity level (exercises not at all or rarely, 1 – 2, or ≥ 3 times/wk), and total energy intake (kcal/day); history of CRC in a first degree relative, self-reported heart disease diagnosis, age at entry, sex, and BMI were included in the SAS *STRATA* statement

‡ Covariates in the LIS-weight Cox proportional hazards models were: age at entry (continuous), sex, race (Black, White, or other), education (less than high school and high school graduate, some college, or college graduate or higher), marital status (married or non-married), heart disease or history of stroke at baseline (yes/no), diabetes mellitus at baseline (yes/no), emphysema at baseline (yes/no), gallstone or gallbladder disease at baseline (yes/no), current hormone replacement therapy use (among women), family history of colorectal cancer in a first degree relative, history of colon polyp, total energy intake (kcal/day), former smoker (yes/no), and the equally-weighted DIS; history of CRC in a first degree relative, self-reported heart disease diagnosis, age at entry, and sex were included in the SAS *STRATA* statement

Supplementary Table 4. Associations of the DIS* without Supplemental micronutrients with incident colorectal cancer in the NIH-AARP Diet and Health Study (NIH-AARP; n = 453,465), 1995 – 2011

Quintiles		Overall	Men	Women
		Adjusted HR† (95% CI)	Adjusted HR† (95% CI)	Adjusted HR† (95% CI)
	1	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
	2	1.02 (0.96, 1.09)	1.04 (0.96, 1.12)	0.97 (0.87, 1.09)
	3	1.06 (1.00, 1.13)	1.10 (1.02, 1.19)	0.99 (0.88, 1.11)
	4	1.08 (1.01, 1.15)	1.10 (1.02, 1.19)	1.04 (0.93, 1.17)
	5	1.21 (1.14, 1.29)	1.24 (1.14, 1.34)	1.16 (1.04, 1.30)

Abbreviations: BMI, body mass index; CI, confidence interval; CRC, colorectal cancer; DIS, dietary inflammation score; HR, hazard ratio; LIS, lifestyle inflammation score; NIH-AARP, National Institutes of Health-American Association for Retired Persons Diet and Health Study

* Inflammation score constructed as described in the text and Table 1; a higher score reflects a higher balance of pro-inflammatory exposures

† Covariates in the DIS Cox proportional hazards models were: age at entry (continuous), sex, race (Black, White, or other), education (less than high school and high school graduate, some college, or college graduate or higher), marital status (married or non-married), heart disease or history of stroke at baseline (yes/no), diabetes mellitus at baseline (yes/no), emphysema at baseline (yes/no), gallstone or gallbladder disease at baseline (yes/no), current hormone replacement therapy use (among women), family history of colorectal cancer in a first degree relative, history of colon polyp, smoking (current, former, or never), body mass index (in kg/m2; continuous), alcohol intake (non-drinker, moderate-drinker, or heavy-drinker), physical activity level (exercises not at all or rarely, 1 – 2, or ≥ 3 times/wk), total energy intake (kcal/day), supplemental micronutrient score (calculated as described in Table 1); history of CRC in a first degree relative, self-reported heart disease diagnosis, age at entry, sex, and BMI were included in the SAS *STRATA* statement

Supplementary Table 5. Associations of the reverse HEI-2015* and the EDIP* with incident colorectal cancer overall, and by sex; the NIH-AARP Diet and Health Study (NIH-AARP; n = 453,465), 1995 – 2011

	Overall		Men		Women	
	HEI-2015†	EDIP‡	HEI-2015†	EDIP‡	HEI-2015†	EDIP‡
Quintiles	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)
1	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
2	1.07 (1.00,1.14)	1.06 (0.99,1.13)	1.06 (0.98,1.15)	1.09 (1.01,1.18)	1.07 (0.95,1.20)	0.99 (0.88,1.11)
3	1.15 (1.08,1.23)	1.07 (1.01,1.14)	1.17 (1.08,1.26)	1.08 (1.00,1.17)	1.11 (0.99,1.24)	1.06 (0.95,1.18)
4	1.21 (1.13,1.29)	1.09 (1.02,1.16)	1.24 (1.15,1.34)	1.07 (0.99,1.15)	1.14 (1.02,1.28)	1.13 (1.01,1.26)
5	1.36 (1.27,1.45)	1.07 (1.00,1.14)	1.37 (1.26,1.48)	1.08 (1.00,1.16)	1.35 (1.21,1.51)	1.05 (0.94,1.17)

Abbreviations: CI, confidence interval; DIS, dietary inflammation score; EDIP, empirical dietary inflammation index; HEI, Healthy Eating Index 2015; HR, hazards ratio; LIS, lifestyle inflammation score; NIH-AARP, National Institutes of Health-American Association for Retired Persons Diet and Health Study

* The HEI was constructed as described by Krebs-Smith et al.(3), but the scoring was reversed such that a lower score was considered potentially higher risk; the EDIP was constructed as described by Tabung et al.(60) based on servings of intake

