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Doratha A. Byrd Date

Development and Validation of Novel Dietary and Lifestyle Inflammation Scores, and Their Associations with Risk for Colorectal Neoplasms

By

Doratha Byrd
Doctor of Philosophy

Epidemiology

_____
Roberd M. Bostick, M.D., M.P.H.
Advisor

_____
W. Dana Flanders, M.D., S.c.D.
Committee Member

_____
Veronika Fedirko, Ph.D., M.P.H.
Committee Member

_____
Terryl Hartman, Ph.D., M.P.H., R.D.
Committee Member

_____
Suzanne Judd, Ph.D.
Committee Member

Accepted:

_____
Lisa A. Tedesco, Ph.D.
Dean of the James T. Laney School of Graduate Studies

_____
Date

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By

Doratha A. Byrd
B.S., University of Florida, 2013
M.P.H., University of Florida, 2015

Advisor: Roberd M. Bostick, M.D., M.P.H.

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Development and Validation of Novel Dietary and Lifestyle Inflammation Scores, and Their Associations with Risk for Colorectal Neoplasms

By Doratha A. Byrd

Abstract

Chronically higher inflammation, which may partly result from diet and lifestyle, is implicated in risk for multiple chronic diseases, including colorectal cancer (CRC). The dietary inflammatory index (DII) and empirical DII (EDII), previously developed to characterize dietary contributions to systemic inflammation, have several limitations.

To better reflect dietary/lifestyle contributions to inflammation, we developed novel, dietary (DIS) and lifestyle (LIS) inflammation scores in a subset of the Reasons for Geographic and Racial Differences in Stroke Study. To do this, we selected *a priori* 19 food groups and four lifestyle characteristics to comprise the DIS and LIS, respectively, and calculated their weights based on their strengths of association with an inflammation biomarker score using multivariable linear regression. The sums of the weighted components constitute the scores. A higher score reflects, on balance, more pro-inflammatory exposures. To validate the scores, we calculated the DIS, LIS, DII, and EDII using cross-sectional data from three study populations with measured circulating inflammation biomarkers. We found that higher DIS and LIS were more strongly, directly associated with inflammation biomarker concentrations in the validation populations than were the DII and EDII, and that the DIS and LIS associations were particularly strong in combination.

We then investigated associations of the DIS and LIS with incident, sporadic colorectal adenoma in three pooled case-control studies. We found that those in the highest relative to the lowest quintiles of the DIS and LIS had statistically significant higher odds of adenoma. Associations were stronger for high-risk adenomas and for the scores in combination.

We then investigated associations of the DIS and LIS with incident CRC in a large, prospective cohort. We found that higher DIS and LIS were statistically significantly associated with higher risk for incident CRC. Associations were stronger among men, for colon cancers, and for the scores in combination.

Our results support that dietary and lifestyle exposures collectively contribute substantially to systemic inflammation, and support the use of our LIS and of our whole foods-based DIS over the DII and EDII. Our results also suggest that pro-inflammatory diets/lifestyles may be associated with higher risk for colorectal neoplasms.

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Chapter 1. Introduction and Background

Introduction

Deregulation of the inflammation response has been implicated repeatedly in the etiology of chronic diseases, such as atherosclerosis, cardiovascular disease, type-2 diabetes, and autoimmune diseases, and increasing evidence is uncovering the role of inflammation in cancer, particularly colorectal cancer (CRC). Importantly, sources of inflammation likely include lifestyle exposures such as diet, physical activity, alcohol intake, obesity, and smoking.

The contributions of most dietary and lifestyle exposures to inflammation individually are relatively small, but collectively they may be substantial. In order to address this issue, investigators have created questionnaire-based dietary and lifestyle exposure scores to better represent the aggregate of inflammatory exposures. Specifically, two indices were previously developed to characterize inflammation contributed from the diet, the dietary inflammatory index (DII) (1) and the empirical dietary inflammatory index (EDII) (2). Limitations of these indices include issues with reproducibility, generalizability, assumptions, and for the DII specifically, a heavy focus on nutrients.

To address these issues, as described herein, for my dissertation I focused on quantifying the contributions of an aggregate of whole-foods and lifestyle exposures toward systemic inflammation, as measured through biomarker indicators in human subjects, by developing novel whole foods-based, biomarker panel-weighted, dietary-specific (DIS), lifestyle-specific (LIS) inflammation scores based on the premise that focusing on whole foods, encompassing thousands of etiologically active substances (3), and other lifestyle exposures is more productive direction for epidemiologic research on the role of dietary/lifestyle exposures in inflammation and disease states. Additionally, I investigated the associations of the DIS and LIS with incident, sporadic adenoma in a pooled case-control study and incident CRC in a large, prospective cohort study.

Inflammation

Mechanisms

Inflammation is a complex biological response to harmful stimuli, occurring in the vascularized connective tissue. The ultimate goal of the inflammatory response is to eliminate causes of cell injury (e.g., harmful bacteria, pathogens, or other irritants) or the consequences of such injury (e.g., damaged cells or tissues), and initiate tissue repair. This occurs through the delivery of leukocytes to the site of infection or injury, achieved by increasing local blood flow and structural changes in the microvasculature to permit leukocyte emigration. These leukocytes ingest harmful agents, kill pathogens, and degrade necrotic tissue, and can prolong inflammation as needed by inflicting tissue damage and releasing enzymes, chemical mediators, and reactive oxygen species (ROS). The inflammatory response then activates a series of events that heal and reconstitute the damaged tissue, either by regeneration of native parenchymal cells and/or filling the defect with fibroblastic tissue (scarring). Given these vital functions, a controlled inflammation response is normally protective and beneficial; however, deregulated inflammation may be harmful and involved in the etiology of many acute and chronic diseases (4,5).

Inflammation can be broadly classified as acute or chronic. Acute inflammation is brief and is normally considered a protective reaction to injury, disease, or irritation of the tissues. Acute inflammation is characterized by redness, swelling, pain, loss of function, and/or a feeling of heat in an area of the body. When the release of pro-inflammatory molecules is sustained above what is needed for survival, chronic inflammation occurs. In contrast to acute inflammation, chronic, persistent, low-grade inflammation is asymptomatic and prolonged, during which time the body sends an inflammatory response to a perceived internal threat that may not require such response. A chronic inflammation response is characterized by higher circulating concentrations of pro-inflammatory molecules and/or a progressive shift in the type of cells present at sites of inflammation (the most important being monocytes and macrophages). Monocytes attracted to these sites prolong inflammation by transforming into phagocytic macrophages that are activated to continuously secrete a wide variety of biological products, such as enzymes, chemical

mediators, and free radicals, all of which result in tissue damage. The accumulation of these processes results in simultaneous destruction and healing of the tissue and the persistent presence of lymphocytes and macrophages, leading to potentially permanent tissue injury and fibrosis characteristic of chronic inflammation (4,5).

Mediators and Effectors of Inflammation

The inflammation response is complex and involves multiple mechanisms that complement or interact with one another, and an extensive network of mediators and cells (6). Multiple key mediators play a pivotal role in initiating and maintaining the inflammatory response; these generally have functions that include an increased vascular permeability, chemotaxis, leukocyte adhesion and activation, direct toxicity to invading organisms (or to the cells) and to the extracellular matrix, fibroblast proliferation, collagen deposition, angiogenesis, and maintenance of tissue homeostasis.

Some of the commonly known mediators of inflammation and their functions are listed below (4–6):

1) Vasoactive amines mediate vasodilation and vascular permeability. Local blood flow is critical to determining the amount of exudate produced at inflammation sites. These vasoactive amines include histamine and serotonin, which increase vascular permeability by inducing contraction of the endothelial cells, dilating capillaries, and allowing the passage of fluid and proteins through the opening of the inter-endothelial junctions.
2) Several proteolytic enzymes, such as elastin, cathespins, and matrix metalloproteinases (the latter degrades extracellular matrix (ECM) and basement-membrane proteins), in addition to kinins and clotting systems, have roles in host defense, tissue remodeling, and leukocyte migration.
3) Lipid mediators are generated from phospholipids. After metabolism by cyclooxygenase 1 and 2 (COX-1 and COX-2), arachidonic acid is a precursor to a wide variety of molecules, collectively termed eicosanoids, which mediate increased vascular permeability, chemotaxis, and leukocyte adhesion. These include: 1) leukotrienes, such as leukotriene B_4, which aids in chemotaxis of

neutrophils and increases vascular permeability in the presence of prostaglandin E_2 (PGE_2), and leukotriene D_4, which is involved in smooth muscle contraction and increases vascular permeability; 2) prostaglandins, such as PGI_2 and PGE_2, which are involved in vasodilation, increase the permeability effects of histamine, bradykinin, and leukotactic agents; and 3) lipoxins, which inhibit and promote resolution of inflammation, reduce excess tissue damage, and regulate components of the innate and adaptive immune system (7). Phosphatic acid, the precursor to platelet-activating factors (PAFs), is generated by the acetylation of lysophosphatidic acid. PAFs recruit leukocytes, aid in vasodilation and vasoconstriction, and increase vascular permeability and platelet activation.

4) One of the most prominent features of inflammation is an accumulation of monocytes in the tissues; leukocyte chemotaxis agents are key to these functions. Complement fragments, such as such as C3a, C4a, C5a, are cleaved to generate chemoattractant fragments and recruit monocytes to the site of inflammation.
5) Inflammation causes oxidative stress and vice versa. Oxidative stress is defined as the disruption of the balance of pro-oxidants to anti-oxidants. This imbalance leads to higher production of free radicals, ROS, or reactive nitrogen species (RNS), which in turn are damaging and result in an inflammatory response (8). For example, free radicals are chemical species with one or more unpaired electrons in its outer orbit, and can damage cells by inducing protein degradation and peroxidation of lipids in cell and organellar membranes resulting in interference of their function, and reacting with thymine in nuclear and mitochondrial DNA leading to single-stranded breaks in DNA (8,9). Examples of the role of oxidative stress in response to diet, and in carcinogenesis, are described in the sections below.
6) Most of the above described mechanisms result in the expression of chemokines (e.g., IL-8), which control leukocyte extravasation and chemotaxis, and cytokines. Cytokines have crucial roles in amplifying the cascade that elicits the inflammatory response, and are a heterogeneous group of soluble small polypeptides or glycoproteins, which exert pleiotropic effects that promote

growth, differentiation, and activation of normal cells. The body releases cytokines in response to harmful stimuli, which then act as a means of communication to amplify and generate the appropriate patterns of immunity, for instance coordinating the response of leukocytes and parenchymal cells to damaged tissues. Immune cells are the major source of cytokines, but many human cells are also capable of producing them. Cytokines can have either pro-inflammatory or anti-inflammatory/immunosuppressive activity, depending on the microenvironment. For example, anti-inflammatory cytokines such as IL-10 and IL-4 neutralize the activity of pro-inflammatory cytokines, and tend to reduce tissue damage, making them essential for controlling autoimmune response (e.g., can contribute to disease remission in diseases like multiple sclerosis) (10).

Measuring Systemic Inflammation

Researchers have most commonly attempted to characterize systemic inflammation in human subjects by measuring panels of circulating plasma concentrations of cytokines, chemokines, and acute phase reactants they induce, such as CRP, due to their influence in all aspects of the inflammation response. Other markers of inflammation include: growth factors, angiogenesis factors, metabolic markers, reactive oxygen species, and mediators of innate and adaptive immunity. Some of the most commonly measured cytokines/chemokines/acute phase reactants, their sources, and primary functions are listed in **Table 1.1**.

Table 1.1. Inflammation-related biomarkers

Markers	Principal source	Primary activity
IL-1β	Macrophages and antigen-presenting cells (APCs)	Stimulation of APCs and T cells, and production of VEGF, IL-8, IL-6, and TNF (11,12)
IL-6	Stimulated monocytes, fibroblasts, endothelial cells, macrophages, T- cells and B-lymphocytes (13,14)	Induces CRP, involved in B cell proliferation, and regulates metabolic, regenerative, and neural processes (4)
IL-8	Pro-inflammatory cytokines, macrophages, other somatic cells (15)	Activates neutrophils, released by phagocytes and a wide variety of tissue cells upon exposure to inflammatory stimuli, activates certain T cell functions such as chemotaxis, suppresses IL-4 (an anti-inflammatory cytokine) (15)
IL-10	Activated Th2 cells, CD8+ cells, T, and B cells, macrophages, dendritic cells (DC)	Anti-inflammatory cytokine that limits production of pro-inflammatory cytokines; reduces tissue damage by inhibiting the activity of Th1 cells, natural killer (NK) cells, and macrophages; directly regulates innate and adaptive Th1 and Th2 responses by limiting T cell activation and differentiation in the lymph nodes (16)

IL-12	B cells, T cells, macrophages, dendritic cells	Promotes proliferation of NK cells; promotes cell-mediated immune functions; induces IFN-γ and Th1 cells (17)
TNF-α	Activated macrophages, stimulated T cells, mast cells, neutrophils, and endothelial cells	Plays a major role in innate immune response; affects the expression of class I and class II major histocompatibility complex (MHC) molecules and adhesion molecules on multiple cell types; stimulates cells to produce numerous cytokines including IL-1, IL- 6, IL-8, and TNF-α itself (18)
CRP	Primarily synthesized in the liver	Acute phase protein; activated by IL-6 and TNF-α; non-specific marker (i.e., can be elevated in relation to both acute and chronic stimuli) (19)
TGF-β	Activated Th1 cells (T-helper cells) and NK cells	Pathway is protective mechanism to control inflammation response; regulates Th1 immune response; suppresses naive T cell proliferation by preventing IL-2 production, and promotes the generation of inducible regulatory T cells; controls B cell isotype switching and tolerance (20)
VEGF	Fibroblasts and tissue monocytes/macrophage	Stimulates angiogenesis at sites of inflammation (promotes and maintains chronic inflammation) and increases vascular permeability (21)

Abbreviations: CRP, C-reactive protein; IL, interleukin; IFN, interferon; TGF, transforming growth factor; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor

Many epidemiologic studies investigating the associations of circulating systemic measures of inflammation with chronic diseases/cancers rely on measurements from a single blood draw or a few blood draws, and consequently must take into consideration whether a single blood draw is representative of an individual's average level of inflammation over time. Furthermore, large-scale prospective epidemiologic studies tend to store biosamples in biobanks for multiple years; bringing into question the influence of storage on the stability of these samples. For some markers of inflammation, there is considerable within-person variability whereas others remain more constant over time; for example, for CRP, numerous studies that examined the intraindividual variability reported intra-class correlation coefficients (ICCs) of 0.6 to 0.8 over a period of 2 weeks to 12 years (22–31). The Prostate, Lung, Colorectal, Ovarian cancer screening (PLCO) trial investigators compared cytokine concentrations in plasma samples collected five years apart in 28 randomly selected individuals, and observed an ICC of 0.84 for IL-6, and 0.84 for TNFα, 0.55 for IL-8, and 0.60 for IL-10 (32). Another larger, more recent study conducted in the Seattle Barrett's esophagus study cohort (N =360) investigated the intraindividual variability of the inflammation biomarkers CRP, IL-6, tumor necrosis factor receptor 1 (TNFRI), and TNFRII in fasting blood samples collected an average of 1.8 years apart. TNF receptors I and II remained strongly stable (ICC=0.79 and 0.85, respectively) and CRP and IL-6 were moderately stable over time (ICC=0.55 and 0.57, respectively). Long-term storage of approximately 13 years decreased the reliability

of CRP and IL-6 slightly, but had no effect on reliability for the TNF factors (33). These and other reliability studies indicate that, generally, a single measurement of certain inflammation biomarkers is likely to be reasonably representative of an individual's average level over a reasonable period of time (approximately two years) relative to another individual's level.

Given the physiological role of the above described markers of inflammation in response to all types of harmful stimuli, including conditions that may not be related to exposure or outcome of interest, one limitation in studying chronic inflammation by measuring circulating concentrations of inflammation biomarkers is the possibility of error due to elevated inflammation marker concentrations from acute medical events, such as infection or cardiovascular events. For example, for circulating CRP, in healthy individuals, concentrations are approximately 1 mg/dL, in individuals with chronic inflammation they are approximately 3 mg/dL, and in individuals with serious medical conditions or acute infection/illness they are above approximately 10 mg/dL. For markers without established cut-points, researchers often exclude individuals with inflammation marker measurements with extreme outlying values in studies of chronic inflammation. Another way to address this limitation is to take measurements at multiple time points, rather than just a single blood draw (but still, excluding participants with higher inflammation biomarker concentrations). Moreover, when studying systemic inflammation prospectively in relation to the incidence of certain conditions, like certain cancers that thrive in and perpetuate the inflammation response, longitudinal sampling is necessary over the course of up to decades. For example, circulating or tissue-specific concentrations of inflammation biomarkers among individuals with colorectal neoplasms may be likely to no longer reasonably represent the pre-tumor environment (34).

Given the complexity and many mediators involved in inflammation as described above, one or even a few measured inflammation biomarkers are likely an incomplete characterization of the underlying variety of biological processes that accompany systemic inflammation, as each marker likely only represents one or a few aspects of the inflammation pathway. To address this, researchers have created

biomarker panels composed of multiple markers to represent different aspects of inflammation in order to more completely represent someone's inflammation state. Even with multiple types and functions of the inflammation markers collected, there will likely always be some overlap and interactions in the pathways represented, and the individual markers will typically be relatively more weakly associated with the exposure/outcome of interest than the panel as a whole. Thus, one can simply calculate standardized inflammation biomarker scores by summing normalized, standardized inflammation biomarker values. The creation and use of such biomarker scores using limited numbers of inflammation markers has been reported in epidemiologic studies (2,35–37).

An alternative approach to creating inflammation biomarker scores, is to use structural equation modeling (SEM), to model systemic inflammation as an unobserved latent variable constructed from the covariance of the measured inflammation markers that are thought to be a consequence of systemic inflammation. Using SEM regression, researchers can calculate loading factors for each inflammation marker that represent the contribution of each marker to total systemic inflammation and apply the loading factors of each marker as weights to calculate a weighted latent variable score. The loading factors of each component can be used to assess content validity based on their magnitude and direction. Construct validity can be assessed by estimating the association of the latent variable with established risk factors for chronically elevated inflammation. The latent systemic inflammation variable can then be standardized and used in analyses to represent systemic inflammation. This process was previously described in detail in relation to biomarkers of oxidative stress (38). The use of SEM and latent variables in this dissertation are described further in Appendix 1.

Diets, Lifestyles, and Inflammation

Environmental exposures can affect various portions of the inflammation response, and in particular, dietary and lifestyle behaviors are highly associated with inflammation, and thus, serve as a potential target for intervention to reduce the burden of inflammation-mediated disease. As summarized in table

1.2, there is considerable biological plausibility/basic science support for the contributions of diet to inflammation. There is even more substantial evidence that individual lifestyle characteristics may be strongly associated with, or strongly affect, inflammation (39–46). Generally, diets that are characterized by high intakes of a diversity in fruits and vegetables, fish and nuts (high in omega-3 fatty acids), whole grains, legumes, coffee/tea, and certain lifestyle behaviors, such as physical activity and moderate alcohol intake, are generally associated with lower concentrations of circulating pro-inflammatory inflammation markers; whereas, diets characterized by high intakes of added sugars, red/processed meats, saturated fats, and refined/processed grains, and certain lifestyle behaviors, such as obesity and smoking, are generally associated with higher concentrations of pro-inflammatory circulating inflammation markers (47,48).

Some of the more common mechanisms by which diet and lifestyle behaviors influence inflammation include: 1) food constituents or lifestyle behaviors that act as a pro-oxidants (e.g., iron) and elevate of circulating concentrations of ROS/RNS and free radicals, or anti-oxidants (e.g., flavonoids and physical activity) that scavenge or neutralize free radicals or ROS/RNS; 2) altering gut microbiota composition, resulting in regulation or deregulation of immune responses in the gut (e.g., legumes and vegetables rich in fiber increase production of beneficial short chain fatty acids) (49); 3) increasing or decreasing binding of harmful bile acids (e.g., calcium or saturated fats); 4) increasing or decreasing endothelial vasodilation (e.g., l-arginine in poultry or hyperglycemia induced by added sugars); and 5) other mechanisms related to carcinogenesis (described further in the 'CRC and carcinogenesis section below').

Table 1.2. Mechanism for the contribution of food groups and lifestyle behaviors to systemic inflammation

Food or lifestyle behavior	Contribution to inflammation
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, Nuclear factor-erythroid 2 (NF-E2)-related factor 2 (Nrf2), which plays a key role in cellular protection against oxidative stress and inflammation (50–60)
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 (61–64)

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 (65–67)
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 (68)
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 (54,69–76)
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 (53,77,78)
Fats	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 (79–81); contain saturated fats that mimic lipopolysaccharide (LPS), a pro-inflammatory stimulant, in the gut; increase cytotoxic, pro-oxidant, and pro-inflammatory bile acids in the colon (79,82)
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 (83–85)
Poultry	Inversely associated with inflammation markers (86); contain low amounts of saturated fat (87); contain *l*-arginine, which improves endothelium-dependent dilation (precursor of the endogenous vasodilator nitric oxide) and decreases platelet aggregation and monocyte adhesion (53)
Red and organ meats	Contain heme iron, which increases the bioavailability of iron, which in turn increases oxidative stress; contain Ω-6 fatty acids and saturated fat (see mechanisms in 'Fats' above)
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 (86,88)
Added sugars	Induce postprandial hyperglycemia, which act as stressful stimuli through subsequent repeated mild postprandial hypoglycemia (89) and reduce nitric oxide availability (play role in regulation of inflammatory response) (90); elevate pro-inflammatory free fatty acid levels (83); produce oxidative stress through oxidation of membrane lipids, proteins, lipoproteins, and DNA (91)
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 conjugated linoleic acids (CLA), *cis*- and *trans*-palmitoleic acid, butyric acid, phytanic acid, and alpha-linolenic acid (92–94)
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) (95); 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 (77,96)
Nuts	Contain Ω -3 fatty acids (83,84,97,98) and *l*-arginine (53) (mechanisms similar to those described above in 'Fish' and 'Poultry')
Refined grains and starchy vegetables	Sparse in nutrients; some processed grains contain emulsifiers, which potentially break down mucin in the gut leading to inflammation (99); and induce hyperglycemia (mechanisms described similar to those described above in 'Added Sugars')
Supplement use	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)
Heavy drinking (> 7 drinks/week women; > 14 drinks/week men)	Heavy alcohol intake results in oxidative stress via oxidation of ethanol to acetaldehyde (39,40)
Moderate drinking (1-7 drinks/week women; 1-14 drinks/week men)	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) (41) and inhibits IL-6 production and activity (42)
Physical activity	Physical activity improves systemic plasma antioxidant capacity (increases adaptive responses to oxidative stress), increases concentrations of anti-inflammatory cytokines, and lowers vascular wall inflammation (43,44)
Tobacco smoking	Toxins injure tissues, upregulating cytokines and acute phase reactants (45)
Overweight (body mass index (BMI) 25 – 29.99)	Adipose tissue synthesizes and releases pro-inflammatory adipokines, such as plasminogen activator inhibitor–1 (PA1) and TNF-α (43,46)

and obesity (BMI ≥ 30 kg/m^2)

Most previous studies on the contributions of diet to inflammation focused on selected dietary constituents (e.g., nutrients); however, there are issues with this approach. First, these constituents are not consumed in isolation, but rather are contained within a matrix of thousands of other known and unknown substances that may be acting and interacting along the same and complementary pathways (3,100). Focusing on a single nutrient may not take into account the complex interactions between the constituents of foods. Second, these nutrients/constituents are all highly correlated, making it difficult to disentangle individual contributions to inflammation. Last, the contributions of most dietary components to inflammation are small, but, an aggregate of dietary exposures may potentially make larger contributions to inflammation. Thus, when conceptualizing the contribution of diet to inflammation, it is more useful to focus on whole foods, rather than solely on nutrients, and on the diet as a whole.

Previous Dietary Inflammation Scores

To address the issues described above, researchers have developed dietary inflammation scores. Two indices were previously developed to characterize inflammation derived from the diet. The first was developed by Shivappa et al, called the dietary inflammation index or the DII (1). Essentially the DII is created based on the sum of previous reported findings relevant to the possible inflammatory associations/effects of dietary components (mostly selected nutrients) on various biomarkers of inflammation (mostly CRP). Some limitations of the DII include that it is primarily based on classically-measured micronutrients and does not account for the myriad, non-classical, unmeasured, natural anti-inflammatory compounds found in whole foods. Additionally, the methods for which the weights for the DII were derived are not completely straightforward, and the authors used a somewhat arbitrary weighting scheme for the contributions of each study type to the net weight of each dietary component. The DII also requires many assumptions, limiting the valid application of this score in some epidemiological studies. Finally, the DII addresses only diet and no lifestyle exposures. Despite the

limitations of the DII, the premise underlying the score is promising, as it was previously positively associated with biomarkers of inflammation in a range of populations (2,101–105). The DII was also associated with inflammation-mediated diseases, such as cardiovascular diseases and colorectal cancer, and with premature mortality (106–110).

The second score to measure dietary inflammatory potential, developed by Tabung et al, is called the empirical dietary inflammation index (EDII) (111). To develop the EDII, reduced rank regression (RRR) models were developed, followed by stepwise linear regression analysis to identify dietary groups that were most associated with plasma inflammation biomarkers in a subset of the Nurse's Health Study. RRR identifies a linear function of food groups that best explain the most variation in a set of response variables, and since it is based on associations with these response variables rather than on reasoned dietary patterns, RRR estimates may be less reproducible in other studies (112). The weights calculated using this approach are more specific to the covariance pattern from the population from which they are derived (in this case a population of mostly postmenopausal, white women who were nurses) and thus, may be less generalizable. As evidence, the weights for some of the components in the EDII were in the opposite direction than would be expected based on previous literature; for example, pizza was the strongest weighted anti-inflammatory component of all 18 components, whereas tomatoes were moderately pro-inflammatory. Additionally, just as the DII, this score only addresses diet. The EDII was previously moderately to strongly, positively associated with a panel of inflammation biomarkers in three studies (2,102,113); however, these studies had a similar composition to the studies in which the score was developed (two populations of mostly post-menopausal women, and one population of mostly white health professional men).

The above mentioned scores use a conventional method in calculating their scores, which is to multiply each dietary component by its respective weight and sum the weighted components (1,2); however, there are issues with this approach. When applying the scores in populations external to the population from

which the score was developed, ideally, these researchers would like to approximate what the strengths of association of dietary/lifestyle exposures with inflammation levels would have been had they measured inflammation markers in populations other than the development population. Instead, we can only make a "guess" about these associations in other populations informed by associations in the development population and hence, this requires accounting for the accompanying random error of the weight estimates. Thus, to calculate an inflammation score in populations external to the development population that includes random error from the weights, it is preferable to conduct sensitivity analyses, and simulate a range of inflammation score weight estimates and their covariance matrix using Monte Carlo methods (114). The simulated parameters would be equal to the maximum likelihood estimates from their regression models, such as the reduced rank regression models described above, or a derived covariance matrix for the literature-review weights for the DII, plus the product of a randomly selected vector of standard normal deviates and the square root of the covariance matrix over approximately 1,000,000/*n* iterations, with *n* being as the number of participants in the external population. The resulting weights, with random error included, can then be applied as weights for each dietary component, and participants could then be categorized into quantiles based on the distribution of inflammation score for each individual iteration. Finally, to additionally simulate the error from the estimated associations of interest in the external populations (e.g., associations of the DII or EDII with inflammation markers or various health states), one could then use the bootstrap technique to randomly re-sample each population with replacement prior to calculating the estimated association.

Chronic Inflammation and Disease

Deregulation of the inflammation response is implicated in several chronic diseases and cancers, particularly colorectal cancer, and reduction of inflammation, such as through interventions to inflammation-associated dietary and lifestyle behaviors described above, can potentially reduce risk for these conditions, and in turn, reduce risk for premature mortality. Broadly, all aspects of the inflammatory process can plausibly be involved in disease development; unregulated inflammation is

characteristic of rheumatoid arthritis; inflammation-related permanent tissue destruction is characteristic of emphysema; excessive tissue healing is characteristic of pulmonary or hepatic fibrosis; higher concentrations of circulating cytokines can interfere with insulin signaling, increasing insulin resistance, and increasing risk for diabetes mellitus; and, gallstones lead to irritation and inflammation of the gallbladder, which results in removal of the gallbladder (cholecystectomy), which increases the exposure of the small intestine to pro-inflammatory bile acids, thus increasing risk for carcinogenesis, which only further thrives in and perpetuates an inflammatory environment (5,6,115).

Another disease for which there is vast literature on the role of inflammation at virtually every step of its development is cardiovascular disease, the leading cause of death in the United States (116). It is well described that initiation, growth, and complication of the atherosclerotic plaque can be linked to an inflammatory response. Atherosclerosis is characterized by oxidation of circulating low density lipoprotein (LDL), which carry cholesterol into the blood stream, a primary step leading to the uptake of oxidized LDL by macrophages inside the arterial wall, leading to the formation of foam cells and atherosclerotic plaques, contributing to the perpetuation of an inflammatory response that attracts and sustains the accumulation of macrophages, monocytes, mast cells, and activated T cells as the lesion grows, leading to inflamed blood vessels and a growing fatty plaque that can cause blockages, blood clots, and ultimately heart attacks (19,117).

Colorectal Cancer – an Inflammation Mediated Disease

Epidemiology of Colorectal Cancer

Inflammation is mechanistically-linked to CRC, the second leading cause of cancer deaths in the United States among men and women combined, and the fourth leading cause of cancer-deaths worldwide. From 2005 to 2014, incidence rates declined 3.8% for colon cancer and 3.5% for rectal cancers among adults aged $\geq$ 55 years, but increased by 1.4% and 2.4%, respectively, for those aged < 55 years. There will be an estimated 50,630 deaths from colon and rectal cancers combined in 2018. Approximately 4.5% of

men and 4.2% of women in the United States will be diagnosed with invasive CRC in their lifetime. Even with advances in surgery, screening, and chemotherapy, mortality due to the CRC has declined only modestly for adults older than 55 (declined 2.9% per year from 2006 to 2015), but for adults younger than 55, increased by 1% per year (118).

Evidence thus far has demonstrated that colorectal cancers are potentially preventable, either through primary prevention such as dietary and lifestyle behaviors, or secondary prevention through the removal of adenomatous polyps, its precursor, during endoscopy screening. The strongest known risk factors for CRC include the autosomal dominant familial adenomatous polyposis (FAP) and hereditary non-polyposis cancer (HNPCC) genetic syndromes; however, these genetic conditions only account for about 5% of CRC risk in the US. FAP is an autosomal dominant disorder that results from mutations in the adenomatous polyposis coli (*APC*) gene and is characterized by multiple colorectal adenomas (100s to several thousands), occurs in about 1 in 8,000 individuals, and is more likely to develop in the left colon. HNPCC is also an autosomal dominant disorder, and usually develops at an early age.

Approximately 95% of CRCs occur in those with minimal or no genetic or hereditary risk. Those with 'minimal' risk are those with family history of CRC in a first degree relative, which confers approximately a 2- to 4- fold higher risk (119). Sixty-five percent of CRC cases are likely totally sporadic, and accumulating evidence supports the importance of environmental exposures in CRC risk. For example, developed, affluent countries have a higher burden of CRC compared to developing countries; and, migrants from high- to low-risk countries develop higher rates similar to those of their adopted countries within one to two generations (120). Additionally, the colonic mucosa has a proliferation rate of 3-10 billion colonocytes per day, the highest of all organs in the human body, making this organ particularly susceptible to environmental factors (121,122).

Incidence rates and risk factors for CRC possibly vary by cancer site. Most CRCs are diagnosed in the colon (approximately 72%) versus in the rectum (approximately 28%). By segment, CRC develops most frequently in the sigmoid colon (approximately 25%), followed by the cecum (approximately 20%), transverse colon (approximately 15%), and ascending colon (approximately 10%) (119,123). The left colon, right colon, and rectum differ with respect to their embryologic origin and their physiologic functions, and furthermore, there is some evidence for differences in risk factors for certain sites. First, women are more likely to be diagnosed with right colon cancer, whereas men are more likely to be diagnosed with rectal cancers. Second, bile-acid metabolism differs across sites, and cholecystectomy, a risk factor for CRC (described above in 'Inflammation and disease'), may be more important for right colon cancers. Third, fecal transit time and composition of metabolically active molecules change throughout the colon; for example, as the fecal stream passes, protective short chain fatty acids (e.g., butyrate, which has anti-proliferative activity and induces apoptosis of CRC cells *in vitro*), fall as its uptake increases and pH levels rise, potentially explaining some differences in risk for CRC by colon site (higher risk in distal vs. proximal colon).

Adenomatous Polyps

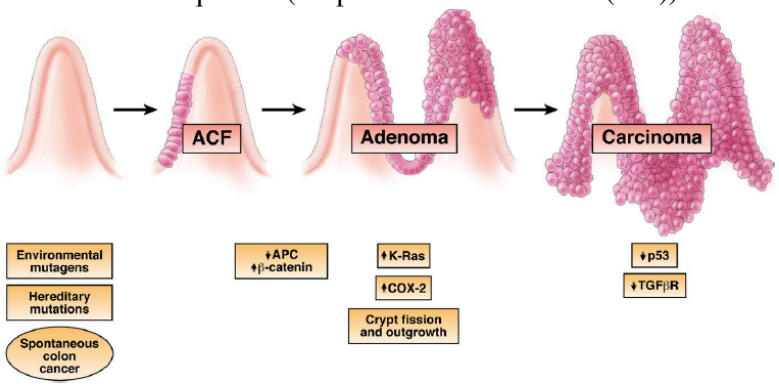
Most colorectal carcinomas are thought to arise from colorectal adenomas; however, only approximately 10% of adenomas develop into a carcinoma, and progression from adenoma to carcinoma can take about 10 years. There are three different subtypes of adenomas: villous, tubulovillous, and tubular adenomas, the majority of which are tubular adenomas (approximately 75-90%). Other subtypes of polyps include hyperplastic polyps, which are generally not neoplastic and not likely to progress to cancer. Multiple adenomas, adenomas that include a villous component, adenomas that are larger than 1 centimeter in diameter, or that have higher degrees of dysplasia are at higher risk for malignant conversion (124,125). Larger adenomas may be more susceptible to environmental exposures, as they are more likely to be exposed to pro-inflammatory, mutagenic, and mitogenic exposures in the fecal stream, and disruptions in the epithelial barrier of more advanced adenomas may result in impaired defenses against these

exposures. For example, as adenomas develop, their tight junctions lose their proper functions, and they can also lose their protective mucin barriers (125,126).

Colorectal Carcinogenesis

Carcinogenesis is the process by which normal cells are transformed into cancer cells, with three types of genes being generally responsible: oncogenes, tumor-suppressor genes, and stability genes. The colorectal adenoma-carcinoma sequence, described by Vogelstein et al (124), is a complex multi-step process by which cells accumulate genetic mutations in oncogenes and tumor suppressor genes that control cell migration, apoptosis, proliferation, and differentiation. The temporal steps (shown in Figure 1.1) include progression from normal epithelium to hyperproliferative epithelium, to aberrant crypt foci and micro-adenomas, to intermediate and late adenomas, to carcinoma and metastasis.

Figure 1.1. Adenoma-carcinoma sequence (adapted from Terzic et al. (127))



Regions of hyperplasia in polyps initially form due to inactivation of the tumor suppressor gene, the *APC* gene, which encodes a protein that regulates the Wnt/β-catenin pathway. Wnt-dependent signaling results in proteolytic degradation of *APC* and activation of β-catenin for transport into the cell nucleus. The Wnt/β-catenin pathway plays a major role in cell proliferation, and cells containing activating mutations in Wnt or β-catenin have high risk for malignancy (124,127).

There are other genetic alterations that may occur in the transition from adenoma to carcinoma. The *K-ras* oncogene plays a crucial role in cytoplasmic signaling, is detected in approximately 40-45% of all colorectal carcinomas and adenomatous polyps > 1 cm in size, and can be an initiating event in the development of some tumors (128). The *K-ras* gene functions as a molecular switch to regulate critical cellular processes such as mitosis, apoptosis, gene expression, and metabolism. Mutations in this gene result in the loss of guanosine triphosphatase (GTP), upregulating cell growth (121).

The adenoma-carcinoma transition also includes mutations in "gatekeeper" genes that maintain DNA integrity. Mutations in these genes result in greater variation in mutations detected overall in colorectal tumors and enable the capacity of the tumor to progress and potentially become resistant to therapy. For example, mutations in mismatch repair genes, commonly through hypermethylation of the promoter region of MutL homolog 1 (MLH1), lead to increased DNA microsatellite instability. Microsatellite instability is found in about 90% of HNPCCs and in up to 15% of sporadic CRCs (129–132). Approximately 65-70% of CRCs (up to 80% in late-stage tumors) have mutations in the chromosomal instability pathway, which are characterized by loss or gains of whole or large portions of chromosomes.

Adenoma to carcinoma progression also includes a series of other mutations that commonly occur, including: activation of the oncogene *B-raf* and activin receptors (involved in cell proliferation, differentiation, and apoptosis), and loss of the tumor suppressor genes: 'deleted in colorectal carcinoma' (DCC), p53 (commonly found in other human cancers and occurs late in the adenoma-carcinoma sequence), and Bax (a pro-apoptotic protein).

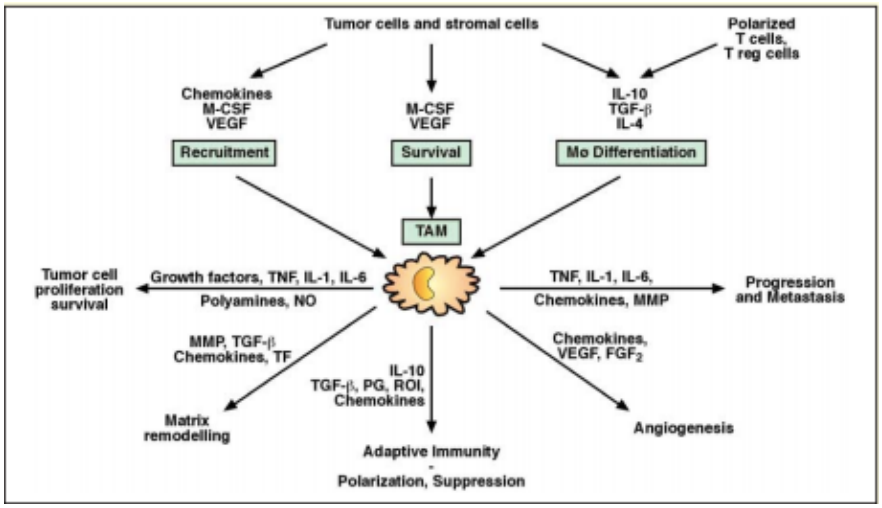
Colorectal Carcinogenesis and Inflammation

In 1863, it was noted 3by Rudolf Virchow that leukocytes infiltrate neoplastic tissue (133). Since then, it has been increasingly suggested that in addition to the six hallmarks for cancer development defined by Hanahan-Weinberg, which include self-sufficiency in growth signals, insensitivity to anti-growth signals,

evasion of apoptosis, unlimited replicative potential, sustained angiogenesis, and metastasis, a seventh hallmark should be a cancer-promoting inflammatory environment that can enhance the proliferation of mutated cells (134). An inflammatory tumor microenvironment consists of complex interactions with macrophages, B and T cells, mast cells, fibroblasts, myofibroblasts, and the extracellular matrix (13,135). Inflammation promotes carcinogenesis by damaging DNA, promoting cell proliferation and angiogenesis, and inhibiting apoptosis; and, epidemiological evidence indicates that over 25% of all cancers are related to a deregulated inflammation response (136).

As tumors develop, they remodel the stroma, and secrete factors that attract inflammatory cells, such as lymphocytes, cytokines, chemokines, growth factors, proteases, tumor-associated macrophages (TAMs), mast cells, dendritic cells, NK cells, neutrophils, and eosinophils. Once immune cells infiltrate a tumor, instead of killing the tumor cells, the tumor uses the nutrients and oxygen that are part of the inflammatory response to promote tumor progression by upregulating growth, differentiation, and survival of cancer cells. For example, type 2 TAMs (shown in figure 1.2) are considered major contributors to the inflammation-cancer association, and are directed into tumors by chemoattractant cytokines, and then stimulate tumor-cell proliferation, promoting angiogenesis, remodeling tissue, and promoting invasion and metastasis. TAMs are also an important source for the production of more cytokines (133,136,137).

Figure 1.2. Function of type 2 TAMs upon infiltration into tumor cells (adapted from Balkwill and Mantovani) (138)



Inflammatory cells that infiltrate the tumor produce a variety of cytotoxic mediators, such as ROS and RNS that are mutagenic and mitogenic, increase cellular damage, DNA oxidation, and the frequency of mutation (139). Cytotoxic mediators also include serine and cysteine proteases, matrix metalloproteinase (aid in invasion and metastasis by degrading extracellular matrix proteins), TNF-α, IL-1, IL-6, IL-8, interferons, COX-2, lipooxygenase-5 (LOX-5), and phospholipase A2 (PLA2) (140). These mediators collectively modulate tumor growth and enhance invasiveness of tumor cells by activating oncogenic signaling pathways, such as nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB), and signal transducers and activators of transcription 3 (STAT3) (141). NFκB signaling, activated by TNFα and IL-1β, plays a pivotal role in the connection of inflammation to carcinogenesis (142,143). Upon activation of NFκB signaling in tumor cells, NFκB binds to the promoter region of genes encoding pro-inflammatory mediators (TNF-α, IL-6, IL-8, and COX-2), adhesion molecules, matrix metalloproteinases, DNA-damaging compounds (e.g., ROS and RNS), inducers of cell proliferation (c-MYC and cyclin D1), and angiogenic factors (e.g., VEGF, which is usually over-expressed in malignant tumor cells (21), and angiopoietin) (144). STAT3, activated by IL-6, VEGF, IL-23, IL-21, ROS, platelet-derived growth factor, and the *Ras* oncogene (mentioned above), activates genes crucial for cell proliferation and survival, angiogenesis, and metastasis (145). Other key molecular players that link inflammation to cancer are: 1) generation of nitric oxides, which can be both pro- or anti-neoplastic by acting as a potent

vasodilators or neutralizing ROS; 2) hypoxia inducible factor-1α, which drives gene transcription involved in adaptations to hypoxic stress and are regulated by various inflammatory mediators (e.g., TNF-α, IL-1α, and TGF-α); 3) Nrf2 , which plays a key role in cellular protection against oxidative stress and inflammation; and 4) and nuclear factor of activated T cells (NFAT), which help regulate immune response (50,90,133).

There is particularly strong evidence supporting a role of systemic inflammation in all stages of colorectal carcinogenesis, including initiation, promotion, progression, and metastasis (121,146–149). In addition to the mechanisms linking inflammation and carcinogenesis described above, carcinogenesis of the colon and rectal epithelium is uniquely linked to inflammation. First, and perhaps most prominently, progression of colorectal carcinogenesis is characterized by increases in COX-2 expression. COX-2 has pro-inflammatory and pro-tumorigenic activities mediated by PGE2, stimulates growth and angiogenesis, and inhibits apoptosis through activation of a number of oncogenic signaling pathways, including Wnt/β-catenin/T-cell factor (TCF), Ras, and phosphoinositide 3-kinase (PI3K; links oncogenes and multiple receptor classes to essential cellular functions to promote carcinogenesis) signaling (13). Expression of COX-2 is elevated in approximately 50% of adenomas and 85% of adenocarcinomas (149). Second, the TGF-β receptor II and components of its pathway, which has key functions in regulation of the inflammation response (described in table 1.1), can play a pro-tumorigenic or anti-tumorigenic role depending on the stage of colorectal carcinogenesis, and is often elevated in advanced colorectal carcinoma patients (150). Finally, activation of oncogenes that are part of the adenoma-carcinoma sequence, such as *k-Ras*, are directly involved in inflammatory pathways, such as NFκB described above (127,133,136).

Circulating serum concentrations of cytokines (and their induced acute phase reactants) involved in activating, or that are activated by, inflammatory pathways involved in carcinogenesis (e.g., NFκB and STAT3) are elevated prior to, and during colorectal carcinogenesis. For example, in a meta-analysis of

18 nested case-control studies, a 12% higher risk for incident CRC for every one unit increase in baseline log-transformed CRP concentrations was found (151), and in a meta-analysis of six studies (three cohort and three nested case-control studies), there was a 10% higher risk for incident CRC for every one unit increase in IL-6 (151).

Other epidemiological evidence has also strongly supported the role of inflammation in colorectal carcinogenesis. First, multiple randomized clinical trials and observational studies found chemopreventive effects against/inverse associations of aspirin and other NSAIDs with risk for colorectal neoplasms. For example, a meta-analysis of four randomized clinical trials found that, relative to those on placebo, individuals randomized to regularly take aspirin had 17% and 28% risk reductions for all or advanced colorectal adenomas, respectively, over a median follow-up of 33 months. Additionally, in a trial of the effect of aspirin on CVD risk over a follow-up of an average of 18.3 years, among those randomized to take aspirin relative to those on placebo, the 20-year risk of CRC was reduced by 24%, and risk of CRC-associated mortality was reduced by 35%, with stronger reductions observed with longer durations of treatment (152). The chemopreventive effects of NSAIDs are thought likely to be through inhibition of the COX-2 enzyme described above (147–149,152–156).

Individuals diagnosed with inflammatory bowel diseases have higher risk for CRC (157), which is strongest for those with longer durations and more severe extents of the disease. One meta-analysis with systematic review found that compared to the general population, patients with Crohn's disease had 2.5-fold higher risk for CRC (157). Another meta-analysis found a 2.9-fold higher risk for CRC among patients with either ulcerative colitis and/or Crohn's disease relative to the general population (158).

Diets, Lifestyles, and Colorectal Neoplasms

Risk for colorectal neoplasms is highly correlated with Westernized dietary and other lifestyle exposures (158,159). In general, dietary patterns characterized by high intakes of fruits, vegetables, whole grains,

low-fat dairy products, fish, poultry, olive oil, and legumes have been inversely associated with colorectal neoplasms; whereas, dietary patterns characterized by high intakes of potatoes, red and processed meats, and refined grains have been positively associated with colorectal neoplasms (160). In the prospective National Institute of Health-AARP study, higher relative to lower Healthy Eating Index (HEI) 2005 and Mediterranean Diet scores were both associated with a 28% lower risk of CRC. A high HEI is characterized by higher intakes of fruits, vegetables, whole grains, and legumes, and lower intakes of oils, sodium, and added sugars; and, high Mediterranean diet scores are characterized by high intakes of whole grains, vegetables, fruit, fish, nuts, legumes, a higher ratio of monounsaturated to saturated fats, and moderate alcohol intake (161,162). In addition, there is even stronger evidence for positive associations of obesity, heavy alcohol intake, and smoking with CRC, and for inverse associations of physical activity with CRC (163–168).

There are many mechanisms by which dietary intake and other lifestyle behaviors may inhibit or promote colorectal carcinogenesis, most of which directly or indirectly involve their influence on inflammation as described in Table 1.2. The rapid replication of colorectal cells requires a steadily available source of nutrients, making the colon particularly susceptible to dietary or other lifestyle changes. For example, such exposures promote or inhibit colorectal carcinogenesis by affecting an increase (e.g., prooxidants, like iron) or reduction (e.g., antioxidants, such as flavonoids) of defects in the epithelial barrier, in turn increasing/reducing oxidative stress and activation of COX-2 (126). Additionally, the colon is host to trillions of bacteria comprising the microbiome, including many strains of bacteria with pro- or anti-inflammatory properties (127). Dietary and lifestyle exposures have great influence on the composition and diversity of the gut microbiota. For example, fermentation of dietary fiber in the colon produces metabolic end-products, such as short chain fatty acids, which include butyrate, acetate, and propionate, which are preferable sources of energy for colonocytes (optimally supplies approximately 90% of energy). Dietary fiber deficiency deprives the gut bacteria of their optimal nutrient source, and thus they

rely on host mucus glycoproteins in the gut as a source for energy, promoting greater epithelial access, leading to inflammatory responses in the gut (169).

Given considerable biological plausibility for the contributions of individual food groups and lifestyle behaviors to systemic inflammation, the above-summarized literature strongly supports inflammation as a major pathway underlying the associations of dietary/lifestyle exposures with colorectal carcinogenesis.

Dietary-Associated Inflammation and Colorectal Neoplasms

Dietary-associated inflammation has previously been studied in relation to colorectal neoplasms. The DII (1) and/or EDII (2) were calculated and their associations with colorectal adenoma and/or CRC were investigated. The association of the previously developed DII (1) was investigated in association with adenomas in two studies. In a cross-sectional analysis of PCLO trial data, men in the highest (most pro-inflammatory) DII quartile relative to those in the lowest, had a statistically significant 40% higher prevalence of adenoma, whereas women in the highest quartile had an estimated non-statistically significant 8% higher prevalence (170). In an observational analysis of data from a clinical trial of wheat bran cereal fiber supplementation and adenoma recurrence, the DII-adenoma recurrence association was null (171).

Four reported prospective cohort studies and five case-control studies investigated a DII-CRC association. In a recent meta-analysis of these studies, there was an estimated 6% higher CRC risk for every one-unit increase in the DII (172), though there was statistically significant heterogeneity in the associations. For example, in the prospective NIH AARP cohort, a high relative to low baseline DII was associated with a statistically significant 44% higher risk for CRC among men, and a non-statistically significant 12% higher risk among women (173).

An EDII-CRC association was investigated in two prospective cohorts. In the Health Professionals Follow-up Study (HPFUS) and the Nurses' Health Study (NHS) cohorts, the EDII was associated with 44% and 22% higher CRC risk among men and women, respectively (174); and, in a subset of these two studies, the EDII was more strongly associated with risk for CRC tumors with absent/low peritumoral lymphocytic reaction, which are possibly more aggressive tumors (175). Though the DII/EDII-CRC associations indicate that dietary-derived inflammation is likely associated with risk for colorectal neoplasms, limitations of these scores support a need to continue research into these associations using a more reproducible, generalizable, whole foods and lifestyle-based tool that can be more directly applicable to dietary and lifestyle recommendations for CRC prevention.

Gaps in the Literature

The limitations of the DII and EDII support continued research into reproducible questionnaire-derived inflammation scores to assess whether dietary and lifestyle exposures can indeed reflect inflammation, and if so, whether diet/lifestyle-related inflammation may affect risk for CRC in humans. Given the limitations of these previously developed scores, we proposed that the next necessary step was to create weights for questionnaire-derived inflammation scores (dietary and lifestyle) that are based on associations of individual components, determined *a priori*, with a panel of inflammation biomarkers in a population with strong heterogeneity in respect to the relevant exposures. Based on the likely small contributions of individual exposures to inflammation in humans, we proposed these scores with the purpose of representing the aggregate contributions of dietary and lifestyle factors that are positively or inversely associated with systemic inflammation in a clear, straightforward fashion that could make this score reproducible in a variety of epidemiological studies.

Broad, Long-Term Goals of Dissertation

The broad and long-term goals for which the specific aims below outline the steps needed are: 1) to quantify the contributions of an aggregate of whole-foods and lifestyle exposures toward systemic

inflammation as measured through biomarker indicators in human subjects, and 2) to characterize the associations of dietary- and lifestyle-derived inflammation with colorectal neoplasms. As outlined in the specific aims below, to do this we proposed to develop and validate an inflammation biomarker-weighted, dietary and lifestyle inflammation score based on food frequency questionnaire (FFQ) and lifestyle questionnaire data and further investigate their associations with risk for incident, sporadic adenoma and incident colorectal cancer. We hypothesized that the whole foods-based and lifestyle-based inflammation scores would be strongly associated with inflammation biomarker levels across many different populations and would also be strongly associated with risk for colorectal neoplasms. Should these hypotheses prove correct, our score and the corresponding weights could be applied to existing and future observational studies assessing associations of dietary- and lifestyle- derived inflammation with chronic disease, cancers, and other health outcomes, with the ultimate goal of informing dietary and lifestyle public health and clinical recommendations.

Specific Aims for Dissertation

1. Develop and validate a biomarker-weighted inflammation score based on FFQ and lifestyle questionnaire responses (**Aim 1**). To do this we proposed to:
    a. Calculate a summary inflammation biomarker score [a sum of z-scores for levels of C-reactive protein, interleukin-6, interleukin-8, and interleukin-10 (the latter with a negative sign)] for a case-cohort subset of male and female, black and white participants (N = 639) in the prospective Reasons for Geographic and Racial Differences in Stroke Study (REGARDS) cohort, aged < 75 years and with < 2 comorbidities.
    b. Using dietary groupings chosen *a priori*, calculate the strength of association of each individual standardized dietary group with the summary inflammation biomarker score. We proposed to repeat this process for selected categorical lifestyle factors, including smoking status, physical activity, alcohol intake, and body mass index (BMI).

c. Use the strengths of the associations of each individual dietary and lifestyle component with the inflammation biomarker summary score to create a respective weight for each of the components. We propose to then sum the weighted components to create dietary-specific (DIS) and lifestyle-specific (LIS) inflammation scores to represent the balance of pro- to anti-inflammatory dietary and lifestyle exposures.

d. Investigate associations of the DIS and LIS with circulating concentrations of inflammation biomarkers using cross-sectional data from diverse populations, including: 1) the remaining participants in the above noted REGARDS cohort with hsCRP measurement (N = 14,210; 2) participants from pooled cross-sectional studies of patients recruited from community-based gastroenterology clinics, scheduled to undergo outpatient, elective colonoscopy (N = 433); and 3) adenoma patients from the Calcium, Colorectal, Epithelial Cell clinical trial (N = 173). We proposed to then apply similar scores, specifically the DII (1) and the EDII (2), to compare the strengths of their associations with circulating inflammation biomarker concentrations to those of the DIS and LIS.

   i. Hypothesis: The DIS and LIS would be more strongly associated with circulating concentrations of inflammation biomarkers in a range of populations, than with the DII and EDII.

2. Using the components and weights indicated in steps 1b and 1c above, calculate weighted FFQ and lifestyle questionnaire-based inflammation scores and investigate their associations with risk for colorectal neoplasms (**Aims 2 and 3**). To do this, we proposed to:

a. Calculate a DIS and LIS for each participant in a pooled case-control study of colorectal adenoma (N = 777 cases and 2,002 controls) and use multivariable logistic regression to estimate their associations with incident, sporadic colorectal adenoma.

b. Calculate a DIS and LIS for each participant in the large, prospective NIH AARP Diet and Health Study cohort and investigate their associations with incident colorectal cancer.

i. Hypothesis: Participants with higher DIS and LIS scores would have higher risk for incident colorectal adenoma and colorectal cancer.

Chapter 2. Development and Validation of Novel Dietary and Lifestyle Inflammation Scores

Doratha A. Byrd,[1] Suzanne E. Judd,[2] W. Dana Flanders,[1] Terryl J. Hartman,[1,3] Veronika Fedirko,[1] Roberd M. Bostick[1,3]

[1]Department of Epidemiology, Emory University Rollins School of Public Health, Atlanta, Georgia. [2]Department of Biostatistics, University of Alabama at Birmingham School of Public Health, Birmingham, Alabama. [3]Winship Cancer Institute, Emory University, Atlanta, Georgia.

Abstract

Chronically higher inflammation, which may partly result from diet and lifestyle, is implicated in risk for multiple chronic diseases. The dietary inflammatory index (DII) and empirical DII (EDII), developed to characterize dietary contributions to systemic inflammation, have several limitations and do not address lifestyle.

To better reflect dietary/lifestyle contributions to inflammation, we developed novel, inflammation biomarker panel-weighted, dietary (DIS) and lifestyle (LIS) inflammation scores in a subset (N = 639) of the Reasons for Geographic and Racial Differences in Stroke Study (REGARDS) cohort.

We selected *a priori* 19 food groups and four lifestyle characteristics to comprise the DIS and LIS, respectively. We calculated the components' weights based on their strengths of association with an inflammation biomarker z-score (comprising high sensitivity C-reactive protein (hsCRP), interleukin [IL]-6, IL-8, and IL-10) using multivariable linear regression. The sums of the weighted components constitute the scores, such that higher scores reflect, on balance, more pro-inflammatory exposures. We calculated the DIS, LIS, DII, and EDII using cross-sectional data from the remaining REGARDS cohort (N = 14,210 with hsCRP measurements) and two other study populations with hsCRP and/or 8-component inflammation biomarker panels and investigated their associations with circulating inflammation biomarker concentrations using multivariable logistic regression.

In REGARDS, those in the highest relative to the lowest DIS, LIS, DII, and EDII quintiles had statistically significant 1.66-, 4.29-, 1.56-, and 1.29-fold higher odds of a high hsCRP concentration (>3 mg/dL), respectively (all *P*-trends <0.001). Those in the highest relative to the lowest joint DIS/LIS quintile had a statistically significant 7.26-fold higher odds of a high hsCRP concentration. Similar findings were noted in the other two validation populations.

Our results support that dietary and lifestyle exposures collectively contribute substantially to systemic inflammation and support the use of our LIS and of our whole foods-based DIS over the DII and EDII.

Introduction

Deregulation of the inflammation response has been implicated repeatedly in the etiology of chronic diseases and cancers, which are leading causes of death in the United States (US) (5,116,118,141). Dietary and lifestyle exposures, such as physical inactivity, obesity, and tobacco smoking, likely contribute to higher chronic inflammation (126,176–178). Consequently, reducing inflammation via dietary or lifestyle interventions, could help reduce risk for cancer, other chronic diseases, and premature death (179,180).

The contributions of most dietary and lifestyle exposures to inflammation individually likely are relatively small, but collectively may be substantial. To address this, investigators have created questionnaire-based dietary inflammation scores to represent aggregates of inflammation-related exposures. Two published scores to characterize inflammation contributed from diet are the dietary inflammation index (DII) (1) and the empirical DII (EDII) (2). The DII (1) is a summation of previously reported effects/associations of the selected dietary factors (mostly micro- and macronutrients) on/with various inflammation biomarkers. The EDII (2) was developed using a data-driven approach to identify food groups most associated with plasma inflammation biomarkers in a subset of the Nurse's Health Study (NHS) cohort. Limitations of these indices include issues with reproducibility, generalizability, assumptions, and for the DII, a heavy focus on nutrients. Also, neither index addresses lifestyle.

To address these issues, we developed and validated weighted dietary- and lifestyle-inflammation scores based on food frequency questionnaire (FFQ) and lifestyle questionnaire responses, by quantifying associations of aggregates of whole-foods and of lifestyle exposures with systemic inflammation, as measured through a panel of inflammation biomarkers in a diverse population. Our premise was that

focusing on whole foods (rather than nutrients), which contain thousands of bioactive substances(3), and lifestyle exposures may be a more productive direction for epidemiologic research on the roles of diet and lifestyle in inflammation and the etiology of inflammation-related diseases. We also compared the strengths of associations of our new inflammation scores with biomarkers of inflammation to those for the DII and EDII in three study populations.

Methods

Study population and data collection for developing the Dietary Inflammation Score (DIS) and Lifestyle Inflammation Score (LIS): REGARDS

REGARDS is a national, on-going prospective cohort study that recruited 30,239 participants ≥45 years old January 2003–October 2007, with oversampling of black individuals and residents in the Southeastern US. Details on the objectives, study population, recruitment, and exclusion criteria were described previously (181). We developed the DIS and LIS using a case-cohort sample nested in REGARDS that had a panel of plasma inflammation biomarkers measured at baseline (N = 639) (182). Cases were those diagnosed with incident ischemic stroke during follow-up. The cohort comparison sample was randomly sampled from 20 strata to ensure sufficient representation of individuals in each race, sex, and 10-year age group. We incorporated sampling weights and stratum/cluster-specific estimates in all case-cohort analyses described further below.

Dietary and supplemental vitamin/mineral intakes were assessed using a self-administered, 109-food item, Block 98 FFQ (NutritionQuest, Berkeley, California) that was validated in multiple diverse populations (183–185). Pictures were provided to assist respondents in identifying standard portion sizes, and nine possible frequency-of-consumption responses, ranging from ‘‘never” to ‘‘every day” were given for each food item. Grams of intake for each line item and total daily energy and nutrient intakes were

calculated by NutritionQuest; the latter two were calculated by summing energy and nutrients, respectively, from all food sources.

Lifestyle information was obtained via a 30–45-minute telephone interview using lifestyle questionnaires similar to those used in previous studies of cerebrovascular and cardiovascular disease (36,186). The lifestyle questionnaire ascertained self-reported frequency of physical activity intense enough to work up a sweat, how many alcoholic drinks the respondent usually consumed, and cigarette smoking status. At an in-home visit, height and weight were measured without shoes using a metal tape measure and balance scale, respectively, and fasting venous blood samples were drawn.

Baseline circulating high-sensitivity C-reactive protein (hsCRP) concentrations were measured in the entire cohort. Baseline circulating interleukin (IL)-6, IL-8, and IL-10 concentrations were also measured in the case-cohort participants. hsCRP was measured via a validated, high-sensitivity, particle-enhanced, immunonephelometric assay in batches using a BNII nephelometer (Dade Behring; Deerfield, IL). The intra-assay coefficients of variation (CV) ranged from 2.3–4.4%, and inter-assay CVs ranged from 2.1–5.7%. IL-6 was measured via an ultra-sensitive ELISA (Quantikine HS Human IL-6 Immunoassay; R&D Systems, Minneapolis, MN); the inter-assay CV range was 6.8–7.3%. IL-10 was measured using the Milliplex MAP Human Cardiovascular Disease Panel 3 (Millipore Corporation; Billerica, MA) run as a single-plex assay; the inter-assay CV range was 8.3–12.1%. IL-8 was measured using the Human Serum Adipokine Panel B LINCOplex Kit (Linco Research, Inc.; St. Charles, MO); the inter-assay CV range was 1.4–7.9% (187).

Validation study populations and data collection

We assessed the validity of the DIS and LIS in three populations: two with hsCRP measurements, including the remaining REGARDS cohort (N = 14,210) and a pooled cross-sectional study (N = 433),

and one with an 8-component inflammation biomarker panel (N = 173). The latter two validation populations are described below.

Pooled Markers of Adenomatous Polyps I and II studies (MAP)

We pooled data from two cross-sectional studies among populations with no history of colorectal neoplasms scheduled for out-patient, elective, colonoscopies in large, community-based gastroenterology practices. These studies, the Markers of Adenomatous Polyps studies I and II (MAP I (188)k and MAP II (189)), were conducted by the same principal investigator (RMB) using virtually identical protocols and questionnaires, and hereinafter are referred to as MAP. MAP I was conducted from 1994 to 1997 in North Carolina, and MAP II was conducted in 2002 in South Carolina. Details on participation rates, exclusion criteria, and biosample collection were described previously (188,189).