† Covariates in the HEI Cox proportional hazards models were: age at entry (continuous), sex, race (Black, White, or other), education (less than high school and high school graduate, some college, or college graduate or higher), marital status (married or non-married), heart disease or history of stroke at baseline (yes/no), diabetes mellitus at baseline (yes/no), emphysema at baseline (yes/no), gallstone or gallbladder disease at baseline (yes/no), current hormone replacement therapy use (among women), family history of colorectal cancer in a first degree relative, history of colon polyp, smoking (current, former, or never), body mass index (in kg/m2; continuous), alcohol intake (non-drinker, moderate-drinker, or heavy-drinker), physical activity level (exercises not at all or rarely, 1 – 2, or ≥ 3 times/wk), and total energy intake (kcal/day); history of CRC in a first degree relative, self-reported heart disease diagnosis, age at entry, sex, and BMI were included in the SAS *STRATA* statement

‡ Covariates in the EDIP Cox proportional hazards models included those described in footnote 'b', except for alcohol intake

Supplementary Table 6. Associations of the individual components of the lifestyle inflammation score (LIS) with incident colorectal cancer overall, and by sex; the NIH-AARP Diet and Health Study (NIH-AARP; n = 453,465), 1995 – 2011

	Overall	Men	Women
Lifestyle factor*	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)
Body mass index†			
Overweight vs. normal	1.11 (1.06, 1.16)	1.14 (1.07, 1.20)	1.07 (0.99, 1.16)
Obese vs. normal	1.24 (1.18, 1.31)	1.30 (1.21, 1.39)	1.15 (1.05, 1.26)
Physical activity level			
Exercises 1 – 2 times/wk vs. rarely/never exercises	0.92 (0.87, 0.98)	0.92 (0.85, 0.98)	0.93 (0.85, 1.01)
Exercises ≥ 3 times/wk vs. rarely/never exercises	0.85 (0.81, 0.90)	0.83 (0.78, 0.89)	0.88 (0.80, 0.96)
Alcohol use‡			
Moderate drinker vs. non-drinker	1.02 (0.98, 1.07)	1.02 (0.96, 1.08)	1.04 (0.96, 1.12)
Heavy drinker vs. non-drinker	1.23 (1.14, 1.33)	1.29 (1.17, 1.42)	1.13 (1.00, 1.28)
Smoking status			
Current smoker vs. never smoker	1.29 (1.21, 1.38)	1.20 (1.13, 1.27)	1.35 (1.22, 1.49)
Former smoker vs. never smoker	1.20 (1.15, 1.26)	1.25 (1.14, 1.36)	1.19 (1.10, 1.28)

Abbreviations: CI, confidence interval; DIS, dietary inflammation score; HR, hazards ratio; LIS, lifestyle inflammation score; NIH-AARP, National Institutes of Health-American Association for Retired Persons Diet and Health Study

* All lifestyle components were included in the Cox proportional hazards models and additionally included: age at entry (continuous), sex, race (Black, White, or other), education (less than high school and high school graduate, some college, or college graduate or higher), marital status (married or non-married), heart disease or history of stroke at baseline (yes/no), diabetes mellitus at baseline (yes/no), emphysema at baseline (yes/no), gallstone or gallbladder disease at baseline (yes/no), current hormone replacement therapy use (among women), family history of colorectal cancer in a first degree relative, history of colon polyp, total energy intake (kcal/day), former smoker (yes/no), and the equally-weighted DIS; history of CRC in a first degree relative, self-reported heart disease diagnosis, age at entry, and sex were included in the SAS *STRATA* statement

† Normal BMI: 18.5 – 24.99 kg/m$_2$; Overweight BMI: 25 – 29.99 kg/m$_2$; Obese BMI: ≥ 30 kg/m$_2$

‡ Moderate drinker: 1 – 7 drinks/wk for women, 1 – 14 drinks/wk for men; heavy drinker: > 7 drinks/wk for women, > 14 drinks/wk drinks for men

Supplementary Table 7. Sensitivity analyses for the associations of the DIS and LIS with incident colorectal cancer in the NIH-AARP Diet and Health Study (NIH-AARP; n = 453,465), 1995 – 2011, excluding those who died or were diagnosed with CRC within two years from baseline

Score form	Inflammation score*	
	DIS†	LIS‡
	Adjusted HR (95% CI)	Adjusted HR (95% CI)
Continuous	1.04 (1.03, 1.05)	1.16 (1.12, 1.19)
Quintiles		
1	1.00 (Referent)	1.00 (Referent)
2	1.02 (0.95, 1.09)	1.12 (1.05, 1.20)
3	1.07 (1.00, 1.14)	1.18 (1.11, 1.27)
4	1.12 (1.05, 1.20)	1.21 (1.13, 1.29)
5	1.27 (1.18, 1.35)	1.37 (1.28, 1.47)