Prior to colonoscopy, participants provided detailed demographic, medical history, diet, lifestyle, and anthropometric information. Diet and supplement intakes over the previous 12 months were assessed using self-administered Willett FFQs (190). A standard portion size and nine possible frequency-of-consumption responses, ranging from ‘‘never, or less than once per month’’ to ‘‘6 or more times per day’’ were given for each item. Total daily energy and nutrient intakes were calculated by summing energy and nutrients, respectively, from all food sources using the dietary database developed by Willett (190,191). Physical activity was assessed using a modified Paffenbarger questionnaire (192). Prior to colonoscopy, fasting peripheral venous blood samples were drawn, and hsCRP was measured via latex-enhanced immunonephelometry on a Behring nephelometer II analyzer (inter-assay CV: 4.0%; Behering Diagnostics).

Calcium and Colorectal Epithelial Cell Proliferation trial (CECP)

We used baseline questionnaire data and blood samples collected from 1990-1991 from CECP participants (all sporadic colorectal adenoma patients) on whom a panel of inflammation biomarkers was

measured in 2013. The purpose of the original trial was to test the efficacy of supplemental calcium in modulating a biomarker of colorectal epithelial cell proliferation in the normal rectal mucosa. Details on the study design and exclusion criteria were described previously (193).

Participants provided detailed demographic, medical history, diet, lifestyle, and anthropometric information using questionnaires identical to those in MAP. Circulating concentrations of inflammation biomarkers were measured at the Emory Multiplexed Immunoassay Core using electrochemiluminescence detection-based immunoassays based on a Meso Scale Discovery Sector 2400 instrument. An individual assay was conducted for hsCRP, and a 10-plex assay was conducted for IL-6, IL-8, IL-10, VEGF, TNF-α, IL-1β, IL-12p40, IL-17, IL-4, and IFN-γ. All biomarkers were measured in duplicate, according to the manufacturer's protocol. The average intra-assay CV for IL-6 was 7.0%, for IL-8 3.5%, for IL-10 5.7%, for hsCRP 4.6%, for TNF-α 4.3%, for VEGF 4.5%, for IL-1β 13.0%, for IL-12p40 6.9%, for IL-17 21.3%, for IL-4 17.6%, and for IFN-γ 16.7%. Biomarkers with CVs ≥15% (IFN-γ, IL-17, and IL-4) were excluded from further analyses. Biomarker measurements below the lower limit of detection were set to the lowest limit of detection for each batch (193).

In addition to the original inclusion/exclusion criteria described for each study above, for the present analyses we excluded participants ≥75 years old or with hsCRP concentrations ≥10 mg/dL (19), extreme outlying values for other measured inflammation biomarkers (REGARDS case-cohort and CECP), end-stage renal disease (estimated glomerular filtration rates <15), implausible total energy intakes (<500 or >6,000 kcal/day), >15% missing FFQ data, or missing lifestyle questionnaire data. In the REGARDS case-cohort, to reduce potential for bias and/or error in estimating the DIS/LIS weights, we used more stringent inclusion/exclusion criteria and excluded those missing >10% FFQ data and those with ≥2 comorbidities (a history of cancer, heart disease, diabetes mellitus, or chronic kidney disease).

All studies were approved by the Institutional Review Boards of their respective institutions. Written informed consent was obtained from each participant in the original studies.

DIS components

Whole foods/beverages for the DIS were selected and grouped into 19 score components (Table 2.1) *a priori* based on biological plausibility, prior literature, and consideration of easily re-creating them using a variety of dietary measurement instruments used in major epidemiologic studies. We eliminated food groups if intake was rare in the REGARDS case-cohort or if measurement was unreliable using the Block 98 FFQ. To account for taking supplemental micronutrients, we calculated a supplement score by ranking supplemental micronutrient intakes, based on the sex-specific distribution, into tertiles. The tertiles were assigned values of 0–2 and multiplied by +1 or -1 based on hypothesized anti- or pro-inflammatory contributions, respectively; then the values were summed. A higher score indicated a predominance of anti-inflammatory supplemental micronutrient intakes.

Mixed dishes (e.g., pizza, spaghetti) in the Block 98 FFQ were disaggregated using the "My Pyramid Equivalents Database" (MPED), which is described elsewhere (194). Briefly, we calculated mean food group equivalents per 100 grams of each mixed dish, weighted by how often each variation of the mixed dish was consumed over two-day food records in black and white individuals ≥45 years old in the National Health and Nutrition Examination Survey (NHANES) 2003-2004 (195), multiplied the equivalent by the gram amount consumed by each individual, converted the equivalent to the appropriate units, and added it to its respective DIS food group.

LIS components

The LIS included four components: smoking status, physical activity, alcohol intake, and body mass index (BMI). Since the weights were developed based on cross-sectional exposure-biomarker associations, smoking was categorized as 'current' or 'former/never'. BMI was categorized as normal

(18.5–24.99 kg/m^2), overweight (25–29.99 kg/m^2), or obese (≥30 kg/m^2). Heavy alcohol consumption was defined as >1 or >2 drinks/day for women and men, respectively; moderate consumption was defined as consumed alcohol, but in less than these amounts. Physical activity in REGARDS was categorized as the frequency of being physically active enough to work up a sweat (0, 1-3, or ≥4 times/week); in MAP and CECP, we ranked participants according to tertiles of weekly metabolic equivalents of task (METs)-minutes of moderate/vigorous physical activity.

Development of the DIS and LIS

First, to represent systemic inflammation, we created an inflammation biomarker score comprising the four available biomarkers in the REGARDS case-cohort: hsCRP, IL-6, IL-8, and IL-10 (the latter considered anti-inflammatory). To do this, we transformed the biomarker values by the natural logarithm (ln), standardized the values to a mean of 0 and standard deviation of 1.0, and then summed the standardized inflammation biomarkers values (IL-10 with a negative sign).

Next, we calculated weights for the DIS and LIS components in the REGARDS case-cohort based on the strengths of the associations of each component with the inflammation biomarker score. To do this, first, for the DIS, we standardized each food group (all continuous), by sex, to a mean of 0 and standard deviation of 1.0. For the LIS, since all components were categorical variables, we created dummy variables. Then, ensuring that linear regression model assumptions were met, and multi-collinearity ruled out, we conducted multivariable linear regression to estimate the maximum likelihood estimates for the β-coefficients, which represent the average change in the inflammation biomarker score, per one standard deviation increase in a dietary component or having a certain lifestyle behavior relative to its referent category. The modeling procedures are described further below in the Statistical Analyses subsection. To calculate a DIS and LIS for participants in other populations, each dietary/lifestyle component can be multiplied by the weight (the β-coefficient) calculated above, and the weighted components summed.

Validation of the DIS and LIS

To assess the validity of the DIS and LIS, we calculated both scores and previously developed dietary inflammation scores (the DII and the EDII; see the components in Appendix Table 2.1) in the remaining REGARDS cohort, MAP, and CECP. We calculated the DII (1) and EDII (2) according to previous reports. In REGARDS, MAP, and CECP, 34, 38, and 37 of the 45 DII components were available, respectively. Briefly, to calculate the DII (1), we first calculated a z-score for each component using the published global means and standard deviations. We then calculated normalized, centered percentiles for each component, and then multiplied each component by its reported respective weight. To calculate the EDII (2), we formed dietary groups based on those described by Tabung et al., multiplied each component by its reported respective weight, and divided the score by 1,000 to scale it. For all inflammation scores, a higher score indicates more pro-inflammatory relative to anti-inflammatory exposures.

Next, we investigated the associations of the various scores with the various inflammation biomarkers in the three other populations as described in the following subsection.

Statistical analyses

We first categorized participants in each study into quantiles of each inflammation score. The characteristics of the study populations were summarized and compared across quantiles of the DIS and LIS, using chi-square tests for categorical variables and ANOVA for continuous variables.

We used multivariable unconditional logistic regression to assess associations of the DIS, LIS, DII, and EDII with high circulating hsCRP concentrations or inflammation biomarker scores. In REGARDS and MAP, we defined a high hsCRP as >3.0 mg/dL, a clinically relevant cut point (19). In CECP, we calculated an inflammation biomarker score (a sum of z-scores for IL-6, IL-8, IL-10 [with a negative sign], hsCRP, VEGF, TNFα, IL-1β, and IL-12p40) and dichotomized the inflammation biomarker score

at the study population's median. A term for the sex-specific median of each inflammation score quantile was entered into the multivariable regression models as a continuous variable to test for trend.

To assess potential interaction between the DIS and LIS, we conducted a joint/combined (cross-classification) analysis using multivariable logistic regression models in which the reference group was participants in the first quintile of both scores.

Consideration for inclusion of covariates in all of the above described multivariable linear and logistic regression models were based on biological plausibility, previous literature, and the magnitude of change in the association of interest when including/excluding the variable from the model. Covariates considered for all models included age, sex, race/ethnicity, income, education, region of the US, comorbidities, hormone replacement therapy use (for women), total energy intake, season of year the participant completed dietary/lifestyle questionnaires and had inflammation biomarkers measured, and regular aspirin, other non-steroidal anti-inflammatory drug (NSAID), or lipid-lowering medication use. Models for the dietary inflammation scores additionally included the LIS components (smoking, BMI, alcohol intake [except for the DII and EDII since alcohol intake is a component], and physical activity). Models to estimate weights for the DIS and LIS additionally included all dietary and lifestyle components as covariates. Although energy intake is typically a DII component, we explored adding and removing energy intake as a covariate in the multivariable regression models for the DII to ensure adequate control for confounding by energy intake. The final covariates for all models are listed in the tables' footnotes.

To investigate potential effect modification, separate analyses were conducted for each dietary/lifestyle inflammation score within categories of age (dichotomized at 65 years old), sex, race (black or white), comorbidity status (yes/no), aspirin or other NSAID use (take NSAID ≥ twice/week or < twice/week); and for the dietary inflammation scores, within categories of current smoking status (former and never or current), BMI (normal, overweight, or obese), alcohol status (current non-drinker, moderate drinker, or

heavy drinker), and physical activity (none, moderate, or heavy). We assessed effect modification by comparing the stratum-specific estimates and by calculating Wald test p-values for model interaction terms.

Sensitivity analyses

To assess the sensitivity of the associations to various considerations, we repeated the analyses with the following variations: 1) assigned positive or negative equal weights to dietary/lifestyle components we hypothesized *a priori* to be pro-inflammatory or anti-inflammatory, respectively; 2) calculated and compared adjusted mean ln-transformed hsCRP concentrations (REGARDS and MAP) and inflammation biomarker scores (CECP) by quantile of each inflammation score using multivariable general linear models; and 3) recognizing that the estimated strengths of associations of the DIS and LIS components with inflammation biomarker concentrations contain some uncertainty, we simulated a range of DIS and LIS weight estimates using Monte Carlo methods (MCM) (114) over 1,000,000/*n* iterations, with *n* being the number of participants in the external population. For each iteration, the resulting β-coefficients were then applied as weights for the DIS and LIS components, participants were categorized into quantiles based on the iteration-specific DIS or LIS distribution, and the bootstrap technique was used to simulate the error from the DIS and LIS weights and the estimated DIS/LIS–inflammation biomarker associations.

All analyses were conducted using SAS statistical software, version 9.3. All statistical tests were two-sided, and *P* values <0.05 or 95% CIs that excluded 1.0 were considered statistically significant.

Results

The weights for the 19-component DIS and the 4-component LIS are presented in Table 2.1. All β-coefficient weights were in the hypothesized directions, and there was a wide range of weights.

Selected characteristics of the participants in the REGARDS case-cohort according to DIS and LIS quintiles are summarized in Table 2.2. The population age range was 45–74 (mean [SD] = 61.7 [8.0]), 48.7% were men, 51.3% were women, 65.0% were white, and 35.0% were black. The DIS and LIS ranges were -1.7–1.9 and -1.1–2.4, respectively. Those in the highest relative to the lowest DIS quintile were more likely to be black, have an income <$20,000/year, have less than a college education, be a current smoker, be overweight or obese, and participate in physical activity ≤3 times/week. On average, they had lower daily dietary fiber intakes; higher plasma IL-6, IL-8, and hsCRP concentrations; and higher inflammation biomarker scores. Those in the highest relative to the lowest LIS quintile were more likely to be female or black, have less than a college education, live in the stroke belt or stroke buckle region, have a comorbidity, be a current smoker, be overweight or obese, be a non-drinker, and participate in physical activity ≤3 times/week. On average they had lower dietary fiber intakes, higher plasma IL-6 and hsCRP concentrations, and higher inflammation biomarker scores. Differences in participant characteristics across quantiles of the DIS and LIS in the entire REGARDS cohort, MAP, and CECP populations were similar to those in the REGARDS case-cohort (Appendix Tables 2.2, 2.3, and 2.4).

Pearson correlations of the DIS with the DII in the three validation populations were: r=0.67 in REGARDS, 0.64 in MAP, and 0.60 in CECP, and for the DIS and the EDII they were 0.33 in REGARDS, 0.22 in MAP, and 0.13 in CECP. There was greater quantile classification agreement between the DIS and DII than between the DIS and the EDII (Appendix Table 2.5). For example, in REGARDS, in the first and fifth quintiles there was approximately 55% and 35% agreement between the DIS and DII, and the DIS and EDII, respectively.

Associations of the DIS, LIS, DII, and EDII with inflammation biomarkers in REGARDS, MAP, and CECP are shown in Table 2.3. Higher dietary and lifestyle inflammation scores of all types were generally strongly, positively associated with inflammation biomarkers in all three studies. In REGARDS, there was a statistically significant trend of increasing odds of high plasma hsCRP

concentrations with an increasing DIS, and for those in the highest relative to the lowest DIS quintile, there was a statistically significant 66% higher odds of having a high plasma hsCRP concentration. In MAP, there was a similar trend pattern, and those in the highest relative to the lowest DIS quartile had 94% higher odds of having a high hsCRP concentration. Similarly, in CECP, those in the highest relative to the lowest DIS quantile had an estimated 42% higher odds of having a high inflammation biomarker score, although this finding was not statistically significant in this small study. The findings for the LIS were stronger than those for the DIS in all three study populations. There were statistically significant trends of increasing odds of having a high hsCRP concentration with an increasing LIS in REGARDS and MAP, with a statistically significant 4.3-fold and 7.2-fold higher odds for those in the upper LIS quantile in REGARDS and MAPs, respectively. In the small CECP study, those in the highest relative to the lowest LIS quantile had an estimated 56% higher odds of having a high inflammation biomarker score, although this finding was not statistically significant.

As also shown in Table 2.3, in REGARDS, the findings for the DIS and DII were similar, but the strengths of the associations for the EDII were much weaker, although still statistically significant. However, in MAP, the estimated positive associations involving the DIS were larger than those for the DII and EDII, whereas in CECP, these associations were larger than for those for the DII (which were close to the null), but smaller than those for the EDII, although none of the findings for the CECP study was statistically significant and the confidence intervals around the estimated associations were wide.

The joint/combined (cross-classification) associations of the DIS and LIS with high plasma hsCRP concentrations in REGARDS are presented in Table 2.4. Being in the highest relative to the lowest joint quintile of the DIS and LIS was associated with the highest odds (OR 7.3 [95% CI 6.1, 8.6]) of a high hsCRP concentration. Among those in the lowest LIS quintile, there was increasing odds of a high hsCRP concentration with a higher DIS, culminating in a statistically significant 69% higher odds for those in the highest DIS quintile. Among those in the lowest DIS quintile, there was increasing odds of a

higher hsCRP concentration with a higher LIS, culminating in a statistically significant 4.3-fold higher odds for those in the highest LIS quintile.

Associations of the DIS and LIS with hsCRP concentrations in REGARDS according to selected participant characteristics are shown in Figure 2.1 and Appendix Table 2.6. The pattern of findings across participants with different characteristics were similar, although the DIS-hsCRP association tended to be stronger among those who were not obese (similar findings for the DII/EDII-hsCRP associations shown in Appendix Table 2.7) and not a heavy drinker, and the LIS-hsCRP association tended to be somewhat stronger among those who were younger, female, had no comorbidity, and did not regularly take aspirin.

In sensitivity analyses, the associations of the equally-weighted DIS with inflammation biomarkers (Appendix Table 2.8) were similar to those for the DIS in REGARDS, somewhat weaker in MAP, and stronger in the smaller CECP. The associations of the equally-weighted LIS with inflammation biomarkers (Appendix Table 2.9) were weaker than those for the LIS in REGARDS and MAP, but stronger in CECP. The findings from the analyses of multivariable-adjusted mean inflammation biomarker values and their proportional differences across the quantiles of each dietary and lifestyle inflammation score (Appendix Table 2.10) closely paralleled those in Table 2.4. Applying the MCM/bootstrap-technique (Appendix Table 2.11) resulted in slight attenuation of the estimated associations of the DIS with inflammation biomarkers in REGARDS and MAP, but not in CECP. The estimated associations of the LIS with inflammation biomarkers were somewhat stronger when applying the MCM/bootstrap technique in MAP and CECP, but not in REGARDS. In REGARDS, the joint/combined associations of the MCM/bootstrap technique DIS and LIS (Appendix Table 2.12) and their associations according to selected characteristics (Appendix Table 2.13) followed similar patterns. The confidence intervals using the MCM/bootstrap-technique were wider, reflecting the additional random error incorporated into the estimated associations.

Discussion

Our results support that 1) individual dietary and lifestyle components contribute modestly to systemic inflammation, and 2) diet and lifestyle in aggregate both contribute substantially—lifestyle more than diet—but especially in interaction with one another. Our results also support the use of our whole foods-based DIS over the more nutrient-based DII and data-driven EDII. As discussed below, the DIS has theoretical advantages, is applicable to different populations and methods of dietary assessment and may be more useful for translation into clinical and public health dietary recommendations for inflammation reduction.

As summarized in Table 2.1, there is considerable biological plausibility/basic science support for the contributions of our dietary and lifestyle inflammation score components to inflammation. While most previous studies on the contributions of diet to inflammation focused on selected dietary constituents (e.g., nutrients), these constituents are not consumed in isolation, but rather are contained within a matrix of thousands of other known and unknown substances that may be acting and interacting along the same and complementary pathways (3,100). There is even more substantial evidence that individual lifestyle characteristics may be strongly associated with, or strongly affect, inflammation (39–46). Our findings of possible, particularly strong aggregate contributions of lifestyle to inflammation, and even stronger, synergistic contributions of diet and lifestyle to inflammation, support further investigation of dietary and lifestyle contributions to inflammation.

The DIS was more strongly, directly associated with circulating inflammation biomarkers than was the DII in REGARDS, MAP, and CECP—findings for which were robust to variations in sensitivity analyses. The DII was previously positively associated with biomarkers of inflammation in a range of populations (2,101–105). The DII was also associated with inflammation-mediated diseases, such as cardiovascular diseases and colorectal cancer, and with premature mortality (106–110). However, the DII has several limitations. First, the DII is primarily based on classically-measured nutrients and does not account for

the myriad non-classical, unmeasured, natural, anti- or pro-inflammatory compounds found in whole foods and beverages. Also, although the DII weights were drawn from findings of many studies, the weighting scheme for the contributions of the findings from those studies was somewhat arbitrary, and the developers keep some methods and data underlying the weights proprietary. Finally, the DII addresses only dietary/supplement exposures.

The DIS was also more strongly, directly associated with circulating inflammation biomarkers than was the EDII in the larger REGARDS and MAP study populations, but not in the small CECP study in which the results were unstable. The EDII was previously moderately to strongly, positively associated with a panel of inflammation biomarkers in three studies (2,102,113). The more attenuated associations of the EDII with hsCRP in REGARDS and MAP may in part be because the EDII was developed in a relatively homogenous population using a population-dependent, *a posteriori,* data-driven (vs. driven by biological plausibility) reduced rank regression approach. Dietary patterns and weights derived using reduced rank regression can be specific to the data in the population from which they are derived, making them less reproducible in other studies. For example, the weights for some EDII components were in opposite directions than would be hypothesized based on previous literature (e.g., pizza was given the strongest anti-inflammatory weight of any EDII component). Finally, the EDII addresses only dietary exposures.

The DIS and LIS have several strengths, many of which address limitations of the DII and EDII, including that: 1) both were developed in a clear, straightforward fashion, making them easy to reproduce and apply using different dietary and lifestyle measurement instruments in different study populations; 2) their relative weights are biologically plausible; 3) the use of both accounts for the contributions of both diet and lifestyle to systemic inflammation; 4) composing the DIS of whole foods facilitates clinical and public health applications; and 5) we addressed limitations in studying associations of mixed dishes with inflammation biomarker concentrations by disaggregating mixed dishes into their component parts using the MPED database.

The DIS and LIS also have some limitations. First, we developed the DIS and LIS weights in a population enriched with future stroke cases and with a sample size that limited stratified analyses. However, the cohort comparison sample was selected randomly, all individuals were disease free at the time of biomarker measurement and dietary/lifestyle questionnaire completion, and adjustment for future case status did not meaningfully affect the DIS and LIS weights. It is possible that a more comprehensive inflammation biomarker panel with which to assess the strengths of associations of the diet/lifestyle factors with systemic inflammation would have yielded more accurate associations, and in the REGARDS and MAP validation populations, only hsCRP was available. However, the REGARDS case-cohort biomarker panel was reliably measured in a heterogeneous population, and the validation results were similar across three validation populations, including one with a larger inflammation biomarker panel. Inherent to studying dietary data are the known limitations of FFQs (e.g., respondent error, limited food options, and unmeasured food preparation methods). The DIS and LIS components' weights are based on cross-sectional associations, so it is possible that if diet and biomarkers had been assessed at intervals over, say, a year, and averaged, the associations may have been somewhat different. However, FFQs are designed to capture dietary patterns over an extended period, and have been found to do so reasonably well (190).

Taken together with previous literature, our findings support that individual components of diet and lifestyle may contribute modestly to systemic inflammation, but that diet in aggregate and lifestyle in aggregate, contribute substantially—lifestyle more so than diet—and especially in interaction with one another. Our results also support the use of our whole foods-based dietary inflammation score over the more nutrient-based DII and data-driven EDII. The DIS and LIS address some of the limitations of previous dietary inflammations scores, are applicable to different populations and methods of dietary/lifestyle assessment, and may be more useful for formulating clinical and public health dietary recommendations for inflammation reduction for disease prevention.

Tables and Figure

Table 2.1. Components of the dietary (DIS) and lifestyle (LIS) inflammation scores, their descriptions, rationales for inclusion, and assigned weights

Components	General descriptions	Rationales for inclusion	Weights[a]
DIS components[b]			
Leafy greens and cruciferous vegetables	Kale, spinach, lettuce (iceberg, head, romaine, or leaf), broccoli, Brussels sprouts, cabbage, cauliflower, parsley, watercress	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, Nuclear factor-erythroid 2 (NF-E2)-related factor 2 (Nrf2), which plays a key role in cellular protection against oxidative stress and inflammation(50–60)	-0.14
Tomatoes	Tomatoes, tomato juice, tomato sauce, salsa	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(61–64)	-0.78
Apples and berries	Fresh apples, pears, apple juice or cider, strawberries, blueberries, raspberries, cherries	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(65–67)	-0.65
Deep yellow or orange vegetables and fruit	Cantaloupe, peaches, carrots, dark yellow or orange squash, figs	Contain pro-vitamin A carotenoids (e.g., β-carotene and α-carotene), which have a conjugated double-bond structure making them strong antioxidants(68)	-0.57
Other fruits and real fruit juices	Other fresh fruits than those listed above (e.g., pineapples, honeydew, grapes, kiwi, watermelon, lemon, grapefruit, and oranges), orange juice, grapefruit juice, apple juice, grape juice, and other real fruit juice	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(54,69–76)	-0.16
Other vegetables	Other vegetables than those listed above (e.g., okra, green peppers, onions, zucchini, and eggplant)	Contain antioxidants and polyphenols with similar mechanisms to those described above	-0.16
Legumes	String beans, peas, lima beans, lentils, and beans (excluding soybeans)	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(53,77,78)	-0.04

Fats	Mayonnaise, margarine, butter, vegetable oil	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(79–81); contain saturated fats that mimic lipopolysaccharide (LPS), a pro-inflammatory stimulant, in the gut; increase cytotoxic, pro-oxidant, and pro-inflammatory bile acids in the colon(79,82)	0.31
Fish	Tuna fish, salmon, other light and dark meat fish, breaded fish cakes or fish sticks	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(83–85)	-0.08
Poultry	Chicken or turkey with and without skin	Inversely associated with inflammation markers(86); contain low amounts of saturated fat(87); contain *l*-arginine, which improves endothelium-dependent dilation (precursor of the endogenous vasodilator nitric oxide) and decreases platelet aggregation and monocyte adhesion(53)	-0.45
Red and organ meats	Hamburger, beef, pork, lamb, liver, gizzards, other organ meats	Contain heme iron, which increases the bioavailability of iron, which in turn increases oxidative stress; contain Ω-6 fatty acids and saturated fat (see mechanisms in 'Fats' above)	0.02
Processed meats	Bacon, beef or pork hotdogs, chicken or turkey hot dogs, salami, bologna, other 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(86,88)	0.68
Added sugars	Sugar-sweetened soda, punch, lemonade, fruit drinks, chocolate candy bars, other mixed candy bars, candy without chocolate, jams, jellies, preserves, syrup or honey, dried or canned fruit	Induce postprandial hyperglycemia, which act as stressful stimuli through subsequent repeated mild postprandial hypoglycemia(89) and reduce nitric oxide availability (play role in regulation of inflammatory response(90)); elevate pro-inflammatory free fatty acid levels(83); produce oxidative stress through oxidation of membrane lipids, proteins, lipoproteins, and DNA(91)	0.56
High-fat dairy	Whole milk, 2% milk, cream, high-fat ice cream, high-fat yogurt, cream cheese, other high-fat cheeses	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 conjugated linoleic acids (CLA), *cis*- and *trans*-palmitoleic acid, butyric acid, phytanic acid, and alpha-linolenic acid(92–94)	-0.14
Low-fat dairy	Skim milk, 1% milk, low-fat yogurt, low-fat ice cream, low-fat cottage or ricotta cheese, low-fat cheeses	Similar mechanisms to high-fat dairy (see above), with lower fat content	-0.12
Coffee and tea	Coffee (decaffeinated and regular), herbal and non-herbal tea	Tea contains flavonoids and antioxidants (e.g., epicatechin and quercetin)(95); 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(77,96)	-0.25
Nuts	Peanut butter, peanuts, other nuts	Contain Ω -3 fatty acids(83,84,97,98) and *l*-arginine(53) (mechanisms similar to those described above in 'Fish' and 'Poultry')	-0.44

Refined grains and starchy vegetables	Cold and cooked breakfast cereal, white or dark bread, bagels, English muffins, rolls, corn bread, white rice, pasta, pancakes, waffles, potatoes (French fried, scalloped, baked, boiled or mashed), sweet potato/yams, potato chips, crackers, tortillas, popcorn, pretzels, cookies, brownies, doughnuts, cake, pie, sweet rolls, coffee cakes, granola bars	Sparse in nutrients; some processed grains contain emulsifiers, which potentially break down mucin in the gut leading to inflammation(99); and induce hyperglycemia (mechanisms described similar to those described above in 'Added Sugars')	0.72
Supplement score[c]	Ranked score of supplements, including: vitamins A, B_1, B_{12}, B_6, C, D, and E; and β-carotene, folate, niacin, riboflavin, calcium, copper, iron, magnesium, selenium, and zinc	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)	-0.80
LIS components[d]			
Heavy drinker	Heavy (> 7 drinks/wk for women, > 14 drinks/wk drinks for men) vs. non-drinker	Heavy alcohol intake results in oxidative stress via oxidation of ethanol to acetaldehyde(39,40)	0.30
Moderate drinker	Moderate (1 – 7 drinks/wk for women, 1 – 14 drinks/wk for men) vs. non-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)(41) and inhibits IL-6 production and activity(42)	-0.66
Moderately physically active[e]	Exercises 1 – 3 times/wk vs. does not exercise	Physical activity improves systemic plasma antioxidant capacity (increases adaptive responses to oxidative stress), increases concentrations of anti-inflammatory cytokines, and lowers vascular wall inflammation(43,44)	-0.18
Heavily physically active[e]	Exercises ≥ 4 times/wk vs. does not exercise	Mechanisms similar to those described above	-0.41
Current smoker	Currently smokes tobacco vs. does not currently smoke tobacco	Toxins injure tissues, upregulating cytokines and acute phase reactants(45)	0.50
Overweight BMI	Overweight BMI vs. normal BMI	Adipose tissue synthesizes and releases pro-inflammatory adipokines, such as plasminogen activator inhibitor–1 (PA1) and TNF-α(43,46)	0.89
Obese BMI	Obese BMI vs. normal BMI	Mechanisms similar to those described above	1.57

Abbreviations: BMI, body mass index; hsCRP, high-sensitivity C-reactive protein; DIS, dietary inflammation score; LIS, lifestyle inflammation score; hsCRP, high-sensitivity C-reactive protein; IL, interleukin; NSAID, nonsteroidal anti-inflammatory drug

[a] Weights are β coefficients from multivariable linear regression models conducted in the REGARDS case-cohort sample (N = 639), representing the average change in a summary inflammation biomarker z-score (sum of z-scores for hsCRP, IL-6, IL-8, IL-10 [the latter with a negative sign]) per one standard deviation increase in a dietary component or the presence of lifestyle component. Covariates in the final model 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), regular use of aspirin, other NSAIDs, or lipid-lowering medications (≥ twice/wk), hormone replacement therapy (among women), total energy intake (kcal/day), season of baseline interview (Spring, Summer, Fall, or Winter); and all the dietary/lifestyle components in the DIS and LIS

[b] Dietary components were standardized to the case-cohort sample, by sex, to a mean of zero and standard deviation of 1

[c] 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)

[d] All lifestyle components were dummy variables, coded as '1' for the non-referent category and '0' for the referent category

[e] When calculating the LIS using lifestyle behavior measurement instruments where 'times physically active per week' cannot be derived, the given variables (e.g., METs/wk) were ranked into quantiles, which were taken to construct dummy variables, and the respective weights were similarly applied

Table 2.2. Selected characteristics of the participants in the REGARDS case-cohort (N = 639) across quintiles of the DIS and LIS

	DIS Quintile				LIS Quintile			
Characteristics[a]	1 (N =129)	3 (N =127)	5 (N =127)	p^b	1 (N =132)	3 (N =131)	5 (N =113)	p^b
Score range	-1.7 to -0.4	-0.1 to 0.2	0.6 to 1.9		-1.1 to -0.2	-0.5 to 0.7	1.4 to 2.4	
Demographics								
Age, y	62.8 (7.8)	61.6 (8.1)	60.3 (8.2)	0.09	62.1 (9.1)	62 (7.1)	61.2 (7.9)	0.83
Male, %	48.8	48.8	48.8	1.00	54.4	51.7	39.3	0.03
White, %	79.8	60.6	41.7	<0.001	80.9	61.1	57.8	<0.001
Income < $20k, %	6.2	14.2	24.4	0.001	20.6	15.4	21.5	0.02
College graduate or higher, %	59.7	40.2	21.3	<0.001	52.9	40.3	25.2	<0.001
Stroke Belt or Buckle resident, %	47.3	52.0	63.8	0.22	48.5	61.7	63.0	0.003
Medical history								
Has comorbidity[c], %	37.2	33.1	44.9	0.11	26.5	37.6	49.6	0.003
Take NSAID/aspirin ≥ twice/wk, %	55.8	44.9	50.4	0.50	48.2	49.0	53.3	0.89
HRT user (women), %	65.7	64.6	49.2	0.15	64.5	69.4	61.5	0.62
Lifestyle behaviors								
Current smoker, %	10.1	11.8	25.2	<0.001	5.2	18.1	23.0	<0.001
Normal BMI, %	33.6	17.5	16.0	<0.001	79.0	4.7	0.0	<0.001
Non-drinker, %	48.8	48.0	61.4	0.46	37.5	53.7	88.2	<0.001
Exercises ≥ 4 times/wk, %	37.2	33.1	21.3	<0.001	57.4	29.5	0.7	<0.001
Dietary intake								
Total energy intake, kcal/day	1,717 (670)	1,809 (713)	1,902 (905)	0.23	1,728 (550)	1,845 (798)	1,844 (896)	0.20
Dietary fiber, g/1,000 kcal/day	12.5 (3.9)	9.2 (3.0)	6.7 (2.5)	<0.001	10.2 (3.7)	9.3 (3.3)	9.1 (3.9)	0.003
Total fat intake, % kcal/day	0.4 (0.1)	0.4 (0.1)	0.4 (0.1)	0.21	0.4 (0.1)	0.4 (0.1)	0.4 (0.1)	0.05
Carbohydrates, % kcal/day	0.5 (0.1)	0.5 (0.1)	0.5 (0.1)	0.20	0.5 (0.1)	0.5 (0.1)	0.5 (0.1)	0.08
Protein, % kcal/day	0.2 (0.0)	0.1 (0.0)	0.1 (0.0)	<0.001	0.1 (0.0)	0.2 (0.0)	0.1 (0.0)	0.73
Inflammation markers								
Plasma IL-6, pg/mL	2.2 (1.7)	2.6 (1.7)	3.2 (1.7)	<0.001	2.0 (1.7)	2.7 (1.7)	3.2 (1.7)	<0.001
Plasma IL-8, pg/mL	2.1 (1.6)	2.2 (1.8)	2.6 (1.5)	0.003	2.2 (1.8)	2.2 (1.6)	2.4 (1.7)	0.10
Plasma IL-10, pg/mL	7.3 (2.1)	9.0 (2.0)	8.0 (1.8)	0.12	8.0 (2.1)	8.3 (1.9)	8.4 (2.0)	0.98
Plasma hsCRP, mg/dL	1.2 (2.7)	1.7 (2.7)	2.5 (2.5)	<0.001	0.9 (2.6)	2.0 (2.4)	2.7 (2.4)	<0.001
Inflammation biomarker score	-0.6 (2.2)	-0.2 (2.2)	1.1 (1.8)	<0.001	-1.1 (2.2)	0.2 (2.1)	1.0 (1.9)	<0.001

Abbreviations: BMI, body mass index; DIS, dietary inflammation score; HRT, hormone replacement therapy; hsCRP, high-sensitivity C-reactive protein; IL, interleukin; LIS, lifestyle inflammation score; NSAID, nonsteroidal anti-inflammatory drug; REGARDs, Reasons for Racial and Geographic Differences in Stroke Study

[a] Presented as means (standard deviation) unless otherwise specified

[b] p-values calculated using χ^2 test for categorical variables and ANOVA for continuous variables

[c] Includes a history of cancer, heart disease, diabetes mellitus, or chronic kidney disease

Table 2.3. Cross-sectional associations of the dietary and lifestyle inflammation scores with plasma inflammation biomarker concentrations[a] in the REGARDS (N = 14,210), MAP (N = 433), and CECP (N = 173) study populations

	Inflammation Score[b]							
	DIS[c]		LIS[d]		DII[e]		EDII[e]	
	N	Adjusted OR (95% CI)	N	Adjusted OR (95% CI)	N	Adjusted OR (95% CI)	N	Adjusted OR (95% CI)
REGARDS, Quintiles								
Q1	2,843	1.00	3,149	1.00	2,843	1.00	2,843	1.00
Q2	2,842	1.25 (1.10, 1.41)	2,226	1.58 (1.38, 1.82)	2,842	1.32 (1.17, 1.50)	2,842	1.09 (0.96, 1.23)
Q3	2,842	1.38 (1.22, 1.56)	3,263	2.31 (2.05, 2.61)	2,842	1.31 (1.15, 1.48)	2,842	1.16 (1.02, 1.31)
Q4	2,842	1.50 (1.32, 1.70)	2,582	2.74 (2.42, 3.12)	2,842	1.42 (1.25, 1.62)	2,842	1.15 (1.02, 1.30)
Q5	2,841	1.66 (1.46, 1.90)	2,990	4.29 (3.79, 4.87)	2,841	1.56 (1.35, 1.81)	2,841	1.29 (1.14, 1.46)
P_{trend}		*<0.001*		*<0.001*		*<0.001*		*<0.001*
MAP, Quartiles								
Q1	110	1.00	116	1.00	110	1.00	110	1.00
Q2	108	1.66 (0.89, 3.12)	108	2.39 (1.28, 4.46)	108	1.08 (0.57, 2.02)	108	1.54 (0.84, 2.82)
Q3	109	1.33 (0.70, 2.53)	113	2.53 (1.35, 4.72)	109	1.50 (0.79, 2.85)	109	0.85 (0.45, 1.62)
Q4	106	1.94 (1.00, 3.79)	96	7.24 (3.70, 14.17)	106	1.33 (0.66, 2.68)	106	1.21 (0.63, 2.33)
P_{trend}		*0.12*		*<0.001*		*0.63*		*0.91*
CECP, Quantiles								
Q1	87	1.00	85	1.00	87	1.00	87	1.00
Q2	86	1.42 (0.71, 2.82)	88	1.56 (0.82, 2.97)	86	0.94 (0.44, 2.01)	86	1.72 (0.87, 3.42)

Abbreviations: BMI, body mass index; CECP, Calcium and Colorectal Epithelial Cell Proliferation trial; CI, confidence interval; DII, dietary inflammatory index; DIS, dietary inflammation score; EDII, empirical dietary inflammation index; hsCRP, high-sensitivity C-reactive protein; MAPs, Markers of Adenomatous Polyps; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; REGARDS, Reasons for Racial and Geographic Differences in Stroke Study

[a] In the REGARDS and MAPs studies, the outcome was hsCRP concentrations categorized as ≤/> 3 mg/dL, and in the CECP trial, the outcome was the inflammation biomarker score (comprising IL-1β, IL-6, IL-8, IL-12p40, TNF-α, VEGF, and IL-10 [the latter with a negative sign]) dichotomized as ≤/> 0 (based on the study population median); all associations assessed using multivariable logistic regression

[b] Weights for all dietary and lifestyle components in the DIS and LIS are equal to the maximum likelihood for the β coefficients obtained from multivariable linear regression models (dependent variable: summary inflammation biomarker z-score) in the REGARDS case-cohort sample; DII and EDII: weights and components derived from Shivappa, et al (1) and Tabung, et al (2), respectively

[c] For each study, covariates in the DIS logistic regression models were:

REGARDS: age, sex, race (Black or White), education (less than high school and high school graduate or some college or more), region (Belt, Buckle, Other), comorbidity score (comprises a history of cancer, heart disease, diabetes mellitus, or chronic kidney disease), current hormone replacement therapy use (among women), smoking (current or former and never), body mass index (BMI; kg/m^2), alcohol intake (non-drinker, moderate-drinker, or heavy-drinker), physical activity level (exercises 0, 1-3, or ≥ 4 times/wk), total energy intake (kcal/day), season of baseline interview (Spring, Summer, Fall, or Winter), and regular use of aspirin, other NSAIDs, or lipid lowering medications (≥ twice/wk)

MAP: age, sex, education (less than high school and high school graduate or some college or more), current hormone replacement use (among women), smoking (current or former and never), BMI category (based on World Health Organization BMI classifications), alcohol intake (non-drinker, moderate-drinker, or heavy-drinker), physical activity level (tertiles based on the distribution of weekly metabolic equivalents of task–min/wk expenditure in the study population), total energy intake (kcal/day), study (MAP I or MAP II), and regular (≥ once/wk) aspirin or other NSAID use

CECP: age, sex, a comorbidity score (comprising diabetes mellitus or heart disease), smoking (current or former and never), BMI (kg/m^2), alcohol intake (non-drinker, moderate-drinker, or heavy-drinker), physical activity level (tertiles based on the distribution of weekly minutes of physical activity in the study population), and total energy intake (kcal/day), and regular (≥ once/wk) aspirin or other NSAID use

[d] For each study, covariates in the LIS logistic regression models were:

REGARDS: age, sex, race (Black or White), education (less than high school and high school graduate or some college or more), region (Belt, Buckle, Other), comorbidity score (comprises a history of cancer, heart disease, diabetes mellitus, or chronic kidney disease), current hormone replacement therapy use (among women), energy intake (kcal/day), season of baseline interview (Spring, Summer, Fall, or Winter), the DIS, and regular use of aspirin, other NSAIDs, or lipid lowering medications (≥ twice/wk)

MAP: age, sex, education (less than high school and high school graduate or some college or more), current hormone replacement use (among women), total energy intake (kcal/day), study (MAP I or MAP II), the DIS, and regular aspirin or other NSAID use (≥ once/wk)

CECP: age, sex, a comorbidity score (comprising diabetes mellitus or heart disease), total energy intake (kcal/day), the DIS, and regular aspirin or other NSAID use (≥ once/wk)

[e] For each study, covariates in DII and EDII logistic regression models included those listed in footnote 'c', except for alcohol intake

Table 2.4. Joint/combined associations of the DIS and LIS with plasma hsCRP concentrations[a] in the remaining REGARDs cohort (N = 14,210)

	LIS quintiles[b]										
	1		**2**		**3**		**4**		**5**		*p-interaction*[c]
	n	OR (95% CI)	*n*	OR (95% CI)	*n*	OR (95% CI)	*n*	OR (95% CI)	*n*	OR (95% CI)	
DIS quintiles[b]											
1	938	1.00 (ref)	461	1.58 (1.38, 1.82)	649	2.31 (2.04, 2.61)	410	2.74 (2.41, 3.11)	385	4.30 (3.80, 4.87)	
2	782	1.25 (1.11, 1.42)	464	1.98 (1.65, 2.38)	680	2.89 (2.43, 3.43)	465	3.43 (2.88, 4.09)	451	5.38 (4.52, 6.41)	
3	573	1.41 (1.24, 1.59)	469	2.23 (1.86, 2.67)	664	3.24 (2.74, 3.85)	512	3.85 (3.24, 4.58)	624	6.05 (5.10, 7.16)	
4	497	1.53 (1.35, 1.73)	423	2.42 (2.02, 2.89)	653	3.52 (2.97, 4.17)	572	4.18 (3.52, 4.97)	697	6.56 (5.54, 7.77)	
5	359	1.69 (1.49, 1.92)	409	2.68 (2.23, 3.21)	617	3.90 (3.28, 4.63)	623	4.63 (3.90, 5.50)	833	7.26 (6.13, 8.60)	*0.03*

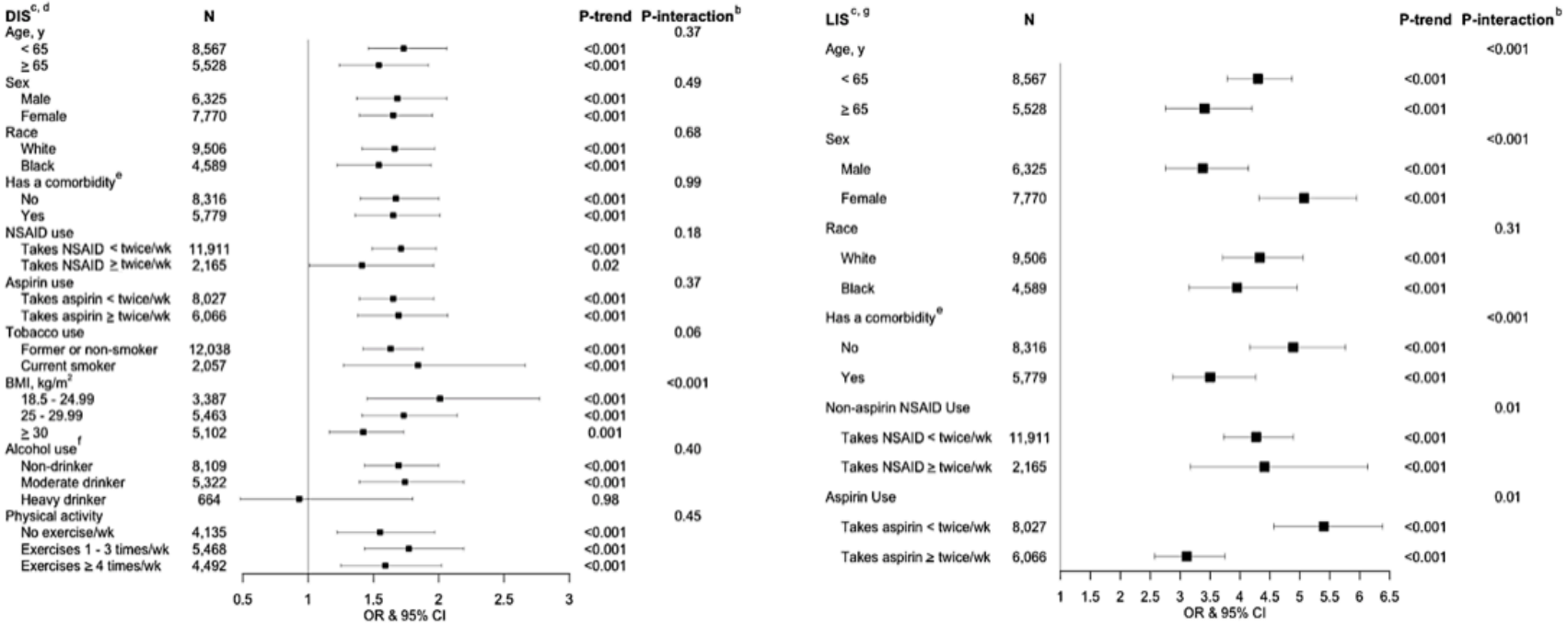
Abbreviations: CI, confidence interval; DIS, dietary inflammation score; hsCRP, high-sensitivity C-reactive protein; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; REGARDS, Reasons for Racial and Geographic Differences in Stroke Study

[a] The outcome was hsCRP concentrations categorized as ≤/> 3 mg/dL; all associations assessed using multivariable logistic regression

[b] Covariates in logistic regression model: age, sex, race (Black or White), education (less than high school and high school graduate or some college or more), region (Belt, Buckle, Other), comorbidity score (comprises a history of cancer, heart disease, diabetes mellitus, or chronic kidney disease), current hormone replacement therapy use (among women), energy intake (kcal/day), season of baseline interview (Spring, Summer, Fall, or Winter), and self-reported regular use of aspirin, other NSAIDs, or lipid lowering medications (≥ twice/wk)

[c] From DIS*LIS interaction term in the full logistic regression model, calculated using the Wald test

Figure 2.1. Associations[a] of the dietary and lifestyle inflammation scores with plasma hsCRP concentrations, by selected participant characteristics in the REGARDs cohort (N = 14,210)



Abbreviations: BMI, body mass index; CI, confidence interval; DIS, dietary inflammation score; hsCRP, high-sensitivity C-reactive protein; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; REGARDS, Reasons for Racial and Geographic Differences in Stroke Study

[a] Only ORs (95% CIs) for fifth relative to first quintiles shown; the outcome was hsCRP concentrations categorized as ≤/> 3 mg/dL; all associations assessed using multivariable logistic regression; ORs and 95% CIs are for comparisons of participants in the fifth relative to first quintile of a score

[b] For interaction term for categorized DIS/LIS in logistic regression models, calculated using the Wald test

[c] Weights for all dietary and lifestyle components in the DIS and LIS are equal to the maximum likelihood for the β coefficients obtained from multivariable linear regression models (dependent variable: summary inflammation z-score) in the REGARDS case-cohort sample.

[d] Covariates in the DIS logistic regression models were: age, sex, race (Black or White), education (less than high school and high school graduate or some college or more), region (Belt, Buckle, Other), comorbidity score (comprises a history of cancer, heart disease, diabetes mellitus, or chronic kidney disease), current hormone replacement therapy use (among women), smoking (current or former and never), body mass index (BMI) (in kg/m^2), alcohol intake (non-drinker, moderate-drinker, or heavy-drinker), physical activity level (exercises 0, 1-3, or ≥ 4 times/wk), total energy intake (kcal/day), season of baseline interview (Spring, Summer, Fall, or Winter), and self-reported regular use of aspirin, other NSAIDs, or lipid lowering medications (≥ twice/wk)

[e] Comorbidities include a history of cancer, heart disease, diabetes mellitus, or chronic kidney disease

[f] Heavy drinker defined as > 7 drinks/wk for women and > 14 drinks/wk drinks for men; moderate drinker defined as 1 – 7 drinks/wk for women, 1 – 14 drinks/wk for men

[g] Covariates in the LIS logistic regression models: age, sex, race (Black or White), education (less than high school and high school graduate or some college or more), region (Belt, Buckle, Other), comorbidity score (comprises a history of cancer, heart disease, diabetes mellitus, or chronic kidney disease), current hormone replacement therapy use (among women), energy intake (kcal/day), season of baseline interview (Spring, Summer, Fall, or Winter), the DIS, and self-reported regular use of aspirin, other NSAIDs, or lipid lowering medications (≥ twice/wk)

Chapter 3. Associations of Novel Dietary and Lifestyle Inflammation Scores with Incident, Sporadic Adenoma

Doratha A. Byrd,[1] Suzanne E. Judd,[2] W. Dana Flanders,[1] Terryl J. Hartman,[1] Veronika Fedirko,[1] Roberd M. Bostick[1,3]

[1]Department of Epidemiology, Emory University Rollins School of Public Health, Atlanta, Georgia. [2]Department of Biostatistics, University of Alabama at Birmingham School of Public Health, Birmingham, Alabama. [3]Winship Cancer Institute, Emory University, Atlanta, Georgia.

Abstract

Colorectal carcinogenesis is mechanistically linked to inflammation and highly associated with diet and lifestyle factors that may affect chronic background inflammation. We previously developed dietary (DIS) and lifestyle (LIS) inflammation scores to characterize the collective contributions of 19 food groups and four lifestyle exposures to systemic inflammation. Both scores, comprising inflammation biomarker-weighted components, were more strongly directly associated with circulating inflammation biomarkers in three validation populations than were the previously reported Dietary Inflammation Index (DII) and Empirical Dietary Inflammation Index (EDII).

We calculated a DIS, LIS, DII, and EDII in three pooled case-control studies of incident, sporadic colorectal adenoma (N = 777 cases, 2,002 controls) in which extensive dietary and lifestyle data were collected, and investigated their associations with adenoma using multivariable unconditional logistic regression. Higher scores reflect higher balances of pro- to anti-inflammatory exposures.

For those in the highest relative to the lowest quintiles of the DIS and LIS, the multivariable-adjusted odds ratios (95% confidence intervals [CIs]) were: 1.4 (95% CI: 1.0, 1.8; P_{trend}: 0.09) and 2.0 (95% CI: 1.5, 2.7; P_{trend}: <0.001), respectively—estimated associations that were stronger than those for the DII and EDII. The DIS and LIS associations were strongest for adenomas with high-risk characteristics. Those in the highest relative to the lowest joint DIS/LIS quintile had a statistically significant 2.9-fold higher odds of colorectal adenoma.

These results support that diets and lifestyles with higher balances of pro- to anti-inflammatory exposures may be associated with higher risk for incident, sporadic colorectal adenoma.

Introduction

Colorectal cancer (CRC) is the second leading cause of cancer death in the United States among men and women combined (179). Chronically higher inflammation may play a role in colorectal carcinogenesis, which is also highly associated with diet and lifestyle factors that may affect chronic background inflammation (139,146–148,176,177,196).

The contributions of individual dietary and lifestyle exposures to systemic inflammation may be small, but collectively may be substantial. To address this, dietary inflammation scores to characterize the collective contributions of dietary factors to systemic inflammation were developed, such as the dietary inflammatory index (DII) (1), which was previously found to be moderately, directly associated with colorectal adenoma prevalence among men, but not women (170). The DII's limitations include issues with reproducibility and assumptions, a heavy focus on nutrients, and exclusion of lifestyle factors; hence, there is a need for further investigation into the role of dietary- and lifestyle-associated inflammation in relation to risk for colorectal neoplasms, using tools that address the DII's limitations.

We previously developed novel, biomarker panel-weighted, dietary (DIS) and lifestyle (LIS) inflammation scores to characterize the collective contributions of dietary and lifestyle exposures to systemic inflammation. The DIS predominantly comprises whole foods and beverages, which encompass thousands of bioactive substances. The LIS includes lifestyle-related exposures. We found that, in three validation populations, both scores were more strongly, directly associated with biomarkers of inflammation than was the DII or another previously developed dietary inflammation score, the empirical DII (EDII) (2). As reported herein, we investigated associations of the DIS and LIS, and for contrast, the DII and EDII, with incident, sporadic adenoma in a pooled case-control study.

Methods

Study population

We pooled data from three methodologically similar case-control studies of incident, sporadic colorectal adenomas conducted by the same principal investigator (RMB). The pooled studies comprised the Cancer Prevention Research Unit Study (CPRU; Minnesota, 1991 – 1994) (197), the Markers of Adenomatous Polyps (MAP) Studies I (MAP l; North Carolina; 1994 – 1997) (188), and II (MAP Il; South Carolina; 2002) (189), which were described previously. Analyses using the pooled data were also published (93,198–200).

Participants in the three studies were recruited from patients scheduled to undergo outpatient, elective colonoscopy for screening or gastrointestinal symptoms in large, community-based gastroenterology practices, using identical recruitment, eligibility criteria, and data collection procedures. Eligible individuals were 30 – 74 years old who could speak English and had no contraindications for colonoscopy, and no history of an inflammatory bowel disease, colorectal adenoma, cancer (except non-melanoma skin cancer), or known genetic syndromes associated with colonic neoplasia. The participation rates were similar in all three studies (68% – 76%).

Using standardized forms, the colonoscopists documented colon sites and in vivo sizes of polyps they found during complete, clean colonoscopies. After removal, all polyps were examined histologically by a single index study pathologist using diagnostic criteria established by the National Polyp Study (201). Participants who had a pathology-confirmed adenoma removed during colonoscopy were considered cases, whereas those with no adenomatous or hyperplastic polyps found during colonoscopy were considered controls. In the CPRU study, there were two additional sets of controls: 1) patients with no adenomatous or hyperplastic polyps on CRC screening using flexible sigmoidoscopy in the same community practices as the colonoscopy-based controls, and 2) individuals randomly selected from the

general population (using electronic drivers' license lists) and frequency matched to the colonoscopy patients by 5-year age group, sex, and zip code) in the Minneapolis–St. Paul metropolitan region who reported no history of colorectal neoplasms. For our analyses, all cases and controls were combined into one case and one control group, respectively.

Of the eligible cases and controls, we additionally excluded those diagnosed with hyperplastic polyps only (N = 298), those with >15% missing FFQ responses or who had implausible estimated energy intakes (<500 and >6,000 kcal/day) (N = 20), and those missing data on smoking status, physical activity, alcohol intake, or body mass index (BMI) (N = 55). The final analytic sample size was 777 cases and 2,002 controls.

The studies were approved by the institutional review boards of the institutions at which they were conducted, and all participants provided written informed consent.

Data Collection

Prior to undergoing endoscopy and determination of case/control status, participants provided detailed information on their demographic characteristics, personal medical history, diet, lifestyle, and anthropometrics.

Self-reported dietary and nutritional supplement intakes over the past 12 months were assessed using validated self-administered Willett food frequency questionnaires (FFQ) (190). A standard portion size and nine possible frequency-of-consumption responses, ranging from ‘‘never, or less than once per month’’ to ‘‘6 or more times per day’’ were given for each line item. Total daily energy and nutrient intakes were calculated by summing energy and nutrients, respectively, from all food and supplement sources with using the dietary database developed by Willett (190,191). Physical activity was assessed using modified Paffenbarger questionnaires (192). Height and weight were self-reported.

Description of the DIS and LIS

The DIS and LIS were developed to characterize the collective contributions of foods and beverages and lifestyle to systemic inflammation. They were developed in a diverse subset of participants in the previously described Reasons for Geographic and Racial Differences in Stroke Study (REGARDS) cohort (181), on whom circulating inflammation biomarker concentrations were measured (N = 639). Briefly, REGARDS is a national, on-going prospective cohort study that recruited 30,239 participants ≥45 years old January 2003 – October 2007, with oversampling of black and Southeastern United States residents. To develop the DIS and LIS, we used a case-cohort sample nested in REGARDS (187) that had a panel of plasma inflammation biomarkers measured at baseline. To be included in the analytic sub-sample, these individuals must have had plausible total energy intakes (500 – 6,000 kcal/day), <10% of FFQ items missing, <2 comorbidities, no end-stage renal disease, and have been <75 years old.

As outlined in Appendix Table 3.1, the DIS includes 19 *a priori*-selected score components comprising whole foods, beverages, and nutritional supplement use based on Block 98 FFQ (183,184) responses in the REGARDS case-cohort. *A priori*-selected components of the LIS include: smoking status, physical activity, alcohol intake, and BMI. We standardized each food group (all continuous), by sex, to a mean of 0 and standard deviation of 1.0. For the LIS, since all components were categorical variables, we created dummy variables. In REGARDS, as previously reported, to create weights for the score components, we used multivariable linear regression to assess the association of each component with a biomarker inflammation score. The biomarker score was the sum of normalized circulating concentrations of high sensitivity C-reactive protein, interleukin (IL)-6, IL-8, and IL-10 [the latter with a negative sign]). The sum of the weighted components comprises the score, such that a higher score indicates a higher balance of pro-inflammatory to anti-inflammatory exposures.

Constructing the DIS and LIS in the pooled case-control studies

The DIS and LIS were constructed in the pooled case-control studies as summarized in Table 3.1. We disaggregated mixed dishes into their component parts using the "My Pyramid Equivalents Database", as described previously (194), and assigned the disaggregated components into the DIS food groups as appropriate. After composing food groups based on responses from the Willett FFQ, we standardized each food group to a mean of 0 and standard deviation of 1.0 based on the distribution among the controls. To account for supplemental vitamin/mineral use, we calculated a supplement score by ranking supplemental micronutrient intakes, based on the sex- and study-specific distributions among the controls, into tertiles. The tertiles were assigned values of 0 – 2 and multiplied by +1 or -1 for hypothesized anti- or pro-inflammatory micronutrients, respectively; then the values were summed.

To construct the LIS, we categorized smoking as 'current' or 'former and never', and BMI according to World Health Organization (WHO) guidelines as normal (18.5 – 24.99 kg/m^2), overweight (25 – 29.99 kg/m^2), or obese (BMI $\geq$30 kg/m^2). Heavy alcohol consumption for men and women was defined as >2 or >1 drinks/day respectively; moderate consumption was defined as individuals who consumed alcohol in less than these amounts. For physical activity, we ranked participants according to tertiles, based on the distribution among the controls, of weekly metabolic equivalents of task (MET)-hours of moderate plus vigorous physical activity.

Statistical analyses

We categorized participants into quintiles of each inflammation score based on its distribution among the controls. The characteristics of the study population were summarized and compared by case/control status, using chi-square tests for categorical variables and ANOVA for continuous variables.

We used multivariable unconditional logistic regression to assess associations of the DIS and LIS with incident, sporadic adenoma. We also examined whether the associations of the inflammation scores with

adenoma differed by adenoma location (right colon, left colon, or rectum) or by advanced adenoma characteristics, including multiplicity (≥2 adenoma), size ≥1 cm, having a villous component or moderate or severe atypia. A term for the sex-specific median (based on the distribution among the controls) of each inflammation score quintile was entered as a continuous variable into the multivariable regression models to test for trend. We also conducted a joint/combined (cross-classification) analysis, in which the reference group was participants in the joint first quintile of both scores, to assess potential interaction between the DIS and LIS.

Consideration for inclusion of covariates in the above described multivariable logistic regression models were based on biological plausibility, previous literature, and the magnitude of change in the odds ratio when including/excluding the variable from the model. Covariates considered for all models included age, sex, education, regular aspirin or other non-steroidal anti-inflammatory drug (NSAID) use, hormone replacement therapy use (for women), family history of CRC in a first degree relative, and total energy intake. Covariates considered for the LIS models also included an equally-weighted DIS (described below) and former smoking status; covariates considered for the DIS models also included smoking status, BMI, alcohol intake, and physical activity.

To investigate potential effect modification, separate analyses were conducted for the DIS and LIS within categories of age (dichotomized at 57 years old), sex, regular (≥once/wk) aspirin or other NSAID use (yes/no), family history of CRC in a first degree relative (yes/no), study (MAP I, MAP II, and CPRU), and for the DIS, within categories of current smoking status (never, former, or current), BMI (normal, overweight, or obese), alcohol status (current non-drinker, moderate drinker, or heavy drinker), and physical activity (tertiles of MET-hrs/wk of moderate and vigorous activity). We assessed effect modification by comparing the stratum-specific estimates and by calculating Wald test p-values for model interaction terms.

Sensitivity analyses

To assess the sensitivity of the associations to various considerations, we repeated the analyses with the following variations. First, we investigated associations of an equally-weighted DIS and LIS with adenoma. We constructed the equally-weighted versions by assigning positive or negative equal weights to dietary/lifestyle components we hypothesized *a priori* to be pro-inflammatory or anti-inflammatory, respectively. Next, we calculated other previously reported dietary inflammation scores, the DII and EDII, as described by Shivappa et al. (1) and Tabung et al. (12), respectively. Finally, recognizing that the estimated strengths of associations of diet/lifestyle behaviors with inflammation biomarker concentrations contain random error and may differ in this external population, we simulated a range of DIS and LIS weight estimates using Monte Carlo methods (MCM) (114) over 360 iterations. For each iteration, the resulting β-coefficients were applied as weights for the DIS and LIS components, participants were categorized into quintiles based on the iteration-specific DIS or LIS distribution among the controls, and the bootstrap technique was used to simulate the error from the DIS and LIS weights and the estimated DIS-/LIS-inflammation biomarker associations.

Two-sided *P* values <0.05 or 95% confidence intervals (CI) that excluded 1.0 were considered statistically significant. All analyses were conducted using SAS statistical software, version 9.3.

Results

Selected characteristics of the study participants are presented in Table 3.2. Cases were more likely than controls to be male, a college graduate or higher, a current smoker, overweight or obese, a non-drinker, and not regularly take aspirin or other NSAIDs. On average, cases were older and consumed greater total energy, percentage of energy from fat, and red and processed meats, but less total calcium and fruit. Cases also, on average, had a higher (more pro-inflammatory) LIS. Among the cases, 32.4% had multiple (≥2) adenomas, 31.7% had a large (≥1 cm) adenoma, 58.6% had their largest adenoma in the left colon,

28.8% had a villous or tubulovillous adenoma, 55.7% had an adenoma with moderate or severe atypia, and 25.0% had at least three high-risk adenoma characteristics.

The associations of the DIS and LIS with incident, sporadic adenoma, overall and by adenoma location and number of high-risk adenoma characteristics (≥3 or <3 high-risk characteristics) are presented in Table 3.3. For those in the highest relative to the lowest DIS quintile, there was a statistically significant 37% higher odds of any adenoma; the direct association was stronger for adenomas of the colon (statistically significant 54% and 79% higher odds for the left and right colon, respectively, vs. non-statistically significant 25% lower odds for rectal adenomas) and for more advanced adenomas (56% higher odds for having ≥3 high-risk adenoma characteristics, vs. 34% higher odds for having <3 high-risk adenoma characteristics).

There was a statistically significant trend of increasing odds of having any adenoma with an increasing LIS, and among those in the highest relative to the lowest LIS quintile, there was a statistically significant 2-fold higher odds of an adenoma (Table 3.3). The LIS was more strongly, directly associated with adenomas in the colon than in the rectum, and with adenomas with ≥3 high-risk characteristics. Consistent with these findings, both the DIS and LIS were most strongly associated with adenoma multiplicity (≥2 adenomas), villous/tubulovillous adenomas, large (≥1 cm) adenomas, and adenomas with moderate or severe atypia (Appendix Table 3.2).