Abbreviations: CI, confidence interval; DIS, dietary inflammation score; HR, hazards ratio; LIS, lifestyle inflammation score; NIH-AARP, National Institutes of Health-American Association for Retired Person Diet and Health Study

* Inflammation scores constructed as described in the text and Table 1; a higher score reflects a higher balance of pro-inflammatory exposures

† Covariates in the DIS Cox proportional hazards models were: age at entry (continuous), sex, race (Black, White, or other), education (less than high school and high school graduate, some college, or college graduate or higher), marital status (married or non-married), heart disease or history of stroke at baseline (yes/no), diabetes mellitus at baseline (yes/no), emphysema at baseline (yes/no), gallstone or gallbladder disease at baseline (yes/no), current hormone replacement therapy use (among women), family history of colorectal cancer in a first degree relative, history of colon polyp, smoking (current, former, or never), body mass index (in kg/m^2; continuous), alcohol intake (non-drinker, moderate-drinker, or heavy-drinker), physical activity level (exercises not at all or rarely, 1 – 2, or ≥ 3 times/wk), and total energy intake (kcal/day); history of CRC in a first degree relative, self-reported heart disease diagnosis, age at entry, sex, and BMI were included in the SAS *STRATA* statement

‡ Covariates in the LIS Cox proportional Hazards models were: age at entry (continuous), sex, race (Black, White, or other), education (less than high school and high school graduate, some college, or college graduate or higher), marital status (married or non-married), heart disease or history of stroke at baseline (yes/no), diabetes mellitus at baseline (yes/no), emphysema at baseline (yes/no), gallstone or gallbladder disease at baseline (yes/no), current hormone replacement therapy use (among women), family history of colorectal cancer in a first degree relative, history of colon polyp, total energy intake (kcal/day), former smoker (yes/no), and the equally-weighted DIS; history of CRC in a first degree relative, self-reported heart disease diagnosis, age at entry, and sex were included in the SAS *STRATA* statement

Supplementary Table 8. Comparison of components and derivations of previously developed dietary and lifestyle inflammation scores (DII, EDIP, DIS, and LIS)

Description	Inflammation score			
	DII (61)	EDIP (4)	DIS*	LIS*
Anti-inflammatory components	Alcohol, β-carotene, caffeine, dietary fiber, folic acid, magnesium, thiamin, riboflavin, niacin, zinc, monounsaturated fats, polyunsaturated fats, Ω-3 fatty acids, Ω-6 fatty acids, selenium, isoflavones, flavan-3-ol, flavones, flavanols, flavanones, anthocyanins, green or black tea, garlic, onion, turmeric, thyme & oregano, pepper, rosemary, eugenol, ginger, saffron, and vitamins A, B-6, C, D, & E	Beer, wine, tea, coffee, dark-yellow vegetables, leafy green vegetables, snacks, fruit juice, and pizza	Leafy greens, tomatoes, apples and berries, deep yellow or orange vegetables and fruit, other fruits and real fruit juices, other vegetables, legumes, fish, poultry, high- and low-fat dairy, coffee and tea, nuts, supplement score	Moderate alcohol intake, moderate or heavy physical activity
Pro-inflammatory components	Vitamin B-12, iron, trans fat, carbohydrates, cholesterol, total energy intake, protein, saturated fat, and total fat	Processed meats, red meat, organ meat, fish (other than dark-meat fish), other vegetables (e.g., celery, mushrooms, green peppers, etc.), refined grains, high-energy beverages, low-energy beverages, and tomatoes	Red and organ meats, processed meats, added sugars, other fats, refined grains and starchy vegetables	Heavy alcohol intake, current tobacco use, overweight BMI, obese BMI
Derivation approach	Performed literature review of observational associations/intervention effects of 45 dietary components (mainly nutrients) with inflammation biomarkers	Used reduced rank regression to identify linear function of food groups that explain the most variation in inflammation biomarkers measured in subset of the Nurses' Health Study	Dietary components selected and grouped based on hypothesized contributions to inflammation; used multivariable linear regression to calculate β coefficients representing the average change in summary inflammation biomarker score per one standard deviation increase in a dietary component	Lifestyle components selected based on previous literature and biological plausibility (3–8,63); used multivariable linear regression to calculate β coefficients representing the average change in summary inflammation biomarker score with the presence of a lifestyle component
Inflammation biomarkers	IL-1β, IL-4, IL-6, IL-10, TNF-α, CRP	IL-6, TNF-α R2, CRP	IL-6, IL-8, IL-10, CRP	IL-6, IL-8, IL-10, CRP

Abbreviations: BMI, body mass index; CRP, C-reactive protein; DII, Dietary Inflammatory Index; DIS, Dietary Inflammation Score; EDIP, Empirical Dietary Inflammatory Pattern; IL, interleukin; LIS, lifestyle inflammation score; TNF-α R2, tumor necrosis factor-alpha receptor 2

* DIS and LIS components are defined in Table 1

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