The joint/combined (cross-classification) associations of the DIS and LIS with incident, sporadic adenoma are presented in Table 3.4. Relative to those in the lowest, most anti-inflammatory joint DIS and LIS quintile, the highest estimated risk was among those in the most pro-inflammatory joint DIS and LIS quintile (OR=2.90, 95% CI=1.94, 4.34). Among those in the lowest DIS quintile, there was a pattern of increasing odds of having an adenoma with an increasing LIS, culminating in statistically significant two-fold higher odds of an adenoma among those in the highest LIS quintile. Among those in the lowest

LIS quintile, the highest odds of an adenoma were among those in the highest DIS quintile (statistically significantly 40% higher).

As illustrated in Figure 3.1 (and shown in Appendix Table 3.3), the associations of the DIS and LIS with adenoma were similar across most stratification categories. However, the DIS-adenoma association tended to be stronger among males, non-smokers, those who were overweight or obese, and not heavy drinkers.

In sensitivity analyses, the associations of the equally-weighted DIS and LIS with adenoma (Appendix Table 3.4) were similar to, but slightly less strong than, those with the weighted scores. The findings for the DII were similar to those for the DIS, but were not statistically significant and were of slightly less magnitude overall and among men (Appendix Table 3.5). The findings for the EDII overall and by sex tended to be slightly inverse and were not statistically significant (Appendix Table 3.5). The associations of the DIS and LIS with adenoma, when estimated by applying the MCM/bootstrap-technique (Appendix Table 3.6), were also generally similar to those found in the a priori analysis. Although there was a more consistent trend of higher odds of having an adenoma with an increasing DIS, the estimated strength of the association for those in the highest relative to the lowest DIS quintile was nearly identical to that from the a priori analysis. The estimated LIS-adenoma association was modestly more attenuated than that from the a priori analysis. The confidence intervals using the MCM/bootstrap-technique were wider, reflecting the additional random error incorporated into the estimated associations.

Discussion

Our findings suggest that a higher balance of more pro- to anti-inflammatory exposures, from either diet or lifestyle, perhaps especially jointly, may be associated with higher risk for incident, sporadic colorectal adenoma. Our findings also suggest that the direct associations of the DIS and LIS with adenoma may be strongest for adenomas with more high-risk characteristics. In addition, the order of the strengths of our

estimated associations of the different inflammation scores with adenoma were: the LIS, DIS, DII, and EDII.

It has been suggested that, in addition to the six hallmarks for cancer development defined by Hanahan-Weinberg, which include self-sufficiency in growth signals, insensitivity to anti-growth signals, evasion of apoptosis, unlimited replicative potential, sustained angiogenesis, and metastasis, a seventh hallmark should be a cancer-promoting inflammatory environment (135). Inflammation promotes carcinogenesis by damaging DNA, promoting cell proliferation and angiogenesis, and inhibiting apoptosis; and, there is strong evidence supporting a role of systemic inflammation in all stages of sporadic colorectal carcinogenesis, including initiation, promotion, progression, and metastasis (121,146–149). For example, individuals diagnosed with inflammatory bowel diseases have higher CRC risk (157), and multiple randomized clinical trials and observational studies found chemopreventive effects against/inverse associations of aspirin and other NSAIDs with risk for colorectal neoplasms. For example, a meta-analysis of four randomized clinical trials found that, relative to placebo, individuals randomized to aspirin had 17% and 28% risk reductions for all or advanced colorectal adenomas, respectively, over a median follow-up of 33 months. The chemopreventive effects of NSAIDs are thought likely to be through inhibiting the pro-inflammatory cyclooxygenase 2 (COX-2) enzyme (147–149,153–156).

Risk for colorectal neoplasms is also highly associated with dietary and other lifestyle exposures (139). For example, in general, dietary patterns characterized by high intakes of fruits, vegetables, whole grains, low-fat dairy products, fish, poultry, olive oil, and legumes have been inversely associated with colorectal neoplasms; whereas dietary patterns characterized by high intakes of red and processed meats, white potatoes, and refined grains have been positively associated with colorectal neoplasms (160). In addition, there is even stronger evidence for positive associations of obesity, heavy alcohol intake, and smoking with CRC, and for inverse associations of physical activity with CRC (163–168). Furthermore, as summarized in Appendix Table 3.1, there is considerable biological plausibility for the associations of

individual food groups and lifestyle characteristics with systemic inflammation. Collectively, the above-summarized literature strongly supports inflammation as a major pathway underlying the associations of dietary/lifestyle exposures with colorectal carcinogenesis.

We found that the associations of the inflammation scores with adenoma were strongest for adenomas with high-risk characteristics. Most CRCs are thought to arise from adenomas; however, most adenomas do not progress to carcinomas, although advanced adenomas (e.g., adenomas with high-grade dysplasia, villous components, and/or large size) are at higher risk for malignancy (124,125). In the progression from normal mucosa to small/low-risk adenoma to large/advanced adenomas to carcinomas, there is a progressive increase in COX-2 expression (127). Also, larger adenomas may be more exposed to pro-inflammatory, mutagenic, and mitogenic exposures in the fecal stream, and larger/advanced adenomas may have impaired defenses against these exposures. Furthermore, inflammation has been more strongly, consistently associated with higher risk for advanced adenoma and CRC (127,202,211,203–210). So, it is plausible that a higher balance of pro- relative to anti-inflammatory dietary and lifestyle exposures may have a stronger role in the progression of adenomas to carcinomas than in their initial appearance.

The association of the previously developed DII (1) was investigated in association with adenomas in two studies. In a cross-sectional analysis of Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PCLO) data, men in the highest (most pro-inflammatory) DII quartile relative to those in the lowest, had a statistically significant 40% higher prevalence of adenoma, whereas women in the highest quartile had an estimated non-statistically significant 8% higher prevalence (170). In an observational analysis of data from a clinical trial of wheat bran cereal fiber supplementation and adenoma recurrence, the DII-adenoma recurrence association was null (171).

Four reported prospective cohort studies and five case-control studies investigated a DII-CRC association. In a recent meta-analysis of these studies, there was an estimated 6% higher CRC risk for every one-unit

increase in the DII (172), though there was statistically significant heterogeneity in the associations. An EDII-CRC association was investigated in two prospective cohorts. In the Health Professionals Follow-up Study (HPFUS) and the Nurses' Health Study (NHS) cohorts, being in the highest relative to lowest EDII quintile was associated with a 44% and 22% higher CRC risk for those in the HPFUS and NHS, respectively (174).

The DII and EDII have several limitations. The DII is primarily based on classically-measured nutrients and does not account for the myriad non-classical, unmeasured, natural anti- or pro-inflammatory compounds found in whole foods. Also, the DII uses a somewhat arbitrary literature review-based weighting scheme to characterize the contributions of dietary factors to systemic inflammation. The EDII is whole foods-based, but was developed in the NHS cohort, a relatively homogenous population, using a population-dependent, *a posteriori,* data-driven (vs. driven by biological plausibility) reduced rank regression approach; hence, the EDII-CRC findings from the NHS and HPFUS cohorts may be less replicable in populations with different characteristics. Neither the EDII nor the DII address lifestyle.

Our study had several strengths. First, previously, the DIS and LIS were validated through assessing and comparing their associations with multiple circulating inflammation-related biomarkers in three populations, and the DIS was more strongly associated with the circulating biomarkers than was the DII and EDII. The findings for the relative strengths of associations of the inflammation scores with biomarkers of inflammation were paralleled in the present study. Second, the inflammation scores-adenoma associations were robust to alternative weighting methods (MCM/bootstrapping or equal weighting). Third, the DIS and LIS, which account for the contributions of whole foods/beverages and lifestyle to inflammation, are more directly translatable into clinical and population recommendations for CRC prevention than are previous dietary inflammation scores. Fourth, there was standardized pathological verification of adenomas, thus reducing outcome misclassification, and subjects completed their questionnaires prior to case/control status determination, minimizing recall bias. Fifth, to our

knowledge, this is the first study to investigate a validated lifestyle inflammation score, alone and jointly with a dietary inflammation score, with colorectal neoplasms.

Our study also had limitations. First, inherent to case-control studies is that temporality of associations involving modifiable exposures cannot be assessed, although dietary and lifestyle exposures typically remain relatively consistent over time (212). The control group included sigmoidoscopy and community controls, possibly resulting in misclassification of some cases as controls; however, excluding these control groups did not change our findings meaningfully. The DIS and LIS also have limitations. The weights were based on cross-sectional associations of the dietary/lifestyle components with a limited inflammation biomarker panel; however, we previously found that the scores were strongly, directly associated with inflammation markers in three validation populations, including a population with a comprehensive inflammation biomarker panel. Also, the Block 98 FFQ used to form the DIS food groups ascertained dietary intake over the past year, and was validated to do this reasonably well (190,213). Finally, FFQs have known limitations (e.g., recall error, limited food choices); however, findings from multiple studies that used various FFQs (including the Willett FFQ) and other dietary assessment methods over the years have yielded remarkable consistency for multiple diet-colorectal neoplasm associations (172,214,215).

In conclusion, our findings, taken together with those from previous studies, suggest that a higher balance of pro- to anti-inflammatory exposures may be associated with higher risk for colorectal adenoma, especially adenomas that are advanced and more likely to be clinically important in relation to CRC prevention. Reducing inflammation, such as through dietary or lifestyle interventions, could potentially reduce risk for adenoma, and thus CRC. Our findings support further study of dietary- and lifestyle-derived inflammation using our novel DIS and LIS in relation to colorectal neoplasms.

Tables and Figure

Table 3.1. Components of the dietary (DIS) and lifestyle (LIS) inflammation scores and their descriptions and weights in three pooled case-control studies (CPRU Study, 1991–1994; MAP I Study, 1994–1997; and MAP II Study, 2003)

Components	Descriptions	β coefficient weights[a]
DIS components		
Leafy greens and cruciferous vegetables	Kale, spinach, broccoli, Brussels sprout, cabbage or coleslaw, cauliflower, and iceberg, head lettuce, romaine, or leaf lettuce	-0.14
Tomatoes	Tomatoes, tomato juice, tomato sauce, salsa, and ketchup	-0.78
Apples and berries	Fresh apples or pears, applesauce, apple juice or cider, strawberries, and blueberries	-0.65
Deep yellow or orange vegetables and fruit	Cantaloupe, peaches, and carrots	-0.57
Other fruits and real fruit juices	Pineapples, honeydew, watermelon, grapes, prunes, oranges, orange juice, grapefruit, grapefruit juice, and other real fruit juices	-0.16
Other vegetables	Beets, celery, eggplant, garlic, green peppers, mushrooms, and onions	-0.16
Legumes	String beans, peas, lima beans, lentils, and other beans	-0.04
Fish	Canned tuna fish or salmon, dark meat fish, other fish, and breaded fish cakes or fish sticks	-0.08
Poultry	Chicken and turkey with and without skin	-0.45
Red and organ meats	Beef, pork, lamb, liver, and other organ meats	0.02
Processed meats	Bacon, salami, bologna, other processed meats, and beef, pork, chicken, or turkey hot dogs	0.68
Added sugars	Soda, punch, lemonade, fruit drinks, chocolate candy bars, other mixed candy bars, candy without chocolate, jams, jellies, preserves, and syrup or honey	0.56
High-fat dairy	Whole milk, ice cream, cream cheese, full-fat cheeses, and sour cream	-0.14
Low-fat dairy	Low-fat yogurt, low-fat cottage or ricotta cheese, other low-fat cheeses, and skim, 1%, 2%, or low-fat milk	-0.12
Coffee and tea	Coffee (decaf and regular) and tea (herbal and non-herbal)	-0.25
Nuts	Peanuts, peanut butter, and other nuts	-0.44
Fats	Mayonnaise, margarine, and butter	0.31
Refined grains and starchy vegetables	Cold or cooked breakfast cereal, white or dark bread, bagels, English muffins, rolls, cornbread, white rice, pasta, pancakes or waffles, sweet potatoes or yams, potato chips, crackers, tortillas, popcorn, pretzels, cookies, brownies, doughnuts, cake, pie, sweet rolls or coffee cakes, and French fried, scalloped, baked, boiled, or mashed potatoes	0.72
Supplement score[b]	Ranked score of supplements, including: vitamins A, B_1, B_{12}, B_6, C, D, and E; and β-carotene, folate, niacin, riboflavin, calcium, iron, magnesium, selenium, and zinc	-0.80
LIS components		
Heavy drinker	Heavy (> 7 drinks/wk for women, > 14 drinks/wk drinks for men) vs. non-drinker	0.30

Moderate drinker	Moderate (1 – 7 drinks/wk for women, 1 – 14 drinks/wk for men) vs. non-drinker	-0.66
Moderately physically active	Based on distribution among controls, individuals in the middle tertile of MET-hours per week	-0.18
Heavily physically active	Based on distribution among controls, individuals in the highest tertile of MET-hours per week	-0.41
Current smoker	Currently smokes tobacco vs. does not currently smoke tobacco	0.50
Overweight BMI	Overweight BMI (25 – 29.99 kg/m^2) vs. normal BMI (18.5 – 24.99 kg/m^2)	0.89
Obese BMI	Obese BMI (≥ 30 kg/m^2) vs. normal BMI (18.5 – 24.99 kg/m^2)	1.57

Abbreviations: BMI, body mass index; CPRU, Cancer Prevention Research Unit; DIS, dietary inflammation score; hsCRP, high sensitivity C-reactive protein; IL, interleukin; LIS, lifestyle inflammation score; MAP, Markers of Adenomatous Polyps; MET, metabolic equivalent of task

[a] Weights are β coefficients from multivariable linear regression models conducted in the REGARDS case-cohort sample (N = 639), representing the average change in a summary inflammation biomarker z-score (sum of z-scores for hsCRP, IL-6, IL-8, IL-10 [the latter with a negative sign]) per one standard deviation increase in a dietary component or the presence of lifestyle component. Covariates in the final models 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 case control studies, all dietary components were standardized based on their distribution among the controls, by sex, to a mean of zero and standard deviation of 1, and all lifestyle components were dummy variables.

[b] All vitamin and mineral supplement intakes measured (from multivitamin/mineral and individual supplements) were ranked into tertiles 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)

Table 3.2. Selected characteristics of participants in three pooled case-control studies (CPRU Study, 1991–1994; MAP I Study, 1994–1997; and MAP II Study, 2002; pooled N = 2,779) of incident, sporadic colorectal adenoma

	Cases (N = 777)		Controls (N = 2,002)		
Characteristics	**Mean (SD)**	**%**	**Mean (SD)**	**%**	***p*[a]**
Demographics					
Age, y	58.2 (9.1)		54.5 (10.9)		<0.001
Male		61.1		43.0	<0.001
White		90.7		95.0	0.002
College graduate or higher		31.9		28.4	<0.001
Medical history					
Takes aspirin/other NSAID ≥ once/wk		35.5		41.7	0.003
HRT user (among women)		35.8		38.1	0.47
Has family history of CRC[b]		16.9		17.8	0.57
Lifestyle					
Current smoker		24.3		13.9	<0.001
Normal BMI[c]		33.0		40.9	<0.001
Non-drinker		35.7		33.0	<0.001
Physical activity[d], MET-hrs/wk	60.4 (56.5)		58 (54.2)		0.30
LIS[e]	0.4 (0.8)		0.2 (0.8)		<0.001
Dietary intakes					
DIS[e]	-0.9 (2.4)		-1.0 (2.4)		0.52
Total energy, kcal/day	2,067 (782)		1,991 (722)		0.01
Dietary fiber, g/1,000 kcal/day	10.9 (3.7)		11.3 (3.9)		0.01
Fat, % kcal	31.3 (0.1)		30.2 (0.1)		<0.001
Total calcium[f], mg/1,000 kcal/day	472 (276)		510 (272)		0.001
Total fruit, servings/day	2.3 (1.8)		2.6 (1.9)		<0.001
Total vegetables, servings/day	3.7 (2.3)		3.7 (2.4)		0.53
Red meat, servings/day	0.7 (0.6)		0.9 (1.6)		0.001
Processed meats, servings/day	0.4 (0.5)		0.3 (0.4)		<0.001

Abbreviations: BMI, body mass index; CPRU, Cancer Prevention Research Unit; CRC, colorectal cancer; DIS, dietary inflammation score; HRT, hormone replacement therapy; LIS, lifestyle inflammation score; MAP, Markers of Adenomatous Polyps; MET, metabolic equivalent; NSAID, non-steroidal anti-inflammatory drug

[a] p-values calculated using χ^2 test for categorical variables and ANOVA for continuous variables

[b] In a first-degree relative

[c] 18.5 – 24.99 kg/m^2

[d] Moderate + vigorous physical activity

[e] For construction of dietary and lifestyle inflammation scores, see text and Table 1; higher scores indicate a higher balance of pro- versus anti-inflammatory exposures

[f] Total = diet + supplements

Table 3.3. Multivariable-adjusted associations of the DIS and LIS with incident, sporadic colorectal adenomas in three pooled case-control studies (CPRU Study, 1991–1994; MAP I Study, 1994–1997; and MAP II Study, 2002; pooled N =2,779), overall and according to selected adenoma characteristics

	Inflammation scores[a]					
	DIS[b]			LIS[c]		
Adenoma characteristics; inflammation score quintiles	**No. cases**	**Adjusted OR (95% CI)**	***p-trend***	**No. cases**	**Adjusted OR (95% CI)**	***p-trend***
Any adenoma						
1	130	1.00		104	1.00	
2	171	1.28 (0.96, 1.70)		118	1.15 (0.84, 1.57)	
3	138	1.01 (0.75, 1.35)		171	1.43 (1.07, 1.91)	
4	155	1.18 (0.88, 1.58)		183	1.61 (1.20, 2.15)	
5	183	1.37 (1.03, 1.83)	*0.09*	201	2.02 (1.51, 2.70)	*<0.001*
Adenoma location						
Left colon[d]						
1	68	1.00		61	1.00	
2	99	1.34 (0.93, 1.91)		73	1.23 (0.84, 1.80)	
3	79	1.07 (0.74, 1.56)		102	1.47 (1.03, 2.10)	
4	97	1.34 (0.93, 1.93)		107	1.58 (1.11, 2.25)	
5	112	1.54 (1.08, 2.20)	*0.03*	112	1.84 (1.29, 2.63)	*<0.001*
Right colon[e]						
1	27	1.00		20	1.00	
2	46	1.85 (1.09, 3.13)		27	1.30 (0.70, 2.40)	
3	31	1.09 (0.62, 1.93)		29	1.17 (0.64, 2.14)	
4	31	1.18 (0.66, 2.08)		46	2.04 (1.16, 3.57)	
5	48	1.79 (1.05, 3.04)	*0.19*	61	3.29 (1.90, 5.68)	*<0.001*
Rectum						
1	30	1.00		22	1.00	
2	21	0.69 (0.38, 1.25)		16	0.82 (0.42, 1.60)	
3	25	0.82 (0.46, 1.44)		30	1.25 (0.70, 2.22)	
4	24	0.82 (0.46, 1.46)		28	1.24 (0.69, 2.23)	
5	21	0.75 (0.41, 1.37)	*0.46*	25	1.33 (0.73, 2.44)	*0.24*
Adenoma characteristics						
< 3 high-risk characteristics[f]						
1	99	1.00		84	1.00	
2	139	1.38 (1.01, 1.89)		92	1.11 (0.79, 1.56)	
3	105	1.03 (0.74, 1.43)		136	1.43 (1.04, 1.96)	
4	110	1.16 (0.84, 1.61)		130	1.42 (1.03, 1.96)	
5	130	1.34 (0.97, 1.85)	*0.23*	141	1.79 (1.30, 2.46)	*<0.001*
≥ 3 high-risk characteristics[f]						
1	31	1.00		20	1.00	
2	32	0.99 (0.58, 1.71)		26	1.33 (0.72, 2.47)	
3	33	0.96 (0.56, 1.65)		35	1.42 (0.80, 2.55)	
4	45	1.22 (0.73, 2.06)		53	2.31 (1.33, 3.99)	
5	53	1.56 (0.94, 2.57)	*0.05*	60	2.98 (1.74, 5.13)	*<0.001*

Abbreviations: CI, confidence interval; CPRU, Cancer Prevention Research Unit; DIS, dietary inflammation score; LIS, lifestyle inflammation score; MAP, Markers of Adenomatous Polyps; MET, metabolic equivalents of task; OR, odds ratio

[a] For construction of inflammation scores, see text and Table 1; higher scores indicate a higher balance of pro- versus anti-inflammatory exposures

[b] Covariates in the DIS unconditional logistic regression models were: age, sex, education (less than college graduate or college graduate or higher), regular aspirin or other nonsteroidal anti-inflammatory drug use (≥ once/week), hormone therapy use (among women), family history of colorectal cancer in a first degree relative (yes/no), smoking status (never, former, or current smoker), body mass index (kg/m^2), alcohol intake (non-drinker, moderate drinker, or heavy drinker), physical activity (categorized into tertiles of MET-hours/wk), total energy intake (kcal/day), and study (MAP I, MAP II, or CPRU)

[c] Covariates in the LIS unconditional logistic regression models were: age, sex, regular aspirin or other nonsteroidal anti-inflammatory drug use (≥ once/week), hormone therapy use (among women), family history of colorectal cancer in a first degree relative (yes/no), former smoking status (former smoker or non-former smoker), total energy intake (kcal/day), study (MAP I, MAP II, or CPRU), and the equally-weighted DIS

[d] Right colon: the largest adenoma was located in the cecum, ascending, hepatic flexure, or transverse colon

[e] Left colon: the largest adenoma was located in the splenic flexure, descending, or sigmoid colon

[f] High-risk adenoma characteristics include multiplicity (≥ 2 adenomatous polyps), size ≥ 1 cm, moderate or severe degree of atypia, or having a villous component

Table 3.4. Joint/combined associations of the DIS and LIS with incident, sporadic adenoma in three pooled case-control studies (CPRU Study, 1991–1994; MAP I Study, 1994–1997; and MAP II Study, 2002; pooled N =2,779)

	LIS quintiles[a,b]										*p-interaction*[c]
	1		2		3		4		5		
DIS quintiles[a,b]	*n*[d]	OR (95% CI)	*n*[d]	OR (95% CI)	*n*[d]	OR (95% CI)	*n*[d]	OR (95% CI)	*n*[d]	OR (95% CI)	
1	24/83	1.00 (ref)	27/82	1.17 (0.85, 1.60)	25/97	1.44 (1.07, 1.93)	22/86	1.68 (1.25, 2.25)	32/56	2.08 (1.55, 2.80)	
2	29/104	1.31 (0.98, 1.75)	29/78	1.53 (0.99, 2.35)	41/74	1.89 (1.24, 2.86)	34/73	2.20 (1.45, 3.33)	38/70	2.73 (1.80, 4.12)	
3	18/102	1.08 (0.80, 1.45)	12/74	1.26 (0.81, 1.95)	38/78	1.55 (1.02, 2.36)	40/91	1.81 (1.19, 2.74)	30/57	2.24 (1.47, 3.41)	
4	17/82	1.21 (0.90, 1.63)	23/67	1.42 (0.92, 2.19)	34/85	1.75 (1.15, 2.65)	44/83	2.04 (1.35, 3.08)	37/82	2.53 (1.67, 3.81)	
5	16/83	1.39 (1.05, 1.86)	27/63	1.63 (1.06, 2.50)	33/72	2.01 (1.33, 3.04)	43/79	2.34 (1.55, 3.53)	64/101	2.90 (1.94, 4.34)	*0.14*

Abbreviations: CI, confidence interval; CPRU, Cancer Prevention Research Unit; DIS, dietary inflammation score; LIS, lifestyle inflammation score; MAP, Markers of Adenomatous Polyps; OR, odds ratio

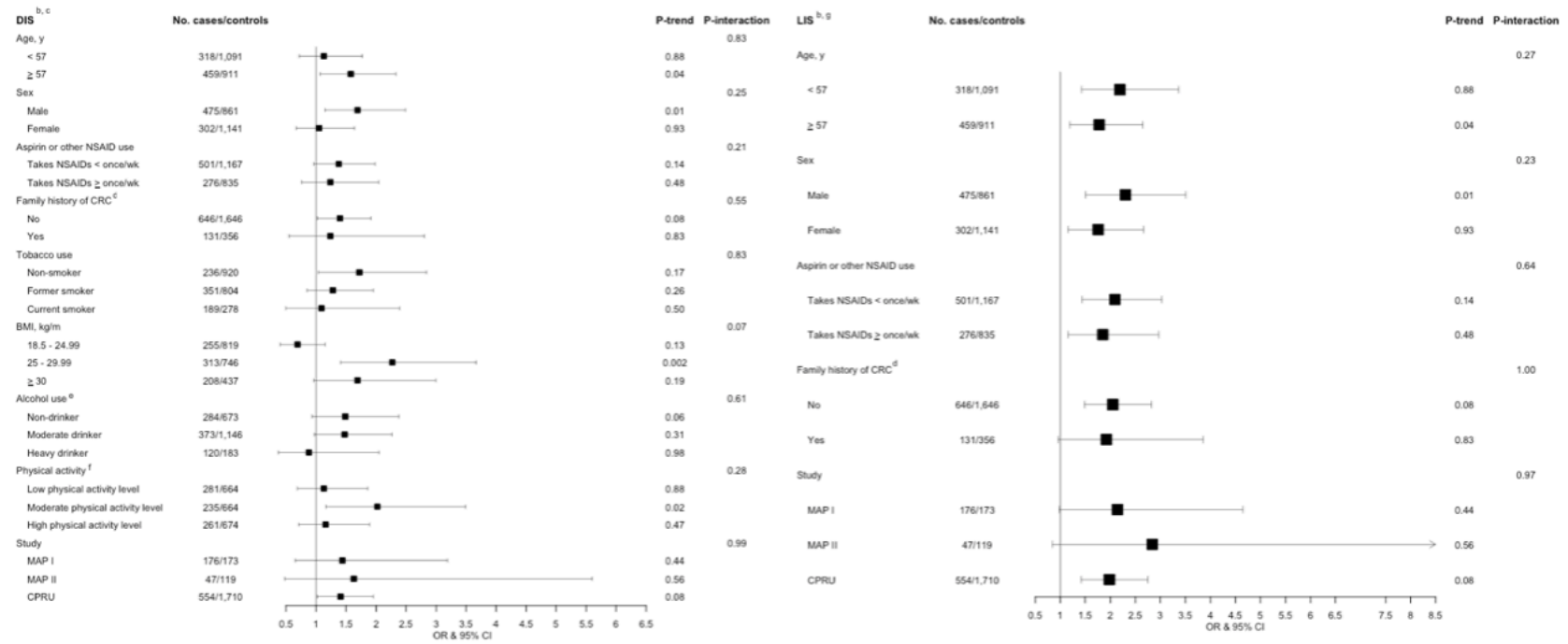
[a] For construction of inflammation scores, see text and Table 1; higher scores indicate a higher balance of pro- versus anti-inflammatory exposures

[b] Covariates in the joint/combined unconditional logistic regression models were: age, sex, education (less than college graduate or college graduate or higher), hormone therapy use (among women), family history of colorectal cancer in a first degree relative (yes/no), regular aspirin or other nonsteroidal anti-inflammatory drug use (≥ once/week), former smoking status (yes/no), total energy intake (kcal/day), and study (MAP I, MAP II, or CPRU)

[c] From lifestyle score*diet score interaction term in the full logistic regression model, calculated using the likelihood ratio test

[d] Number of cases/controls

Figure 3.1. Multivariable-adjusted associations[a] of the DIS and LIS with incident, sporadic colorectal adenoma in three pooled case-control studies (CPRU Study, 1991–1994; MAP I Study, 1994–1997; and MAP II Study, 2002; pooled N = 2,779), according to selected participant characteristics



Abbreviations: BMI, body mass index; CI, confidence interval; CPRU, Cancer Prevention Research Unit; CRC, colorectal cancer; DIS, dietary inflammation score; LIS, lifestyle inflammation score; MAP, Markers of Adenomatous Polyps; MET, metabolic equivalent of task; NSAID, non-steroidal anti-inflammatory3 drug; OR, odds ratio

[a] Only ORs (95% CIs) for fifth relative to first quintiles shown

[b] For construction of inflammation scores, see text and Table 1; higher scores indicate a higher balance of pro- versus anti-inflammatory exposures

[c] Covariates in the DIS logistic regression models were: age, sex, education (less than college graduate or college graduate or higher), regular aspirin/other NSAID use (≥ once/week), hormone therapy use (among women), family history of colorectal cancer in a first degree relative (yes/no), smoking status (never, former, or current smoker), BMI (kg/m^2), alcohol intake (non-drinker, moderate drinker, or heavy drinker), physical activity (categorized into tertiles of MET-hours/wk), total energy intake (kcal/day), and study (MAP I, MAP II, or CPRU)

[d] In a first degree relative

[e] Heavy drinker defined as > 7 drinks/wk for women and > 14 drinks/wk drinks for men; moderate drinker defined as 1 – 7 drinks/wk for women, 1 – 14 drinks/wk for men

[f] Participants categorized into tertiles of MET-hours of moderate and vigorous physical activity per week based on the distribution among the controls

[g] Covariates in the LIS logistic regression models were: age, sex, regular aspirin/other NSAID use (≥ once/week), hormone therapy use (among women), family history of colorectal cancer in a first degree relative (yes/no), former smoking status (non-former smoker or former smoker), total energy intake (kcal/day), study (MAP I, MAP II, or CPRU), and the equally-weighted DIS

Chapter 4. Associations of Novel Dietary and Lifestyle Inflammation Scores with Incident Colorectal Cancer in the NIH-AARP Diet and Health Study

Doratha A. Byrd,[1] Suzanne E. Judd,[2] W. Dana Flanders,[1] Terryl J. Hartman,[1] Veronika Fedirko,[1] Jill Reedy,[4] Tanya Agurs-Collins,[4] Roberd M. Bostick[1,3]

[1]Department of Epidemiology, Emory University Rollins School of Public Health, Atlanta, Georgia. [2]Department of Biostatistics, University of Alabama at Birmingham School of Public Health, Birmingham, Alabama. [3]Winship Cancer Institute, Emory University, Atlanta, Georgia. [4]National Cancer Institute, National Institutes of Health, Rockville, MD, USA.

Abstract

Chronically higher inflammation, likely contributed to by dietary and lifestyle exposures, may play a role in colorectal carcinogenesis. To address this, we investigated associations of novel dietary (DIS) and lifestyle (LIS) inflammation scores with incident colorectal cancer (CRC) in the prospective National Institutes of Health-American Association of Retired Persons (NIH-AARP) Diet and Health Study (N = 453,465).

The components of our previously developed 19-component DIS and 4-component LIS were weighted based on their strengths of associations with a panel of circulating inflammation biomarker concentrations in a diverse subset (N = 639) of participants in the Reasons for Geographic and Racial Differences in Stroke cohort (REGARDS). We calculated the components and applied their weights in the NIH-AARP cohort at baseline, summed the weighted components to constitute the scores such that higher scores reflect a higher balance of pro-inflammatory exposures, and investigated associations of the scores with incident CRC using multivariable Cox proportional hazards regression.

During follow-up, 10,336 participants were diagnosed with CRC. Among those in the highest relative to the lowest quintiles of the DIS and LIS, the multivariable-adjusted hazards ratios (HR) and their 95% confidence intervals [CI]) were: 1.3 (95% CI: 1.2, 1.4; P_{trend}: <0.001) and 1.4 (95% CI: 1.3, 1.5; P_{trend}: <0.001), respectively. The HR for those in the highest relative to the lowest joint DIS/LIS quintile was 1.8 (95% CI: 1.7, 2.0; $P_{interaction}$: <0.001).

These results suggest that aggregates of pro-inflammatory dietary and lifestyles exposures may be associated with higher risk for incident colorectal cancer.

Introduction

While inflammation is normal, chronically higher amounts may be harmful and contribute to the development of chronic diseases and cancer, especially colorectal cancer (CRC). CRC is the second leading cause of cancer death in the United States (US) among men and women combined (179). Inflammation promotes colorectal carcinogenesis by damaging DNA and promoting cell proliferation and angiogenesis (127,138,149). CRC is highly associated with diet and lifestyle factors, which in turn can act as sources of chronic inflammation (139,146–148,176,177,196). Consequently, reducing inflammation, such as through dietary or lifestyle intervention (216–218), may reduce risk for colorectal neoplasms.

The contributions of individual dietary components to systemic inflammation are likely small, but collectively may be substantial. To address this, researchers developed dietary inflammation scores to characterize the aggregate contributions of dietary exposures to systemic inflammation, such as the dietary inflammatory index (DII). In the National Institutes of Health-American Association of Retired Persons (NIH-AARP) Diet and Health Study, a large, prospective cohort study of older US adults, the DII was modestly, statistically significantly associated with higher CRC risk among men, but not women (173). Importantly, the DII has some limitations that limit its interpretability and reproducibility, including that it focuses heavily on classical nutrients and may not account for many other known/unknown dietary constituents, and it does not address lifestyle.

We previously developed novel, inflammation biomarker panel-weighted dietary (DIS) and lifestyle (LIS) inflammation scores to characterize the aggregate contributions of whole foods (rather than micro- or macro-nutrients) and other lifestyle characteristics to systemic inflammation. These scores were developed based on the premise that focusing on whole foods/beverages and other lifestyle exposures is a more useful direction for epidemiologic research on the role of dietary/lifestyle exposures in inflammation and inflammation-mediated health states, such as CRC. Herein, we report an investigation

of associations of the DIS and LIS with incident CRC in the prospective NIH-AARP Diet and Health Study.

Methods

Study population

The NIH-AARP Diet and Health Study, previously described in detail (219), is a large prospective cohort study to investigate diet-cancer associations. In 1995 and 1996, a self-administered questionnaire was mailed to 3.5 million 50–71-year-old adults in six US states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania), and two metropolitan areas (Atlanta, Georgia and Detroit, Michigan). The response rate was 17.6%.

A supplementary Risk Factor Questionnaire (RFQ) was mailed in 1996 and 1997—6 months after the return of the baseline questionnaire—to collect more detailed information on medical and lifestyle behaviors, including aspirin and other non-steroidal anti-inflammatory drug (NSAID) use. A follow-up questionnaire, mailed to those remaining from the baseline cohort in 2004–2005, included questions on cancer screening.

A total of 566,398 respondents completed the baseline questionnaire. 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 diagnoses 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), skipped >15% of DHQ questions (N = 4,346), had missing self-reported height/weight (N = 11,009) or height/weight >3 interquartile ranges outside the 75^{th} and 25^{th} percentiles (N = 818; described previously (220)), or had other missing lifestyle questions (N = 17,509). The final analytic sample size was 453,465.

The NIH-AARP Diet and Healthy Study was approved by the Special Studies Institutional Review Board of the US National Cancer Institute.

Data collection

Mailed questionnaires included a detailed, 124-item, grid-based version of the NCI Diet History Questionnaire (DHQ) that was validated against two 24-hour dietary recalls (via telephone, 25 days apart) in a calibration sub-study of 2,000 men and women in the NIH-AARP cohort (213,221,222). Ten possible frequency-of-consumption responses, ranging from 'never' to '6+ times per day' were given for each food item. The DHQ also ascertained frequencies of alcohol consumption and supplemental intakes of multivitamins/minerals, zinc, iron, selenium, folic acid, calcium, β-carotene, and vitamins A, C, and E. Energy and nutrient intakes were calculated using the nutrient composition database derived from the United States Department of Agriculture (USDA) Continuing Survey of Food Intakes by Individuals (CSFII) national survey data. The questionnaire also ascertained self-reported smoking status, weight, height, and physical activity lasting ≥ 20 minutes intense enough to work up a sweat or increase breathing/heart rate.

Outcome ascertainment

Incident CRC cases were identified using probabilistic linkage (by name, address, sex, date of birth, and if available, Social Security Number) of the cohort participants to cancer registries of the states that participants resided in at baseline, and three states (Arizona, Texas, and Nevada) to which participants were most likely to move during follow-up. Approximately 90% of cancer cases were validly identified (223). Incident CRC cases were defined according to the *International Classification of Diseases for Oncology* codes C180-C189, C199, or C209. We defined right colon as extending from the cecum through the transverse colon, and left colon as the splenic flexure through the sigmoid colon.

Description of the DIS and LIS

The development and validation of the DIS and LIS was described previously. Briefly, the 19 and four components of the DIS and LIS, respectively, were determined and grouped a priori based on their expected contributions to systemic inflammation using Block 98 FFQ (183,184) and lifestyle questionnaire responses (outlined in Appendix Table 4.1) in a diverse subset (N = 639) of participants in the previously-described Reasons for Geographic and Racial Differences in Stroke Study (REGARDS) cohort (181,187). REGARDS is a national, on-going prospective cohort study that recruited 30,239 participants ≥45 years old January 2003 – October 2007, with oversampling of black and Southeastern US residents. Exclusion criteria from the analytic sample included 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, and 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 models. The β-coefficient from each score component-biomarker score association was taken as the weight for that component.

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

The DIS and LIS were constructed in the NIH-AARP cohort as summarized in Table 4.1. Mixed dishes were disaggregated into their components using the “My Pyramid Equivalents Database”, as described

previously (194), and the disaggregated components were added to the DIS food groups as appropriate. After composing food groups based on responses from the DHQ, we standardized each food group to a mean of 0 and standard deviation of 1.0, by sex, based on the study baseline distribution. To account for supplemental vitamin/mineral use, we calculated a supplement score by ranking supplemental micronutrient intakes measured in the DHQ, based on the sex-specific distributions, into tertiles. The tertiles of the supplemental micronutrients were assigned values of 0–2 and multiplied by +1 or -1 for hypothesized anti- or pro-inflammatory micronutrients, respectively, and then the values were summed.

To construct the LIS, baseline smoking status was categorized as 'current' or 'former and never'. Baseline body mass index (BMI) was categorized according to World Health Organization (WHO) guidelines as normal (18.5 – 24.99 kg/m^2), overweight (25 – 29.99 kg/m^2), or obese (BMI ≥30 kg/m^2). 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.

Next, the value for each NIH-AARP cohort participant's DIS and LIS component was multiplied by its respective weight, which had been calculated in the REGARDS development population. Finally, the weighted values for each participant's score components were summed to constitute their DIS or LIS, a higher score indicating a higher balance of pro- to anti-inflammatory exposures.

Statistical analyses

All analyses were conducted using SAS statistical software, version 9.3. Total follow-up time was calculated as the time between the baseline questionnaire (beginning October 25, 1995) until the date of a participant's first CRC diagnosis, date of death, date they moved from the catchment area, or the last

study follow-up (December 31, 2011), whichever came first. Those non-contemporaneously diagnosed with both colon and rectal cancers were censored based on the date of whichever diagnosis came first.

We compared participants' characteristics across sex-specific DIS and LIS quintiles at baseline using chi-square tests for categorical variables and ANOVA for continuous variables. We used Cox proportional hazards regression to estimate multivariable-adjusted hazards ratios (HRs) and 95% confidence intervals (CIs) for the associations of the DIS and LIS (as continuous variables and categorized according to quintiles) with incident CRC. We also examined whether the associations of the inflammation scores with CRC differed by colorectal site (right colon, left colon, or rectum). Prior to conducting the Cox proportional hazards regression, the proportional hazards assumption was assessed by calculating Martingale and Schoenfeld residuals, testing time-dependent covariates, and by inspecting ln(-ln) 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; these variables included a history of CRC in a first degree relative, self-reported heart disease diagnosis, age at entry, sex, and, in the dietary score models, BMI. Multicollinearity was tested and a condition index ≥30 and a variance decomposition proportion ≥0.5 was considered as evidence of multicollinearity. We tested for linear trend by entering a term for the sex-specific median of each inflammation score quintile into the multivariable Cox proportional hazards regression models as a continuous variable.

To assess potential interaction between the DIS and LIS, we conducted a joint/combined (cross-classification) analysis using multivariable Cox proportional hazards regression models in which the reference group was participants in the first quintile of both scores.

Consideration for inclusion of covariates in the multivariable Cox proportional hazards regression models were based on biological plausibility, previous literature, and the magnitude of change in the association of interest when including/excluding the variable from the model. Covariates considered for all models

included age, sex, race, education, marital status, comorbidities (self-reported gallbladder stone or disease, heart disease, emphysema, or diabetes mellitus), hormone replacement therapy use (for women), family history of CRC in a first degree relative, self-reported history of colon polyps, and total energy intake. Covariates considered for the LIS models also included an equally-weighted DIS (described below) and former smoking status, and covariates considered for the DIS models also included smoking status, BMI, alcohol intake, and physical activity.

To investigate potential effect modification, separate analyses were conducted 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.

Sensitivity analyses

To assess the sensitivity of the associations to various considerations, we repeated the analyses with the following variations. First, 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, and investigated their associations with incident CRC. Second, we used Monte Carlo methods (MCM) (114) to simulate a range of possible DIS/LIS weights

over 10 iterations. For each iteration, the resulting β-coefficients were applied as weights for the DIS and LIS components, participants were categorized into quintiles based on the iteration-specific DIS or LIS distribution, and the bootstrap technique was used to simulate the error from the DIS and LIS weights and the estimated DIS-/LIS-inflammation biomarker association. Third, we calculated the Health Eating Index (HEI), as described by Krebs-Smith (162), and the empirical DII (EDII), as described by Tabung et al. (12), 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 one or two years from baseline, and censored individuals who reached the age of 75 during follow-up. Finally, we explored censoring individuals at the date of any first cancer diagnosis rather than at the first CRC diagnosis date.

All statistical tests were two-sided, and *P* values <0.05 or 95% CIs that excluded 1.0 were considered statistically significant.

Results

Over an average of 13.5 years of follow-up, 10,336 participants developed CRC (76% developed colon cancer, 22.1% rectal cancer, and 1.9% both colon and rectal cancer).

Selected baseline characteristics of the NIH-AARP analytic cohort according to DIS and LIS quintiles are presented in Table 4.2. Those in the highest relative to the lowest DIS and LIS quintiles were more likely to be less educated, not use HRT (among women), be a current smoker, be overweight or obese, be a non-drinker, exercise <3 times per week, and for the LIS, were more likely to have a comorbidity. On average, those in the highest DIS and LIS quintiles had lower dietary fiber intakes and HEI-2015 scores, and for the DIS, lower total calcium intakes, and for the LIS, higher total energy intakes. The DIS ranged from -14.9 to 12.8 and the LIS from -1.1 to 2.4.

Multivariable-adjusted associations of the DIS and LIS with incident CRC, overall, by tumor site, and by sex, are presented in Table 4.3. Among men and women combined, there was a statistically significant trend of increasing incident CRC risk with an increasing DIS, and when analyzed continuously, there was a statistically significant 4% higher CRC risk per 1-point DIS increase. For those in the highest relative to the lowest DIS quintile, there was a statistically significant 27% higher risk for incident CRC (29% higher among men, and 21% higher among women). For men and women, the DIS was similarly directly associated with right and left colon cancers, and risks for colon and rectal cancers were statistically significantly 29% and a 21% higher, respectively.

The LIS was more strongly, directly associated with incident CRC risk than was the DIS, particularly among men (Table 4.3). When the LIS was treated as a continuous variable, risk per 1-point increase was 16% higher overall, and 20% and 10% higher among men and women, respectively. When the LIS was treated as a categorical variable, among those in the highest relative to the lowest LIS quintile, risk was 38% higher overall, and 49% and 22% higher among men and women, respectively. Overall, among those in the highest relative to the lowest LIS quintiles, risk for left- and right-side colon cancers was statistically significantly 59% and 40% higher, respectively, but for rectal cancers it was an estimated non-statistically significant 13% higher. The estimated colorectal site differences were larger among men than among women.

The joint/combined (cross-classification) associations of the DIS and LIS with risk for incident CRC are presented in Table 4.4. Overall and among men and women separately, there was a pattern of increasing risk with an increasing DIS among those in the lowest LIS quintile, and with an increasing LIS among those in the lowest DIS quintile. The highest CRC risk was among those in the highest relative to the lowest joint DIS/LIS quintile (83% higher overall, 2-fold higher among men, and 55% higher among women; all p-interactions statistically significant).

DIS and LIS associations with incident CRC according to selected participant characteristics (Appendix Table 4.2) were generally similar across most baseline characteristics. There were no consistent, clear patterns of differences in DIS-CRC associations; however, the LIS associations tended to be stronger among men and among women using hormone replacement therapy.

In sensitivity analyses, the equally-weighted DIS and LIS (Appendix Table 4.3) were somewhat more strongly, directly associated with CRC than were the weighted scores (overall, the estimated risks among those in the highest relative to the lowest equal-weight DIS and LIS quintiles were statistically significantly 35% and 55% higher, respectively). The associations of the DIS and LIS with CRC, when estimated by applying the MCM/bootstrap-technique (Appendix Table 4.4), were modestly more attenuated than those from the *a priori* analysis, and the confidence intervals were somewhat wider, reflecting the additional random error incorporated into the estimated associations. The findings for the HEI were somewhat stronger than those for the DIS, but were very similar to those for the equally-weighted DIS, and the findings for the EDII were much weaker and closer to the null than those for the DIS (Appendix Table 4.5). The findings for individual LIS components (Appendix Table 4.6) were weaker than those for the LIS. For example, current relative to never smokers had 29% higher risk for CRC, those who were obese relative to those who were normal weight had a 24% higher risk, heavy relative to non-drinkers had a 23% higher risk, and those who exercised ≥3 or 1-2 times weekly relative to those who rarely or never exercised had 15% and 8% lower risk, respectively. Excluding those who died or were diagnosed with CRC within one or two years of follow up, censoring participants upon reaching the age of 75 during follow-up (Appendix Table 4.7), or censoring participants based on the diagnosis date of any primary cancer instead of the first CRC diagnosis date (Appendix Table 4.8) had negligible impact on our estimated associations.

Discussion

Our findings suggest that higher pro- to anti-inflammatory balances of either dietary or lifestyle exposures, and especially of both combined, may be associated with higher risk for incident CRC. Our findings suggest that these direct associations may be stronger among men and for colon than for rectal cancers.

Inflammation is strongly mechanistically linked to colorectal carcinogenesis. First, colorectal carcinogenesis is characterized by progressive increases in the expression of COX-2, which is pro-inflammatory and pro-tumorigenic (13), and approximately 85% of colorectal adenocarcinomas express it (149). NSAIDs are associated with lower risk for colorectal neoplasms, likely through COX-2 inhibition (147–149,152–156). For example, in a pooled analysis of four randomized controlled trials (N = 14,033), those randomized to aspirin (75-500 day), relative to placebo, had a 24% lower CRC incidence over 20 years (152,224). Second, higher circulating inflammation biomarker concentrations have been associated with risk for CRC. For example, in a meta-analysis of 18 nested case-control studies, 12% higher risk for incident CRC for every one unit increase in baseline log-transformed CRP concentrations was found, and in a meta-analysis of six studies (three cohort and three nested case-control studies), there was a 10% higher incident CRC risk per unit increase in IL-6 (151). Finally, individuals diagnosed with inflammatory bowel diseases have higher CRC risk (157,225), especially among those with greater disease extent and duration.

Risk for colorectal neoplasms is also highly associated with dietary and other lifestyle exposures (139,158). There is considerable evidence for positive associations of obesity, heavy alcohol intake, and smoking with CRC, and for inverse associations of physical activity with CRC (163–168,220). Furthermore, dietary patterns characterized by high intakes of vegetables, fruits, whole grains, low-fat dairy, fish, poultry, olive oil, and legumes have been inversely associated with colorectal neoplasms; whereas, dietary patterns characterized by high intakes of red and processed meats, refined grains, foods

with added sugars, potatoes, saturated/trans fats, and low intakes of fruits and vegetables have been positively associated with colorectal neoplasms (159,160). In the NIH-AARP cohort, several dietary patterns encompassing similarities to the patterns described above, were associated with CRC risk (161,226–228). For example, higher relative to lower HEI-2005 and Mediterranean Diet scores were associated with a 28% lower CRC risk (161). Our finding of a direct DIS-CRC association was slightly weaker than those for the reversed HEI and equally-weighted DIS. This can be expected since, given that the intent of the DIS is to assess the collective contributions of foods to systemic inflammation, the DIS comprises components weighted according to their estimated contributions to systemic inflammation. Thus, the DIS would not include other potential independent pro- and anti-carcinogenic effects of its components. However, the similarity of our DIS findings with our HEI and equally-weighted DIS findings suggest that the strong associations of diet with CRC risk may largely involve their contributions to inflammation (described in Appendix Table 4.1).

Associations of the DII and EDII with CRC were previously reported. In a recent meta-analysis of four prospective cohort studies and five case-control studies , there was an estimated 6% higher CRC risk for every one-unit increase in the DII (172). One of the included studies was the NIH-AARP Diet and Health study (with follow-up until 2006); among those in the highest relative to the lowest DII quartile, the estimated CRC risk was statistically significantly 44% higher among men, and non-statistically significantly 12% higher among women (173). An association of the EDII, which was developed in a subset of the Nurses' Health Study (NHS) cohort, with CRC, was investigated in two prospective cohorts, the NHS (all women) and the Health Professionals Follow-up Study (HPFUS) (all men) cohorts. Among those in the highest relative to the lowest EDII quintile, CRC risk was 44% and 22% higher in the NHS, and 44% higher in the HPFUS (174). The findings reviewed above are similar to our findings of statistically significant 29% and 21% higher CRC risk among men and women, respectively, in the highest relative to the lowest DIS quintiles.

When conceptualizing the implications of the DII/EDII-CRC associations, it is important to consider their limitations. The DII is primarily nutrient-based, and thus does not account for many other whole food constituents that affect inflammation, and it does not facilitate translation into dietary recommendations for CRC prevention. Although the EDII is whole foods-based, it was developed using a data-driven approach in a relatively homogenous population; accordingly, some of the directions of the component's weights are inconsistent with previous literature (e.g., pizza has a strongly anti-inflammatory weight, whereas tomatoes have a pro-inflammatory weight). For this reason, the EDII weights may not be reproducible in other, different populations; this may account for the more attenuated EDII-CRC associations observed in our study. Finally, neither the DII nor the EDII address lifestyle. The DIS and LIS were developed to address many of these limitations.

Our study had several strengths. First, was the prospective design; the large sample size and number of cases, which allowed stratified analyses; and the excellent case ascertainment and participant follow-up (223). Second, our findings were robust to multiple sensitivity analyses. Third, strengths of the DIS and LIS include their previous validation via estimating and comparing their associations with multiple circulating inflammation biomarkers in three study populations. In those validation studies, the DIS was more strongly, directly associated with the circulating biomarkers than was the DII and EDII, and the LIS was more strongly, directly associated with the biomarkers than was any diet score. Fourth, the DIS and LIS are based on whole foods and lifestyle factors, which may facilitate application to population and clinical recommendations for CRC prevention. Fifth, to our knowledge, this is the first study to prospectively investigate a validated lifestyle inflammation score, alone or jointly with a dietary inflammation score, in association with incident CRC.

Our study also had limitations. First, there are known issues related to dietary measurement (e.g., limited detail on food preparation, recall error, etc.); however, the DHQ used in this study was validated in a calibration study using 24-hour food recalls in a subset of the NIH-AARP cohort (213,221), and diet

patterns calculated using the DHQ have been consistently associated with CRC (161,226–228). Second, we had data on NSAID use, which is strongly associated with risk for CRC, in only a subset of the cohort; however, among participants with NSAID use data, adjusting for regular aspirin/other NSAID use did not meaningfully affect our findings, and there were no meaningful differences in findings stratified by regular aspirin/other NSAID use. Third, the response rates to the baseline and follow-up questionnaires were low, which may have limited the generalizability of our findings; however, there was strong heterogeneity in dietary intakes among those who returned their questionnaires, relative to participants in other national surveys (219).

In conclusion, our findings, taken together with previous literature, suggest that a higher balance of pro-inflammatory diets and lifestyles, alone and especially in combination, may be associated with higher CRC risk. Our findings support further research into diet- and lifestyle-associated inflammation in relation to colorectal neoplasms using our novel DIS and LIS.

Tables

Table 4.1. Components and weights of the dietary (DIS) and lifestyle (LIS) inflammation scores and their descriptions in the NIH-AARP Diet and Health Study

Components	Descriptions	Weights[a]
DIS components		
Leafy greens and cruciferous vegetables	Cooked or raw spinach, kale, lettuce salad, broccoli, cabbage or coleslaw, cauliflower, Brussel sprouts, and turnip, collard, or mustard greens	-0.14
Tomatoes	Tomatoes, tomato juice, tomato sauce, salsa, and tomato or spaghetti sauce	-0.78
Apples and berries	Apples, applesauce, pears, and strawberries	-0.65
Deep yellow or orange vegetables and fruit	Peaches, nectarines, plums, cantaloupe, and carrots	-0.57
Other fruits and real fruit juices	Watermelon, oranges, tangerines, tangelos, grapefruit, other melon (e.g., watermelon or honeydew), grapes, orange juice, grapefruit juice, and other fruit juice	-0.16
Other vegetables	Sweet peppers (green or red)	-0.16
Legumes	String beans, green beans, peas, and beans	-0.04
Fish	Tuna and other fried or non-fried fish	-0.08
Poultry	Ground chicken or turkey, roast turkey, turkey cutlets, turkey nuggets, fried chicken or chicken nuggets, and baked, broiled, roasted or stewed chicken	-0.45
Red and organ meats	Ground beef, roast beef, steak, roast ham, ham steak, pork chops, pork roasts, and liver or liverwursts	0.02
Processed meats	Hot dogs, frankfurters, bacon, sausage, and ham, bologna, salami, corned beef, pastrami, turkey, or chicken cold cuts/luncheon meats	0.68
Added sugars	Hi-C, Kool-Aid, lemonade, soda, dried fruit, chocolate candy, and other candy	0.56
High-fat dairy	Whole milk, full-fat cottage cheese, full-fat yogurt, cream cheese, sour cream, full-fat cheese or cheese spreads, and full-fat ice cream or ice bars	-0.14
Low-fat dairy	Low-fat frozen yogurt, skim milk, low-fat cottage cheese, low- or reduced-fat cheese; low-fat ice cream, ice milk, or sherbet; and, skim, 1%, or 2% milk	-0.12
Coffee and tea	Iced or hot tea and regular or decaf coffee	-0.25
Nuts	Peanut butter, other nut butter, peanuts, walnuts, seeds, and other nuts	-0.44
Fats	Butter, margarine, mayonnaise, meat gravy, lard, vegetable shortening, and liquid oil (corn, canola)	0.31
Refined grains and starchy vegetables	Cake, cookies, brownies, doughnuts, sweet rolls, Danish, sweet muffins, dessert breads, fruit pie, cream custard or meringue pie, pumpkin or sweet potato pie, pancakes, waffles, French toast, crepes, bran cereal, fiber and non-fiber cereals, French fries, home fries, hash brown potatoes, potato salad, rice, pasta, spaghetti, other noodles, bagels, English muffins, breads, rolls, crackers, cornbread, muffins, biscuits, flour or corn tortillas, potato chips, sweet potatoes or yams; baked, boiled, or mashed potatoes; oatmeal, grits or other cooked cereals	0.72

Supplement score[b]	Ranked score of supplements, including: multivitamins, zinc, iron, selenium, folic acid, calcium, β-carotene, and vitamins A, C, and E	-0.80
LIS components		
Heavy drinker	Heavy (> 7 drinks/wk for women, > 14 drinks/wk drinks for men) vs. non-drinker	0.30
Moderate drinker	Moderate (1 – 7 drinks/wk for women, 1 – 14 drinks/wk for men) vs. non-drinker	-0.66
Moderately physically active	Exercises 1 – 3 times per month or 1 – 2 times/week vs. never or rarely exercises	-0.18
Heavily physically active	Exercises ≥ 3 times/wk vs. never or rarely exercises	-0.41
Current smoker	Currently smoked tobacco at baseline vs. did not currently smoke tobacco	0.50
Overweight BMI	Overweight BMI (25 – 29.99 kg/m^2) vs. normal BMI (18.5 – 24.99 kg/m^2)	0.89
Obese BMI	Obese BMI (≥ 30 kg/m^2) vs. normal BMI (18.5 – 24.99 kg/m^2)	1.57

Abbreviations: BMI, body mass index; DIS, dietary inflammation score; hsCRP, high sensitivity C-reactive protein; IL, interleukin; LIS, lifestyle inflammation score; NIH-AARP, National Institute of Health-American Association for Retired Person; REGARDS, Reasons for Geographic and Racial Differences in Stroke study

[a] Weights are β coefficients from multivariable linear regression models conducted in a subset of the REGARDS cohort (N = 639), and represent the average change in an inflammation biomarker score (sum of z-scores for hsCRP, IL-6, IL-8, and IL-10 [the latter with a negative sign]) 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 the sex-specific distribution in the analytic cohort at baseline, and all lifestyle components were dummy variables.

[b] 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., selenium), and 0 (low or no intake), -1, or -2 (highest intake) for hypothesized pro-inflammatory supplements (e.g., iron)

Table 4.2. Selected baseline characteristics of the NIH-AARP Diet and Health Study participants (N = 453,465) across quintiles of the dietary (DIS) and lifestyle (LIS) inflammation scores[a]

	DIS Quintile			LIS Quintile		
Characteristics[b]	1 (N = 90,743)	3 (N = 90,744)	5 (N = 90,743)	1 (N = 91,994)	3 (N = 91,456)	5 (N = 82,198)
Score range	-14.9 to -2.0	-0.6 to 0.6	2.0 to 12.8	-1.1 to -0.7	-0.2 to 0.2	0.8 to 2.4
Demographics						
Age at entry, y	61.6 (5.3)	61.6 (5.4)	61 (5.5)	61.6 (5.4)	61.5 (5.4)	61.2 (5.3)
Male, %	59.9	59.9	59.9	54.5	59.7	53.6
White, %	93.1	92.6	89.5	93.2	92.4	90.1
College graduate or higher, %	48.0	40.5	27.6	48.9	39.6	29.0
Marital status, %	67.8	70.1	68.8	68.7	69.9	63.6
Medical history						
No comorbidity[c], %	71.0	70.4	70.0	78.9	73.6	59.9
HRT user (women), %	49.6	46.8	36.8	55.2	47.6	34.7
Family history of CRC[d], %	9.1	8.9	8.3	9.2	8.9	8.6
Previously diagnosed with colon polyp, %	9.1	9.7	8.9	8.2	9.2	9.8
Lifestyle						
Current smoker, %	6.9	10.8	20.9	0.0	6.2	20.7
Normal BMI[e], %	38.6	34.9	33.5	100	33.9	1.4
Non-drinker, %	21.0	22.6	29.7	0.0	17.6	50
Exercises ≥ 3 times/wk, %	60.7	45.9	32.9	57.6	10.1	25.6
Dietary intakes						
Total energy, kcal/day	1,917 (812)	1,785 (767)	1,924 (870)	1,710 (674)	1,789 (755)	2,011 (960)
Carbohydrates, % kcal/day	0.6 (0.1)	0.5 (0.1)	0.5 (0.1)	0.6 (0.1)	0.5 (0.1)	0.5 (0.1)
Proteins, % kcal/day	0.2 (0.0)	0.2 (0.0)	0.1 (0.0)	0.2 (0.0)	0.2 (0.0)	0.2 (0.0)
Total fats, % kcal/day	0.3 (0.1)	0.3 (0.1)	0.3 (0.1)	0.3 (0.1)	0.3 (0.1)	0.3 (0.1)
Total calcium[f], mg/day	896 (493)	757 (429)	705 (446)	753 (417)	739 (428)	793 (489)
Dietary fiber, g/1,000 kcal/day	14.0 (4.2)	10.7 (3.2)	8.0 (2.7)	11.8 (4)	10.4 (3.6)	9.8 (3.7)
HEI-2015 Score[g]	74.3 (6.9)	68.7 (7.7)	58.6 (9.1)	70 (9.1)	67.1 (9.5)	65.6 (9.7)

Abbreviations: BMI, body mass index; CRC, colorectal cancer; DIS, dietary inflammation score; HEI, Healthy Eating Index; HRT, hormone replacement therapy; LIS, lifestyle inflammation score; NIH-AARP, National Institute of Health-American Association for Retired Persons

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

[b] Presented as means (standard deviation) unless otherwise specified

[c] Comprises self-reported baseline gallstone or gallbladder disease, emphysema, heart disease, or diabetes mellitus

[d] In a first degree relative

[e] 18.5 – 24.99 kg/m^2

[f] Total = diet + supplements

[g] Calculated as described in Krebs-Smith et al. (162)

Table 4.3. Associations of the dietary (DIS) and lifestyle (LIS) inflammation scores[a] with incident colorectal cancer overall, and by sex and colorectal cancer site; the NIH-AARP Diet and Health Study (N = 453,465)

	Overall				Men				Women			
	No. cases	DIS [b] Adjusted HR (95% CI)	No. cases	LIS [c] Adjusted HR (95% CI)	No. cases	DIS [b] Adjusted HR (95% CI)	No. cases	LIS [c] Adjusted HR (95% CI)	No. cases	DIS [b] Adjusted HR (95% CI)	No. cases	LIS [c] Adjusted HR (95% CI)
Colorectal												
Continuous		1.04 (1.03,1.05)		1.16 (1.13,1.19)		1.04 (1.03,1.05)		1.20 (1.15,1.24)		1.03 (1.02,1.05)		1.10 (1.05,1.15)
Quintiles												
Q1	1,877	1.00	1,727	1.00	1,243	1.00	1,052	1.00	634	1.00	675	1.00
Q2	1,905	1.01 (0.95,1.08)	1,978	1.13 (1.05,1.20)	1,297	1.04 (0.96,1.12)	1,454	1.15 (1.06,1.24)	608	0.96 (0.86,1.08)	524	1.11 (0.99,1.25)
Q3	2,008	1.06 (0.99,1.13)	2,155	1.21 (1.14,1.29)	1,340	1.07 (0.99,1.15)	1,477	1.29 (1.19,1.39)	668	1.04 (0.93,1.16)	678	1.08 (0.97,1.20)
Q4	2,126	1.11 (1.05,1.19)	2,315	1.22 (1.15,1.30)	1,397	1.10 (1.02,1.19)	1,588	1.26 (1.16,1.36)	729	1.13 (1.01,1.27)	727	1.16 (1.04,1.30)
Q5	2,420	1.27 (1.19,1.35)	2,161	1.38 (1.30,1.48)	1,628	1.29 (1.19,1.39)	1,334	1.49 (1.37,1.62)	792	1.21 (1.08,1.36)	827	1.22 (1.10,1.36)
P-trend		*<0.0001*		*<0.0001*		*<0.0001*		*<0.0001*		*<0.0001*		*<0.0001*
Colon												
Continuous		1.04 (1.03,1.05)		1.19 (1.16,1.23)		1.05 (1.04,1.06)		1.24 (1.19,1.29)		1.03 (1.02,1.05)		1.13 (1.07,1.18)
Quintiles												
Q1	1,466	1.00	1,294	1.00	955	1.00	775	1.00	511	1.00	519	1.00
Q2	1,464	1.00 (0.93,1.07)	1,530	1.17 (1.08,1.26)	979	1.01 (0.93,1.11)	1,120	1.20 (1.10,1.32)	485	0.97 (0.85,1.10)	410	1.13 (0.99,1.29)
Q3	1,536	1.04 (0.96,1.12)	1,669	1.26 (1.17,1.35)	1,017	1.06 (0.96,1.15)	1,117	1.33 (1.21,1.46)	519	1.01 (0.89,1.14)	552	1.14 (1.01,1.29)
Q4	1,672	1.13 (1.05,1.21)	1,844	1.31 (1.22,1.41)	1,084	1.12 (1.02,1.22)	1,255	1.36 (1.24,1.49)	588	1.15 (1.01,1.30)	589	1.22 (1.08,1.38)
Q5	1,911	1.29 (1.20,1.38)	1,712	1.47 (1.36,1.59)	1,275	1.33 (1.22,1.45)	1,043	1.60 (1.45,1.76)	636	1.21 (1.07,1.38)	669	1.29 (1.14,1.45)
P-trend		*<0.0001*		*<0.0001*		*<0.0001*		*<0.0001*		*0.0001*		*0.01*
Left colon[d]												
Continuous		1.04 (1.03,1.06)		1.23 (1.17,1.3)		1.05 (1.03,1.07)		1.29 (1.21,1.37)		1.02 (0.99,1.05)		1.14 (1.04,1.25)
Quintiles												
Q1	512	1.00	432	1.00	357	1.00	274	1.00	155	1.00	158	1.00
Q2	534	1.04 (0.92,1.17)	527	1.17 (1.03,1.33)	380	1.03 (0.89,1.20)	403	1.21 (1.04,1.41)	154	1.04 (0.83,1.31)	124	1.12 (0.89,1.42)
Q3	557	1.08 (0.95,1.22)	628	1.38 (1.22,1.56)	387	1.06 (0.91,1.22)	451	1.48 (1.27,1.72)	170	1.14 (0.91,1.43)	177	1.20 (0.97,1.49)
Q4	596	1.12 (0.99,1.27)	699	1.43 (1.26,1.61)	409	1.09 (0.95,1.27)	503	1.49 (1.28,1.73)	187	1.20 (0.96,1.51)	196	1.32 (1.07,1.64)
Q5	724	1.33 (1.18,1.50)	637	1.59 (1.40,1.80)	523	1.37 (1.19,1.58)	425	1.75 (1.50,2.05)	201	1.24 (0.99,1.56)	212	1.32 (1.06,1.64)
P-trend		*<0.0001*		*<0.0001*		*<0.0001*		*<0.0001*		*0.03*		*0.002*
Right colon[e]												
Continuous		1.05 (1.03,1.06)		1.17 (1.12,1.22)		1.05 (1.03,1.07)		1.21 (1.15,1.28)		1.04 (1.02,1.06)		1.12 (1.05,1.19)
Quintiles												
Q1	858	1.00	792	1.00	528	1.00	455	1.00	330	1.00	337	1.00
Q2	842	0.99 (0.90,1.09)	902	1.15 (1.04,1.26)	539	1.03 (0.91,1.16)	643	1.18 (1.05,1.34)	303	0.93 (0.79,1.09)	259	1.1 (0.93,1.29)
Q3	880	1.02 (0.93,1.12)	937	1.17 (1.06,1.29)	564	1.08 (0.95,1.21)	594	1.22 (1.08,1.38)	316	0.93 (0.80,1.09)	343	1.09 (0.94,1.27)
Q4	985	1.15 (1.05,1.27)	1,034	1.23 (1.12,1.35)	609	1.16 (1.03,1.31)	668	1.26 (1.12,1.43)	376	1.14 (0.98,1.33)	366	1.18 (1.01,1.37)
Q5	1,083	1.30 (1.18,1.43)	983	1.40 (1.27,1.55)	680	1.35 (1.20,1.52)	560	1.52 (1.34,1.73)	403	1.22 (1.04,1.42)	423	1.26 (1.08,1.46)
P-trend		*<0.0001*		*<0.0001*		*<0.0001*		*<0.0001*		*0.001*		*<0.0001*
Rectum/ rectosigmoid												
Continuous		1.03 (1.01,1.04)		1.05 (0.99,1.11)		1.03 (1,1.05)		1.06 (0.99,1.14)		1.02 (0.99,1.05)		1.01 (0.92,1.11)
Quintiles												
Q1	450	1.00	462	1.00	313	1.00	293	1.00	137	1.00	169	1.00
Q2	475	1.04 (0.91,1.19)	489	1.02 (0.90,1.16)	343	1.09 (0.94,1.28)	369	1.04 (0.89,1.21)	132	0.91 (0.71,1.16)	120	1.02 (0.81,1.29)
Q3	501	1.08 (0.95,1.23)	531	1.10 (0.97,1.24)	348	1.09 (0.93,1.27)	398	1.22 (1.05,1.43)	153	1.06 (0.84,1.34)	133	0.84 (0.67,1.06)
Q4	490	1.05 (0.92,1.20)	523	1.01 (0.89,1.15)	337	1.05 (0.90,1.23)	372	1.03 (0.88,1.21)	153	1.04 (0.82,1.32)	151	0.97 (0.77,1.21)
Q5	568	1.21 (1.06,1.38)	479	1.13 (0.99,1.29)	398	1.21 (1.04,1.42)	307	1.18 (1.00,1.40)	170	1.18 (0.93,1.50)	172	1.02 (0.81,1.28)
P-trend		*0.01*		*0.15*		*0.04*		*0.09*		*0.10*		*0.99*

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

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

[b] 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)

[c] Covariates in the LIS Cox proportional Hazards models were: age (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

[d] Splenic flexure, descending, sigmoid

[e] Cecum, descending, hepatic flexure, transverse

Table 4.4. Joint/combined associations of the dietary (DIS) and lifestyle (LIS) inflammation scores[a] with incident colorectal cancer overall, and by sex; the NIH-AARP Diet and Health Study (N = 453,465)

	LIS quintiles[b]										
	1		2		3		4		5		
	No. cases	HR (95% CI)	No. cases	HR (95% CI)	No. cases	HR (95% CI)	No. cases	HR (95% CI)	No. cases	HR (95% CI)	*p-interaction*
Overall											
DIS quintiles[b]											
1	361	1.00 (ref)	478	1.13 (1.06, 1.20)	351	1.22 (1.15, 1.30)	381	1.23 (1.16, 1.31)	306	1.41 (1.32, 1.50)	
2	371	1.02 (0.96, 1.09)	398	1.15 (1.05, 1.26)	362	1.25 (1.14, 1.36)	436	1.26 (1.15, 1.37)	338	1.43 (1.31, 1.57)	
3	341	1.07 (1.01, 1.14)	391	1.21 (1.10, 1.32)	423	1.31 (1.20, 1.43)	474	1.32 (1.21, 1.44)	379	1.51 (1.38, 1.65)	
4	335	1.14 (1.07, 1.21)	365	1.28 (1.17, 1.40)	469	1.39 (1.27, 1.51)	479	1.40 (1.28, 1.53)	478	1.60 (1.46, 1.74)	
5	319	1.30 (1.22, 1.38)	346	1.46 (1.34, 1.60)	550	1.59 (1.46, 1.73)	545	1.60 (1.47, 1.75)	660	1.83 (1.68, 1.99)	*0.0002*
Men											
DIS quintiles[b]											
1	214	1.00 (ref)	337	1.15 (1.06, 1.24)	229	1.30 (1.20, 1.41)	269	1.27 (1.17, 1.37)	194	1.52 (1.40, 1.65)	
2	225	1.04 (0.97, 1.13)	304	1.20 (1.07, 1.34)	250	1.36 (1.22, 1.52)	297	1.33 (1.19, 1.48)	221	1.59 (1.42, 1.78)	
3	193	1.08 (1.00, 1.17)	292	1.24 (1.11, 1.39)	287	1.41 (1.26, 1.57)	329	1.37 (1.23, 1.53)	239	1.64 (1.47, 1.84)	
4	201	1.12 (1.04, 1.21)	268	1.29 (1.15, 1.44)	326	1.46 (1.31, 1.63)	312	1.42 (1.28, 1.59)	290	1.71 (1.53, 1.91)	
5	219	1.32 (1.23, 1.43)	253	1.52 (1.36, 1.70)	385	1.72 (1.55, 1.92)	381	1.68 (1.51, 1.87)	390	2.01 (1.80, 2.24)	*<0.0001*
Women											
DIS quintiles[b]											
1	147	1.00 (ref)	141	1.11 (0.99, 1.25)	122	1.08 (0.97, 1.21)	112	1.17 (1.05, 1.3)	112	1.23 (1.11, 1.37)	
2	146	0.97 (0.87, 1.09)	94	1.08 (0.92, 1.27)	112	1.05 (0.90, 1.23)	139	1.13 (0.97, 1.32)	117	1.20 (1.03, 1.39)	
3	148	1.06 (0.95, 1.18)	99	1.18 (1.01, 1.39)	136	1.15 (0.99, 1.34)	145	1.24 (1.07, 1.44)	140	1.31 (1.13, 1.52)	
4	134	1.16 (1.04, 1.29)	97	1.29 (1.10, 1.51)	143	1.26 (1.09, 1.46)	167	1.36 (1.17, 1.58)	188	1.43 (1.24, 1.66)	
5	100	1.26 (1.13, 1.40)	93	1.40 (1.20, 1.64)	165	1.36 (1.18, 1.58)	164	1.47 (1.27, 1.70)	270	1.55 (1.34, 1.79)	*0.004*

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

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

[b] Covariates in the Cox proportional hazards models were: age (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), and former smoker (yes/n

Chapter 5. Conclusions

In this dissertation, we developed novel, inflammation biomarker panel-weighted dietary-specific and lifestyle-specific inflammation scores to characterize the collective associations of whole foods and lifestyle behaviors with systemic inflammation. We then investigated associations of the scores with circulating inflammation biomarker concentrations in three populations, colorectal adenoma in a pooled case-control study, and colorectal cancer in a large, prospective cohort study. The findings from this dissertation suggest that, taken together with previous literature, dietary and lifestyle exposures may contribute substantially to systemic inflammation, and that reducing inflammation, such as through dietary or lifestyle interventions, could potentially reduce risk for colorectal neoplasms.

In the first aim of this dissertation, we selected whole foods and lifestyle characteristics *a priori* to comprise the DIS and LIS, estimated the components' weights based on the strengths of their associations with a panel of inflammation biomarkers, and validated the scores by investigating their associations with circulating inflammation biomarker concentrations in three study populations. We compared these associations to those with previously developed dietary inflammation scores, the DII and EDII, and found that our whole foods-based DIS was more strongly, directly associated with circulating concentrations of inflammation biomarkers than were the previously developed dietary inflammation scores, and that the LIS was more strongly, directly associated with inflammation biomarker concentrations than were all of the dietary inflammation scores. Based on these findings, we believe that our scores successfully addressed many of the limitations of previously developed dietary inflammation scores and that our scores may better reflect dietary- and lifestyle-associated systemic inflammation.

For our second aim, we calculated the DIS and LIS (developed in Aim 1) in a pooled case-control study to investigate their associations with incident, sporadic colorectal adenoma. The findings from this study supported our hypothesis that pro-inflammatory diets and lifestyles are associated with higher risk for

colorectal neoplasms. These associations were particularly strong for adenomas that were at higher risk for malignancy, indicating that dietary- and lifestyle-associated inflammation may play more of a role in the progression of adenomas, rather than in their initial formation. This hypothesis was further supported by our findings for the third aim of this dissertation, which was focused on investigating associations of the DIS and LIS with incident CRC among participants in the large, prospective NIH-AARP Diet and Health Study cohort. In that study, we found that pro-inflammatory diets and lifestyles were associated with higher risk for incident CRC.

In both Aims 2 and 3 we found that the associations of the DIS and LIS with colorectal neoplasms were generally stronger for adenomas/cancers of the colon than of the rectum. The left colon, right colon, and rectum differ with respect to their embryologic origin and physiologic functions (119). From the colon to the rectum, as the fecal stream passes, the composition of metabolically active molecules and the gut microbiota are altered (121). Also, there is some evidence for anatomical differences in the associations of certain risk factors (e.g., BMI, alcohol intake, red meat intake) with colorectal carcinoma (119,229,230). Further investigation into differences in associations of pro-inflammatory exposures with colorectal cancer by anatomical site is needed.

In both Aims 2 and 3, the DIS/LIS-colorectal neoplasm associations were also generally stronger among men. Stronger associations of various dietary patterns with CRC among men have frequently been reported; however, it is unclear whether this is due to artifacts of dietary measurement or to true biological differences. First, it is possible that women may have more homogeneity in their dietary and lifestyle exposures than do men, resulting in more attenuated DIS/LIS-CRC associations. To test this hypothesis, we compared the quintile medians of the DIS and LIS by sex in the NIH-AARP Diet and Health Study cohort, but found that the differences between the quintile medians of the scores were similar for males and females. Second, women in the case-control and cohort studies may have tended to under-report dietary intakes, alcohol intake, and BMI, as found in previous studies (231–234). Finally, it

is also plausible that women may respond differently biologically to inflammatory dietary and lifestyle exposures than do men, as some evidence indicates that estrogen regulates inflammatory cytokine production and stimulates the production of anti-oxidant enzymes (138,235,236).

Overall, our findings taken together suggest that the novel dietary and lifestyle inflammation scores we developed address limitations of studying individual contributions of foods/nutrients/lifestyles to systemic inflammation and of previous dietary inflammation scores. The DIS and LIS are easily replicable, applicable to diverse populations, robust across methods of dietary/lifestyle assessment, and may be useful for formulating clinical and public health dietary/lifestyle recommendations for inflammation reduction and disease/colorectal cancer prevention. Our findings also suggest that pro-inflammatory diets and lifestyles may be associated with higher risk for colorectal neoplasms, and, taken together with previous literature, support inflammation as a major pathway underlying the associations of dietary/lifestyle exposures with colorectal carcinogenesis. Given our findings, diet/lifestyle interventions aimed to reduce systemic inflammation, may potentially reduce CRC risk and risk for other inflammation-mediated diseases.

Future Directions

While the DIS and LIS were strongly, directly associated with biomarkers of systemic inflammation in the three study populations, the scores do have certain limitations that can be addressed in future studies. To develop weights for our scores we ideally would conduct a large randomized trial in healthy adults with multiple arms to assess the effects of different dietary and lifestyle interventions on circulating inflammation biomarker concentrations over an ideal length of time. However, such studies would be highly impractical, and the cost would be prohibitive and not justified at this time. Instead, we outline below more practical, cost-effective approaches to improve upon the DIS and LIS in future studies:

1) We propose collecting more comprehensive panels of reliably measured systemic inflammation biomarkers for which to assess the strengths of associations of the *a priori*-selected diet/lifestyle

components with systemic inflammation. The panels would ideally include biomarkers representing multiple independent and overlapping inflammation pathways, and could include mediators of innate and adaptive immunity, mediators that promote or inhibit inflammation, and multiple cytokines/chemokines from different sources and with different effects.

2) To address the known limitations of FFQs, we propose collecting Willett FFQs, extended to include questions regarding food preparation methods, whole grain intake, and detailed vegetable and fruit intake. The FFQs would ideally be administered over at least 2–3 time points spread out over the course of a year. We also propose collecting multiple, interviewer-administered 24-hour dietary recalls in a subset of the study participants and using a combination of the FFQ and recalls to assess the validity and sensitivity of the DIS weights.

3) To address issues with the cross-sectional nature of the weights, we propose collecting the above described dietary/lifestyle data and circulating plasma inflammation biomarker concentrations at multiple time points prospectively, over the course of at least a year.

4) Finally, we propose developing the score in a larger population, which would allow for stratification by sex, race, and other participant characteristics that incorporate heterogeneity in systemic levels of inflammation and potentially in inflammatory response to dietary intakes and other lifestyle exposures.

We found that a higher balance of pro-inflammatory diets and lifestyles may be associated with higher risk for colorectal neoplasms. Therefore, I propose expanding on these findings by calculating the DIS and LIS in other large, prospective cohort studies, such as the Iowa Women's Health Study cohort, the entire REGARDs cohort, and the American Cancer Society Cancer Prevention Study cohort, and investigating their associations with incident colorectal cancer. Replication of our findings would add to the evidence for the role of diet- and lifestyle-associated inflammation in colorectal carcinogenesis.

I also propose further investigation, using data from large, prospective cohort studies, into the associations of the DIS and LIS with the incidence of other inflammation-mediated diseases, such as

cardiovascular disease, diabetes mellitus, other cancers, and all-cause/cause-specific mortality. The DII was previously found to be modestly to strongly, directly associated with cardiovascular disease, prediabetes, metabolic syndromes, cognitive outcomes, and mortality (237–242). A higher EDII was found to be associated with 38% higher risk for rheumatoid arthritis (243). Given that the DIS and LIS address many of the limitations of the DII and EDII, we hypothesize that our scores will be more strongly, directly associated with inflammation-mediated diseases than were the previously developed inflammation scores.

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Appendix 1. Latent Variable for Systemic Inflammation

Introduction

As described in Chapter 1, as an alternative to calculating a summary inflammation biomarker score to characterize the complexity of systemic inflammation, we used structural equation modeling (SEM) to model systemic inflammation as an unobserved latent variable constructed using the covariance of measured circulating inflammation biomarkers in the REGARDS case-cohort subset (N = 639) that are thought to be a consequence of systemic inflammation. We proposed that, given content validity and construct validity be deemed sufficient, the latent variable would be used as a dependent variable in multivariable linear regression models estimating the strengths of associations of the dietary and lifestyle components comprising the DIS and LIS with systemic inflammation.

Methods

Analyses were conducted using SAS statistical software, version 9.3 (Proc CALIS) and R software (package 'lavaan'). The latent variable for systemic inflammation was constructed from the four inflammation biomarkers measured in the REGARDS case-cohort subset: IL-6, IL-8, IL-10, and CRP. Prior to calculating the latent variable, we transformed the inflammation biomarker values to a normal distribution using a natural log transformation, and standardized them to a mean of 0 and standard deviation of 1.0. We then conducted structural equation modeling to calculate loading factors representing the contribution of the latent variable to the four inflammation biomarkers. In these models, because IL-6 induces activation of CRP, we specified a covariance between IL-6 and CRP, and specified a variance of 1.0 for the latent variable since it cannot be defined in any unit of measurement. Using the Proc CALIS PLATCOV statement, we computed the latent variable score coefficients for each of the inflammation biomarkers representing the β-coefficients from a linear regression of the inflammation biomarkers on the latent variable. The standardized inflammation biomarker values were then multiplied by the latent variable score coefficient, and the weighted inflammation biomarkers summed to comprise the latent

variable for systemic inflammation. The latent variable was standardized to a mean of 0 and variance of 1.0.

We assessed content validity of the latent variable based on the magnitude and direction of the estimated contributions of each inflammation biomarker to the latent variable. We assessed construct validity by estimating the associations of established risk/protective factors for chronic, low-grade inflammation with the latent variable and, for comparison, with the summary inflammation biomarker score described in Chapter 2, using multivariable linear regression.

Results

Both R and SAS software yielded identical loading factors and latent variable score coefficients for each inflammation biomarker. The latent variable score model had good fit (Chi-square p-value = 0.11, root mean square error of approximation (RMSEA) = 0.05, comparative fit index (CFI) = 0.99).

The loading factors are presented in Appendix Table 1.1. All markers, except CRP, statistically significantly contributed to the latent variable score. The latent variable score coefficients are shown in Appendix Table 1.2. The coefficients for IL-6 and IL-8 were consistent with biological plausibility; whereas, IL-10 had a positive coefficient and CRP had a negative coefficient.

The associations of the established risk/protective factors for chronic/low-grade inflammation with the latent variable and summary inflammation biomarker score are shown in Appendix Table 1.3. For the summary inflammation biomarker score associations, all β-coefficients were consistent with biological plausibility; however, for the latent variable score associations, heavy drinking was inversely associated with the latent variable, and the BMI—latent variable associations were slightly weaker than the BMI—summary inflammation biomarker score associations.

Discussion

Based on our findings, the latent variable did not meet content validity criteria. Our findings also suggested that the summary inflammation biomarker score had stronger construct validity, and may be a better reflection of systemic inflammation than the latent variable.

The lack of content and construct validity of the latent variable may have been due, in part, to violations of certain assumptions necessary for using structural equation models to calculate a latent variable. First, the values of the manifest variables should be conditionally uncorrelated given the value of the latent variable; however, IL-6 activates CRP and thus, if we were able to condition on systemic inflammation, IL-6 and CRP would remain correlated. Second, CRP, unlike IL-6, IL-8, and IL-10, is a non-specific marker of inflammation and has different physiological functions, and thus, may be unreliably correlated with the other circulating inflammation biomarker concentrations. Third, IL-10 may increase as IL-6 and IL-8 increase and basing its function strictly on the data (rather than biological plausibility) may incorrectly indicate that IL-10 upregulates the inflammation response.

In conclusion, our findings suggest that using structural equation modeling to calculate an unobserved latent variable for systemic inflammation may have many limitations. A more useful direction to characterize inflammation may be to development summary scores of standardized, *a priori*-selected inflammation biomarkers.

Tables

Table A1.1. Loading factors for the contributions of the latent variable to each inflammation biomarker in the REGARDS case-cohort (N = 639)

Inflammation Biomarkers	Loading factor	*p*	Covariance with latent variable
IL-6	0.39	<0.001	1.72
IL-8	0.38	<0.001	1.65
IL-10	0.45	<0.001	1.97
CRP	0.08	0.26	0.36

Abbreviations: CRP, C-reactive protein; IL, interleukin

Table A1.2. Latent variable coefficients for inflammation biomarkers in the REGARDS case-cohort (N = 639)

Inflammation Biomarker	Latent Variable Score Coefficient[a]	*p*
CRP	-0.02	0.26
IL-10	0.08	<0.001
IL-6	0.07	<0.001
IL-8	0.06	<0.001

Abbreviations: CRP, C-reactive protein; IL, interleukin

[a] Calculated using the 'platcov' function in PROC CALIS

Table A1.3. Estimated associations of protective/risk factors for systemic inflammation with systemic inflammation latent variable and with summary inflammation biomarker score in the REGARDS case-cohort (N = 639)

Risk/protective Factor for Inflammation	Summary Inflammation Biomarker Score	Latent Variable for Systemic Inflammation[a]
	β[b]	β[b]
Heavy drinker vs. non-drinker[c]	0.28	-0.17
Moderate drinker vs. non-drinker[c]	-0.65	-0.42
Overweight BMI vs. normal BMI[d]	0.89	0.03
Obese BMI vs. normal BMI[d]	1.56	0.46
Current smoker vs. never/former smoker	0.50	1.04
Exercises 1-3 times/week vs. does not exercise	-0.15	-0.17
Exercises ≥ 4 times/week vs. does not exercise	-0.42	-0.41
Takes aspirin/other NSAIDs ≥ once/week vs. does not take NSAIDs	-0.15	-0.25

Abbreviations: BMI, body mass index; NSAID, non-steroidal anti-inflammatory drug

[a] Calculated by multiplying the latent variable coefficients (shown in A1.2) by the standardized inflammation biomarker values and summing the weighted inflammation biomarker components

[b] Covariates in the linear regression model 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); all the dietary/lifestyle components in the DIS and LIS; and all listed risk/protective factors for inflammation

[c] Heavy drinker (> 7 drinks/wk for women, > 14 drinks/wk drinks for men); moderate drinker (1 – 7 drinks/wk for women, 1 – 14 drinks/wk for men)

[d] Overweight BMI (25 – 29.99 kg/m^2); obese BMI (≥ 30 kg/m^2)

Appendix 2. Chapter 2 Supplemental Tables

Table A2.1. Comparison of components and derivation of the DIS, LIS, DII, and EDII

	Inflammation score		
	DIS and LIS	DII	EDII
Pro-inflammatory components	Red and organ meats, processed meats, added sugars, fats, refined grains and starchy vegetables, heavy alcohol intake, current tobacco use, overweight BMI, obese BMI	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, refined grains, high-energy beverages, low-energy beverages, and tomatoes
Anti-inflammatory components	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	Alcohol, β-carotene, caffeine, dietary fiber, folic acid, magnesium, thiamin, riboflavin, niacin, zinc, monounsaturated fats, polyunsaturated fats, Ω-3 fats, Ω-6 fats, selenium, isoflavones, flavan-3-ol, flavones, flavanols, flavanones, anthocyanins, green or Black tea, garlic, onion, turmeric, thyme & oregano, hot pepper, rosemary, eugenol, ginger, saffron, and vitamins A, B_6, C, D, & E	Beer, wine, tea, coffee, dark-yellow vegetables, green-leafy vegetables, snacks, fruit juice, and pizza
Derivation approach	Used multivariable linear regression to calculate β coefficients representing the average change in summary inflammation biomarker z-score per one standard deviation increase in a dietary component or the presence of a lifestyle component	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 summary biomarker score
Inflammation biomarkers	IL-6, IL-8, IL-10, CRP	IL-1β, IL-4, IL-6, IL-10, TNF-α, CRP	IL-6, TNF-α R2, CRP

Abbreviations: BMI, body mass index; DII, Dietary Inflammatory Index; DIS, dietary inflammation score; EDII, Empirical Dietary Inflammation Index; LIS, lifestyle inflammation score

Table A2.2. Selected characteristics of the participants in REGARDs cohort (N = 14,210) across quintiles of the DIS and LIS

	DIS Quintiles				LIS Quintiles			
Characteristics[a]	1 (N =2,843)	3 (N =2,842)	5 (N =2,841)	p^b	1 (N =2,973)	3 (N =3,093)	5 (N =2,291)	p^b
Score range	-25.8 to -15.8	-13.1 to -7.1	-4.5 to 5.0		-1.1 to -0.2	0.5 to 0.7	1.4 to 2.4	
Demographics								
Age, y	63.3 (6.6)	61.7 (7.0)	60.7 (7.4)	<0.001	62.9 (6.8)	62.1 (6.9)	60.9 (7.4)	<0.001
Male, %	44.7	44.7	44.7	1.00	47.8	51.1	31.3	<0.001
White, %	83.1	69.0	47.3	<0.001	80.4	65.4	54.0	<0.001
Income < $20k, %	7.2	12.7	23.6	<0.001	7.7	12.1	20.6	<0.001
College graduate or higher, %	54.8	39.39	21.7	<0.001	24.6	28.6	29.2	<0.001
Stroke Belt or Buckle resident, %	49.9	57.6	63.8	<0.001	56.3	57.1	59.4	<0.001
Medical history								
Has comorbidity[c], %	38.0	41.6	44.5	<0.001	30.4	42.4	52.3	<0.001
Takes NSAID/aspirin ≥ twice/wk, %	56.3	52.2	45.4	<0.001	49.0	53.0	52.9	<0.001
HRT user (women), %	68.8	62.4	53.0	<0.001	67.5	61.7	54.6	<0.001
Lifestyle behaviors								
Current smoker, %	6.4	13.3	25.3	<0.001	6.3	11.2	20.7	<0.001
Normal BMI, %	30.16	21.7	21.0	<0.001	78.0	4.1	0.0	<0.001
Non-drinker, %	48.4	58.3	68.1	<0.001	34.0	62.1	90.8	<0.001
Exercises ≥ 4 times/wk, %	40.8	30.3	26.3	<0.001	57.0	39.0	4.2	<0.001
Dietary intake								
Total energy intake, kcal/day	1,752 (671)	1,689 (712)	1,752 (763)	0.002	1,708 (650)	1,741 (734)	1,718 (746)	0.03
Dietary fiber, g/1,000 kcal/day	12.5 (4.2)	9.5 (3.3)	7 (2.6)	<0.001	10.5 (4.2)	9.7 (3.8)	9.1 (3.5)	<0.001
Total fat intake, % kcal/day	0.4 (0.1)	0.4 (0.1)	0.4 (0.1)	0.11	0.4 (0.1)	0.4 (0.1)	0.4 (0.1)	<0.001
Carbohydrates, % kcal/day	0.5 (0.1)	0.5 (0.1)	0.5 (0.1)	<0.001	0.5 (0.1)	0.5 (0.1)	0.5 (0.1)	<0.001
Protein, % kcal/day	0.2 (0.0)	0.1 (0.0)	0.1 (0.0)	<0.001	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)	<0.001
Inflammation markers								
Plasma hsCRP, mg/dL	1.4 (2.7)	1.8 (2.6)	2.2 (2.7)	<0.001	1.1 (2.7)	1.8 (2.6)	2.8 (2.4)	<0.001

Abbreviations: BMI, body mass index; DIS, dietary inflammation score; HRT, hormone replacement therapy; hsCRP, high-sensitivity C-reactive protein; LIS, lifestyle inflammation score; NSAID, nonsteroidal anti-inflammatory drug; REGARDs, Reasons for Racial and Geographic Differences in Stroke Study

[a] Presented as means (standard deviation) unless otherwise specified

[b] p-values calculated using χ^2 test for categorical variables and ANOVA for continuous variables

[c] Includes a history of cancer, heart disease, diabetes mellitus, or chronic kidney disease

Table A2.3. Selected characteristics of the participants in the MAP studies (N = 433) across quartiles of the DIS and LIS

	DIS Quartiles					LIS Quartiles				
Characteristics[a]	1 (N =110)	2 (N =108)	3 (N =109)	4 (N =106)	p[b]	1 (N =114)	2 (N =112)	3 (N =103)	4 (N =104)	p[b]
Score range	-26.5 to -16.4	-18.2 to -7.3	-11.6 to -3.6	-9.1 to 3.3		-1.1 to .02	-0.2 to 0.7	0.3 to 1.4	0.9 to 2.1	
Demographics										
Age, y	57.4 (7.9)	57.6 (9.2)	55.9 (9.7)	53.8 (8.4)	0.01	55.6 (9.6)	56.5 (8.2)	56 (8.9)	56.8 (9.0)	0.79
Male, %	52.7	51.9	52.3	52.8	1.0	51.7	55.6	53.1	49.0	0.82
White, %	91.8	84.3	85.3	84.0	0.28	92.2	93.5	84.1	74.0	<0.001
College graduate or higher, %	40.9	31.5	28.4	16.0	0.001	36.2	34.3	24.8	20.8	0.03
Medical history										
Takes NSAID/aspirin ≥ once/wk, %	66.4	52.8	55.1	48.1	0.05	52.8	55.1	48.1	61.5	0.48
HRT user (women), %	70.6	46.2	46.2	34.0	0.003	50.0	58.3	41.5	47.9	0.41
Prevalent adenoma status, %	33.6	37.0	42.2	34.0	0.53	33.6	41.7	33.6	38.5	0.53
Lifestyle behaviors										
Current smoker, %	18.2	25.0	22.9	29.3	0.29	14.7	17.6	23.0	42.7	<0.001
Normal BMI, %	42.2	43.8	26.4	30.5	0.01	86.6	41.0	10.7	0.0	<0.001
Non-drinker, %	60.0	58.3	62.4	74.5	0.11	43.1	56.5	72.6	86.5	<0.001
Physical activity, METs/wk	222 (147)	218 (173)	223 (162)	212 (165)	0.95	269 (161)	240 (154)	208 (161)	148 (145)	<0.001
Dietary intake										
Total energy intake, kcal/day	1,891 (699)	2,029 (930)	1,836 (740)	1,962 (765)	0.30	1,868 (672)	1,980 (889)	1,836 (758)	2,054 (827)	0.16
Dietary fiber, g/1,000 kcal/day	12.5 (4.7)	12.1 (3.7)	11 (3.3)	9 (3.2)	<0.001	11.6 (3.4)	11.8 (4.9)	10.7 (3.8)	10.5 (3.4)	0.04
Total fat intake, % kcal/day	0.3 (0.1)	0.3 (0.1)	0.3 (0.1)	0.3 (0.1)	<0.001	0.3 (0.1)	0.3 (0.1)	0.3 (0.1)	0.3 (0.1)	0.01
Carbohydrates, % kcal/day	0.5 (0.1)	0.5 (0.1)	0.5 (0.1)	0.5 (0.1)	<0.001	0.5 (0.1)	0.5 (0.1)	0.5 (0.1)	0.5 (0.1)	0.01
Protein, % kcal/day	0.2 (0.0)	0.2 (0.0)	0.2 (0.0)	0.2 (0.0)	<0.001	0.2 (0.0)	0.2 (0.0)	0.2 (0.0)	0.2 (0.0)	0.81
Inflammation markers										
Plasma hsCRP, mg/dL	1.8 (2.4)	2.1 (2.5)	2.2 (2.5)	2.4 (2.5)	0.06	1.4 (2.5)	2 (2.3)	2.3 (2.3)	3.4 (2.2)	<0.001

Abbreviations: BMI, body mass index; DIS, dietary inflammation score; HRT, hormone replacement therapy; hsCRP, high-sensitivity C-reactive protein; LIS, lifestyle inflammation score; MAP, Markers of Adenomatous Polyps; METs, metabolic equivalent of tasks; NSAID, nonsteroidal anti-inflammatory drug

[a] Presented as means (standard deviation) unless otherwise specified

[b] p-values calculated using χ^2 test for categorical variables and ANOVA for continuous variables

Table A2.4. Selected characteristics of the participants in the CECP study (N = 173) across quantiles of the DIS and LIS

	DIS Quantiles			LIS Quantiles		
Characteristics[a]	1 (N = 87)	2(N = 86)	p[b]	1 (N = 87)	2 (N = 86)	p[b]
Score range	-19.2 to -6.9	-10.0 to 3.1		-1.1 to 0.5	0.5 to 2.4	
Demographics						
Age, y	60.7 (8.8)	58.2 (10.5)	0.09	58.2 (10.2)	60.6 (9.1)	0.10
Male, %	63.2	64.0	0.92	60.0	67.1	0.34
Medical history						
Takes NSAID/aspirin ≥ once/wk, %	29.9	27.9	0.77	23.5	34.1	0.13
College graduate or higher, %	32.2	27.9	0.54	35.3	25.0	0.14
HRT user (women), %	11.5	10.5	0.98	11.8	10.2	0.62
Lifestyle behaviors						
Current smoker, %	12.6	24.4	0.05	16.5	20.5	0.50
Normal BMI, %	26.4	24.4	0.70	49.4	2.3	<0.001
Non-drinker, %	43.7	44.2	0.95	29.4	58.0	<0.001
Physical activity, minutes/wk	32.3 (51.6)	21.1 (40.0)	0.11	37.3 (52.7)	16.5 (37.0)	0.003
Dietary intake						
Total energy intake, kcal/day	2,063 (649)	2,074 (686)	0.91	2,134 (622)	2,005 (702)	0.20
Dietary fiber, g/1,000 kcal/day	11.8 (3.3)	10.2 (3.3)	0.002	11.2 (3.2)	10.8 (3.6)	0.40
Total fat intake, % kcal/day	0.3 (0.1)	0.3 (0.1)	0.02	0.3 (0.1)	0.3 (0.1)	0.38
Protein, % kcal/day	0.2 (0.0)	0.2 (0.0)	0.15	0.2 (0.0)	0.2 (0.0)	0.86
Inflammation markers						
Plasma IL-6, pg/mL	1.8 (1.7)	2.7 (1.9)	<0.001	1.7 (1.7)	2.7 (1.9)	<0.001
Plasma IL-8, pg/mL	5.4 (1.5)	5.7 (1.4)	0.32	5.4 (1.5)	5.6 (1.4)	0.48
Plasma IL-10, pg/mL	1.9 (3.0)	2.0 (3.4)	0.82	1.9 (3.0)	2.0 (3.3)	0.86
Plasma hsCRP, mg/L	1.3 (3.2)	2.4 (2.8)	<0.001	1.2 (3.1)	2.4 (2.8)	<0.001
Plasma VEGF, pg/mL	77.4 (2.0)	78.2 (2.0)	0.93	77.7 (2.0)	77.9 (2)	0.99
Plasma TNF-α, pg/mL	1.4 (1.4)	1.4 (1.4)	0.53	1.3 (1.4)	1.5 (1.5)	0.08
Plasma IL-1β, pg/mL	1.2 (1.1)	1.2 (1.1)	0.61	1.2 (1.1)	1.2 (1.1)	0.009
Inflammation biomarker score	0.1 (3.7)	-0.1 (3.9)	0.74	-1.1 (3.6)	1.0 (3.7)	<0.001

Abbreviations: BMI, body mass index; CECP, Calcium and Colorectal Epithelial Cell Proliferation trial; DIS, dietary inflammation score; HRT, hormone replacement therapy; hsCRP, high-sensitivity C-reactive protein; LIS, lifestyle inflammation score; NSAID, nonsteroidal anti-inflammatory drug; TNF-α, tumor necrosis factor-alpha; VEGF, vascular endothelial growth factor

[a] Presented as means (standard deviation) unless otherwise specified

[b] p-values calculated using χ^2 test for categorical variables and ANOVA for continuous variables

Table A2.5. Correlations of the DIS with the DII and EDII, and for each quantile of the DIS, the number and percentages of study participants who were in the same and different quantiles of the DII and EDII[a] in three study populations

Study														
CECP			*MAP*					*REGARDS*						
DIS quantile (N = 173)			DIS quartile (N = 433)					DIS quintile (N = 14,210)						
DII quantile	1	2	DII quartile	1	2	3	4	DII quintile	1	2	3	4	5	
1	61 (70.1)	26 (30.2)	1	61 (55.5)	40 (37.0)	6 (5.5)	3 (2.8)	1	1,552 (54.6)	719 (25.3)	380 (13.4)	147 (5.2)	45 (1.6)	
2	26 (29.9)	60 (69.8)	2	32 (29.1)	34 (31.5)	32 (29.4)	10 (9.4)	2	764 (26.9)	937 (33.0)	610 (21.5)	383 (13.5)	148 (5.2)	
Total	87	86	3	14 (12.7)	23 (21.3)	40 (36.7)	32 (30.2)	3	352 (12.4)	649 (22.8)	788 (27.7)	672 (23.7)	381 (13.4)	
	r = 0.60		4	3 (2.7)	11 (10.2)	31 (28.4)	61 (57.6)	4	140 (4.9)	421 (14.8)	683 (24.0)	851 (29.9)	747 (26.3)	
EDII quantile			Total	110	108	109	106	5	35 (1.2)	116 (4.1)	381 (13.4)	789 (27.8)	1,520 (53.5)	
1	47 (46.5)	40 (436.5)			r = 0.64			Total	2,843	2,842	2,842	2,842	2,841	
2	40 (53.5)	46 (53.5)	EDII quartile								r = 0.67			
Total	87	86	1	44 (40.0)	28 (25.9)	23 (21.1)	15 (14.2)	EDII quintile						
	r = 0.13		2	24 (21.8)	34 (31.5)	34 (31.2)	16 (15.1)	1	977 (34.4)	724 (25.5)	526 (18.5)	404 (14.2)	212 (7.5)	
			3	27 (24.6)	28 (25.9)	28 (25.7)	26 (24.5)	2	644 (22.7)	684 (24.1)	608 (21.4)	546 (19.2)	360 (12.7)	
			4	15 (13.6)	18 (16.7)	24 (22.0)	49 (46.2)	3	504 (17.7)	606 (21.3)	613 (21.6)	604 (21.6)	515 (18.1)	
			Total	110	108	109	106	4	395 (13.9)	476 (16.8)	618 (21.8)	680 (23.9)	673 (23.7)	
					r = 0.22			5	323 (11.4)	352 (12.4)	477 (16.8)	608 (21.4)	1,081 (38.1)	
								Total	2,843	2,842	2,842	2,842	2,841	
											r = 0.33			

Abbreviations: CECP, Calcium and Colorectal Epithelial Cell Proliferation trial; DII, dietary inflammatory index; DIS, dietary inflammation score; EDII, empirical dietary inflammation index; MAP, Markers of Adenomatous Polyps; REGARDS, Reasons for Racial and Geographic Differences in Stroke Study

[a] Values are Pearson correlation coefficients, and n (%) of participants in each quantile of the DIS, by quantile of the DII and EDII

Table A2.6. Associations of the DIS and LIS with plasma hsCRP concentrations[a], by selected participant characteristics in the REGARDs cohort (N = 14,210)

Characteristic	*N*	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	*p-trend*	*p-interaction*[b]
DIS[c,d]								
Age, y								
< 65	8,567	1.00	1.34 (1.13, 1.59)	1.43 (1.21, 1.69)	1.68 (1.42, 1.99)	1.73 (1.46, 2.06)	*<0.001*	
≥ 65	5,528	1.00	1.11 (0.91, 1.36)	1.29 (1.06, 1.58)	1.22 (0.99, 1.50)	1.54 (1.24, 1.92)	*<0.001*	*0.37*
Sex								
Male	6,325	1.00	1.17 (0.96, 1.44)	1.30 (1.07, 1.59)	1.37 (1.12, 1.67)	1.68 (1.37, 2.06)	*<0.001*	
Female	7,770	1.00	1.29 (1.10, 1.51)	1.43 (1.22, 1.68)	1.57 (1.34, 1.85)	1.65 (1.39, 1.95)	*<0.001*	*0.49*
Race								
White	9,506	1.00	1.29 (1.11, 1.49)	1.46 (1.26, 1.69)	1.52 (1.31, 1.78)	1.66 (1.41, 1.97)	*<0.001*	
Black	4,589	1.00	1.10 (0.85, 1.43)	1.18 (0.92, 1.51)	1.36 (1.07, 1.72)	1.54 (1.22, 1.94)	*<0.001*	*0.68*
Has a comorbidity[e]								
No	8,316	1.00	1.21 (1.03, 1.42)	1.32 (1.12, 1.56)	1.46 (1.23, 1.72)	1.67 (1.40, 2.00)	*<0.001*	
Yes	5,779	1.00	1.29 (1.06, 1.57)	1.44 (1.19, 1.74)	1.55 (1.28, 1.88)	1.65 (1.36, 2.01)	*<0.001*	*0.99*
Non-aspirin NSAID use								
Takes NSAID < twice/wk	11,911	1.00	1.24 (1.08, 1.42)	1.41 (1.23, 1.62)	1.49 (1.30, 1.71)	1.71 (1.49, 1.98)	*<0.001*	
Takes NSAID ≥ twice/wk	2,165	1.00	1.26 (0.93, 1.69)	1.21 (0.89, 1.65)	1.49 (1.10, 2.03)	1.41 (1.01, 1.96)	*0.02*	*0.18*
Aspirin use								
Takes aspirin < twice/wk	8,027	1.00	1.20 (1.01, 1.43)	1.41 (1.19, 1.67)	1.56 (1.32, 1.85)	1.65 (1.39, 1.96)	*<0.001*	
Takes aspirin ≥ twice/wk	6,066	1.00	1.29 (1.08, 1.55)	1.32 (1.10, 1.60)	1.39 (1.14, 1.68)	1.69 (1.38, 2.07)	*<0.001*	*0.37*
Tobacco use								
Former or non-smoker	12,038	1.00	1.28 (1.13, 1.46)	1.35 (1.18, 1.54)	1.50 (1.31, 1.72)	1.63 (1.42, 1.88)	*<0.001*	
Current smoker	2,057	1.00	0.97 (0.63, 1.49)	1.63 (1.11, 2.41)	1.53 (1.05, 2.23)	1.84 (1.27, 2.66)	*<0.001*	*0.06*
BMI, kg/m^2								
18.5 – 24.99	3,387	1.00	1.51 (1.12, 2.03)	1.51 (1.10, 2.06)	2.04 (1.49, 2.78)	2.01 (1.45, 2.77)	*<0.001*	
25 – 29.99	5,463	1.00	1.17 (0.95, 1.43)	1.39 (1.14, 1.69)	1.49 (1.22, 1.83)	1.73 (1.41, 2.14)	*<0.001*	
≥ 30	5,102	1.00	1.20 (0.98, 1.46)	1.25 (1.03, 1.52)	1.26 (1.04, 1.53)	1.42 (1.16, 1.73)	*0.001*	*<0.001*
Alcohol use[f]								
Non-drinker	8,109	1.00	1.27 (1.07, 1.51)	1.37 (1.16, 1.61)	1.58 (1.34, 1.86)	1.69 (1.43, 2.00)	*<0.001*	
Moderate drinker	5,322	1.00	1.24 (1.02, 1.50)	1.43 (1.17, 1.74)	1.40 (1.13, 1.72)	1.74 (1.39, 2.19)	*<0.001*	
Heavy drinker	664	1.00	1.00 (0.55, 1.83)	1.28 (0.71, 2.31)	1.17 (0.64, 2.13)	0.93 (0.48, 1.80)	*0.98*	*0.40*
Physical activity								
No exercise/wk	4,135	1.00	1.22 (0.95, 1.58)	1.37 (1.07, 1.74)	1.27 (0.99, 1.61)	1.55 (1.22, 1.97)	*<0.001*	
Exercises 1-3 times/wk	5,468	1.00	1.22 (1.01, 1.49)	1.22 (1.00, 1.48)	1.72 (1.41, 2.10)	1.77 (1.43, 2.19)	*<0.001*	
Exercises ≥ 4 times/wk	4,492	1.00	1.29 (1.04, 1.60)	1.59 (1.28, 1.98)	1.46 (1.16, 1.83)	1.59 (1.25, 2.02)	*<0.001*	*0.45*
LIS[c,g]								
Age, y								
< 65	8,567	1.00	1.58 (1.38, 1.82)	2.31 (2.05, 2.61)	2.75 (2.42, 3.12)	4.30 (3.79, 4.87)	*<0.001*	
≥ 65	5,528	1.00	1.73 (1.39, 2.16)	1.95 (1.60, 2.38)	2.37 (1.92, 2.91)	3.41 (2.76, 4.20)	*<0.001*	*<0.001*
Sex								
Male	6,325	1.00	1.52 (1.23, 1.87)	1.94 (1.61, 2.33)	2.24 (1.84, 2.73)	3.38 (2.76, 4.14)	*<0.001*	
Female	7,770	1.00	1.63 (1.36, 1.95)	2.67 (2.26, 3.14)	3.19 (2.70, 3.77)	5.07 (4.32, 5.95)	*<0.001*	*<0.001*
Race								
White	9,506	1.00	1.64 (1.40, 1.92)	2.42 (2.09, 2.80)	3.04 (2.60, 3.54)	4.33 (3.71, 5.05)	*<0.001*	
Black	4,589	1.00	1.43 (1.09, 1.86)	2.02 (1.61, 2.54)	2.21 (1.75, 2.79)	3.95 (3.15, 4.95)	*<0.001*	*0.31*
Comorbidity[e]								

No	8,316	1.00	1.60 (1.35, 1.90)	2.51 (2.15, 2.94)	3.11 (2.64, 3.66)	4.89 (4.16, 5.76)	*<0.001*	
Yes	5,779	1.00	1.52 (1.21, 1.91)	1.97 (1.61, 2.40)	2.21 (1.80, 2.71)	3.50 (2.88, 4.26)	*<0.001*	*<0.001*
Non-aspirin NSAID use								
Takes NSAID < twice/wk	11,911	1.00	1.63 (1.40, 1.88)	2.23 (1.95, 2.54)	2.65 (2.31, 3.04)	4.27 (3.73, 4.89)	*<0.001*	
Takes NSAID ≥ twice/wk	2,165	1.00	1.31 (0.89, 1.94)	2.92 (2.10, 4.07)	3.21 (2.29, 4.50)	4.41 (3.17, 6.13)	*<0.001*	*0.01*
Aspirin use								
Takes aspirin < twice/wk	8,027	1.00	1.79 (1.49, 2.14)	2.64 (2.24, 3.12)	3.29 (2.78, 3.90)	5.40 (4.57, 6.38)	*<0.001*	
Takes aspirin ≥ twice/wk	6,066	1.00	1.34 (1.09, 1.65)	1.92 (1.60, 2.30)	2.13 (1.76, 2.59)	3.11 (2.57, 3.75)	*<0.001*	*0.01*

Abbreviations: BMI, body mass index; DIS, dietary inflammation score; hsCRP, high-sensitivity C-reactive protein; NSAID, nonsteroidal anti-inflammatory drug; REGARDS, Reasons for Racial and Geographic Differences in Stroke Study

[a] The outcome was hsCRP concentrations categorized as ≤/> 3 mg/dL; all associations assessed using multivariable logistic regression

[b] For interaction term for categorized DIS/LIS in logistic regression models, calculated using the Wald test

[c] Weights for all dietary and lifestyle components in the DIS and LIS are equal to the maximum likelihood for the β coefficients obtained from multivariable linear regression models (dependent variable: summary inflammation z-score) in the REGARDS case-cohort sample

[d] Covariates in the DIS logistic regression models were: age, sex, race (Black or White), education (less than high school and high school graduate or some college or more), region (Belt, Buckle, Other), comorbidity score (comprises a history of cancer, heart disease, diabetes mellitus, or chronic kidney disease), current hormone replacement therapy use (among women), smoking (current or former and never), body mass index (BMI) (in kg/m^2), alcohol intake (non-drinker, moderate-drinker, or heavy-drinker), physical activity level (exercises 0, 1-3, or ≥ 4 times/wk), total energy intake (kcal/day), season of baseline interview (Spring, Summer, Fall, or Winter), and self-reported regular use of aspirin, other NSAIDs, or lipid lowering medications (≥ twice/wk)

[e] Comorbidities include a history of cancer, heart disease, diabetes mellitus, or chronic kidney disease

[f] Heavy drinker defined as > 7 drinks/wk for women and > 14 drinks/wk drinks for men; moderate drinker defined as 1 – 7 drinks/wk for women, 1 – 14 drinks/wk for men

[g] Covariates in the LIS logistic regression models: age, sex, race (Black or White), education (less than high school and high school graduate or some college or more), region (Belt, Buckle, Other), comorbidity score (comprises a history of cancer, heart disease, diabetes mellitus, or chronic kidney disease), current hormone replacement therapy use (among women), energy intake (kcal/day), season of baseline interview (Spring, Summer, Fall, or Winter), the DIS, and self-reported regular use of aspirin, other NSAIDs, or lipid lowering medications (≥ twice/wk)

Table A2.7. Associations of the DII and EDII with hsCRP plasma concentrations[a] by selected characteristics in the remaining REGARDs cohort (N = 14,210)

Characteristic	*N*	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	*p-trend*	*p-interaction*
DII[b,c]								
Age, y								
< 65	8,567	1.00	1.40 (1.19, 1.65)	1.30 (1.10, 1.54)	1.46 (1.23, 1.74)	1.61 (1.34, 1.95)	*<0.001*	
≥ 65	5,528	1.00	1.24 (1.02, 1.50)	1.35 (1.11, 1.64)	1.39 (1.13, 1.70)	1.50 (1.20, 1.89)	*<0.001*	*0.44*
Sex								
Male	6,325	1.00	1.22 (1.00, 1.49)	1.25 (1.02, 1.54)	1.42 (1.15, 1.76)	1.48 (1.18, 1.86)	*<0.001*	
Female	7,770	1.00	1.40 (1.19, 1.64)	1.34 (1.14, 1.58)	1.41 (1.19, 1.67)	1.61 (1.33, 1.94)	*<0.001*	*0.41*
Race								
White	9,506	1.00	1.27 (1.09, 1.47)	1.24 (1.06, 1.45)	1.42 (1.21, 1.67)	1.61 (1.34, 1.93)	*<0.001*	
Black	4,589	1.00	1.45 (1.16, 1.83)	1.43 (1.14, 1.79)	1.42 (1.13, 1.78)	1.51 (1.18, 1.92)	*0.01*	*0.29*
Has a comorbidity[d]								
No	8,316	1.00	1.34 (1.14, 1.58)	1.30 (1.10, 1.53)	1.48 (1.24, 1.76)	1.52 (1.25, 1.84)	*<0.001*	
Yes	5,779	1.00	1.30 (1.07, 1.58)	1.33 (1.09, 1.61)	1.38 (1.13, 1.69)	1.64 (1.32, 2.04)	*<0.001*	*0.63*
Non-aspirin NSAID use								
Takes NSAID < twice/wk	11,911	1.00	1.34 (1.17, 1.54)	1.35 (1.18, 1.56)	1.46 (1.26, 1.69)	1.60 (1.36, 1.87)	*<0.001*	
Takes NSAID ≥ twice/wk	2,165	1.00	1.24 (0.93, 1.66)	1.11 (0.82, 1.5)	1.22 (0.88, 1.69)	1.40 (0.99, 1.99)	*0.09*	*0.73*
Aspirin use								
Takes aspirin < twice/wk	8,027	1.00	1.32 (1.12, 1.57)	1.29 (1.09, 1.53)	1.47 (1.23, 1.75)	1.59 (1.32, 1.93)	*<0.001*	
Takes aspirin ≥ twice/wk	6,066	1.00	1.33 (1.11, 1.59)	1.33 (1.10, 1.61)	1.36 (1.11, 1.66)	1.51 (1.21, 1.89)	*0.001*	*0.60*
Tobacco use								
Former or non-smoker	12,038	1.00	1.36 (1.19, 1.55)	1.30 (1.13, 1.49)	1.45 (1.26, 1.68)	1.49 (1.28, 1.75)	*<0.001*	
Current smoker	2,057	1.00	1.06 (0.74, 1.54)	1.35 (0.95, 1.91)	1.30 (0.91, 1.85)	1.79 (1.23, 2.60)	*<0.001*	*0.09*
BMI, kg/m^2								
18.5 – 24.99	3,387	1.00	1.34 (0.99, 1.80)	1.78 (1.32, 2.40)	1.54 (1.12, 2.12)	2.14 (1.52, 3.01)	*<0.001*	
25 – 29.99	5,463	1.00	1.26 (1.03, 1.54)	1.24 (1.01, 1.51)	1.39 (1.13, 1.72)	1.57 (1.25, 1.98)	*<0.001*	
≥ 30	5,102	1.00	1.38 (1.14, 1.68)	1.19 (0.98, 1.45)	1.34 (1.09, 1.64)	1.34 (1.07, 1.67)	*0.04*	*<0.001*
Physical activity								
No exercise/wk	4,135	1.00	1.14 (0.89, 1.45)	1.09 (0.86, 1.38)	1.19 (0.94, 1.52)	1.32 (1.02, 1.71)	*0.04*	
Exercises 1-3 times/wk	5,468	1.00	1.40 (1.15, 1.71)	1.47 (1.20, 1.81)	1.64 (1.32, 2.03)	1.64 (1.29, 2.08)	*<0.001*	
Exercises ≥ 4 times/wk	4,492	1.00	1.41 (1.14, 1.74)	1.35 (1.08, 1.69)	1.40 (1.10, 1.78)	1.72 (1.32, 2.24)	*<0.001*	*0.62*
EDII[b,c]								
Age, y								
< 65	8,567	1.00	1.07 (0.91, 1.26)	1.21 (1.03, 1.42)	1.21 (1.03, 1.42)	1.28 (1.09, 1.50)	*<0.001*	
≥ 65	5,528	1.00	1.10 (0.91, 1.33)	1.07 (0.89, 1.30)	1.06 (0.88, 1.29)	1.33 (1.09, 1.62)	*0.02*	*0.28*
Sex								
Male	6,325	1.00	1.23 (1.01, 1.49)	1.12 (0.92, 1.36)	1.14 (0.94, 1.39)	1.34 (1.10, 1.64)	*0.02*	
Female	7,770	1.00	1.01 (0.87, 1.19)	1.18 (1.01, 1.39)	1.17 (1.00, 1.37)	1.29 (1.10, 1.51)	*<0.001*	*0.29*
Race								
White	9,506	1.00	1.07 (0.93, 1.23)	1.16 (1.00, 1.34)	1.14 (0.98, 1.32)	1.37 (1.17, 1.60)	*<0.001*	
Black	4,589	1.00	1.10 (0.85, 1.42)	1.09 (0.86, 1.39)	1.11 (0.88, 1.40)	1.16 (0.92, 1.45)	*0.23*	*0.41*
Has a comorbidity[d]								
No	8,316	1.00	1.06 (0.91, 1.25)	1.18 (1.01, 1.39)	1.24 (1.06, 1.46)	1.28 (1.09, 1.51)	*<0.001*	
Yes	5,779	1.00	1.13 (0.93, 1.37)	1.11 (0.92, 1.35)	1.04 (0.86, 1.26)	1.28 (1.06, 1.55)	*0.03*	*0.80*

Non-aspirin NSAID use								
Takes NSAID < twice/wk	11,911	1.00	1.15 (1.00, 1.31)	1.18 (1.03, 1.35)	1.17 (1.02, 1.34)	1.29 (1.13, 1.48)	*<0.001*	
Takes NSAID ≥ twice/wk	2,165	1.00	0.86 (0.63, 1.16)	1.08 (0.79, 1.46)	1.05 (0.77, 1.43)	1.31 (0.96, 1.78)	*0.05*	*0.22*
Aspirin use								
Takes aspirin < twice/wk	8,027	1.00	1.06 (0.90, 1.25)	1.19 (1.01, 1.40)	1.13 (0.96, 1.33)	1.31 (1.11, 1.54)	*0.001*	
Takes aspirin ≥ twice/wk	6,066	1.00	1.12 (0.93, 1.35)	1.10 (0.91, 1.33)	1.17 (0.97, 1.41)	1.27 (1.05, 1.53)	*0.02*	*0.61*
Tobacco use								
Former or non-smoker	12,038	1.00	1.11 (0.97, 1.27)	1.17 (1.02, 1.34)	1.19 (1.04, 1.36)	1.27 (1.10, 1.45)	*<0.001*	
Current smoker	2,057	1.00	0.99 (0.74, 1.34)	1.11 (0.82, 1.50)	0.99 (0.72, 1.34)	1.49 (1.11, 2.01)	*0.01*	*0.29*
BMI, kg/m^2								
18.5 – 24.99	3,387	1.00	1.18 (0.90, 1.54)	1.33 (1.01, 1.75)	1.36 (1.02, 1.81)	1.64 (1.23, 2.19)	*<0.001*	
25 – 29.99	5,463	1.00	1.08 (0.89, 1.31)	1.14 (0.94, 1.39)	1.22 (1.01, 1.49)	1.20 (0.98, 1.47)	*0.04*	
≥ 30	5,102	1.00	1.01 (0.83, 1.24)	1.03 (0.84, 1.26)	0.96 (0.79, 1.17)	1.19 (0.98, 1.44)	*0.10*	*<0.001*
Physical activity								
No exercise/wk	4,135	1.00	1.15 (0.92, 1.44)	1.20 (0.96, 1.49)	1.13 (0.90, 1.42)	1.28 (1.03, 1.60)	*0.05*	
Exercises 1-3 times/wk	5,468	1.00	0.99 (0.81, 1.21)	1.13 (0.93, 1.38)	1.06 (0.87, 1.29)	1.40 (1.14, 1.72)	*0.002*	
Exercises ≥ 4 times/wk	4,492	1.00	1.16 (0.93, 1.45)	1.14 (0.91, 1.43)	1.30 (1.04, 1.62)	1.20 (0.96, 1.50)	*0.06*	*0.48*

Abbreviations: DII, dietary inflammatory index; EDII, empirical dietary inflammation index; hsCRP, high-sensitivity C-reactive protein; REGARDS, Reasons for Racial and Geographic Differences in Stroke Study

[a] The outcome was hsCRP concentrations categorized as </≥ 3 mg/L; all associations assessed using multivariable logistic regression

[b] The DII and EDII were calculated using weights and components derived from Shivappa, et al (1) and Tabung, et al (2)

[c] Covariates in logistic regression models were as follows: age, sex, race (Black or White), education (less than high school and high school graduate or some college or more), region (Belt, Buckle, Other), comorbidity score (comprises a history of cancer, heart disease, diabetes mellitus, or chronic kidney disease), current hormone replacement therapy use (among women), smoking (current or former and never), body mass index (BMI) (in kg/m^2), physical activity level (exercises 0, 1-3, or ≥ 4 times/wk), total energy intake (kcal/day), season of baseline interview (Spring, Summer, Fall, or Winter), and self-reported regular use of aspirin, other NSAIDs, or lipid lowering medications (≥ twice/wk)

[d] Comorbidities include a history of cancer, heart disease, diabetes, or chronic kidney disease

Table A2.8. Equal weight components of the DIS and LIS, their descriptions, and assigned equal weights

Components	Descriptions	Equal weights[a]
DIS components[b]		
Leafy greens and cruciferous vegetables	Kale, spinach, lettuce (iceberg, head, romaine, or leaf), broccoli, Brussels sprouts, cabbage, cauliflower, parsley, watercress	-1
Tomatoes	Tomatoes, tomato juice, tomato sauce, salsa	-1
Apples and berries	Fresh apples, pears, apple juice or cider, strawberries, blueberries, raspberries, cherries	-1
Deep yellow or orange vegetables and fruit	Cantaloupe, peaches, carrots, dark yellow or orange squash, figs	-1
Other fruits and real fruit juices	Other fresh fruits than those listed above (e.g., pineapples, honeydew, grapes, kiwi, watermelon, lemon, grapefruit, and oranges), orange juice, grapefruit juice, apple juice, grape juice, and other real fruit juice	-1
Other vegetables	Other vegetables than those listed above (e.g., okra, green peppers, onions, zucchini, and eggplant)	-1
Legumes	String beans, peas, lima beans, lentils, and beans (excluding soybeans)	-1
Fish	Tuna fish, salmon, other light and dark meat fish, breaded fish cakes or fish sticks	-1
Poultry	Chicken or turkey with and without skin	-1
Red and organ meats	Hamburger, beef, pork, lamb, liver, gizzards, other organ meats	1
Processed meats	Bacon, beef or pork hotdogs, chicken or turkey hot dogs, salami, bologna, other processed meats	1
Added sugars	Sugar-sweetened soda, punch, lemonade, fruit drinks, chocolate candy bars, other mixed candy bars, candy without chocolate, jams, jellies, preserves, syrup or honey, dried or canned fruit	1
High-fat dairy	Whole milk, 2% milk, cream, high-fat ice cream, high-fat yogurt, cream cheese, other high-fat cheeses	-1
Low-fat dairy	Skim milk, 1% milk, low-fat yogurt, low-fat ice cream, low-fat cottage or ricotta cheese, low-fat cheeses	-1
Coffee and tea	Coffee (decaffeinated and regular), herbal and non-herbal tea	-1
Nuts	Peanut butter, peanuts, other nuts	-1
Fats	Mayonnaise, margarine, butter, vegetable oil	1
Refined grains and starchy vegetables	Cold and cooked breakfast cereal, white or dark bread, bagels, English muffins, rolls, corn bread, white rice, pasta, pancakes, waffles, potatoes (French fried, scalloped, baked, boiled or mashed), sweet potato/yams, potato chips, crackers, tortillas, popcorn, pretzels, cookies, brownies, doughnuts, cake, pie, sweet rolls, coffee cakes, granola bars	1
Supplement score[c]	Ranked score of supplements, including: vitamins A, B_1, B_{12}, B_6, C, D, and E; and β-carotene, folate, niacin, riboflavin, calcium, copper, iron, magnesium, selenium, and zinc	-1
LIS components[d]		
Heavy drinker	Heavy (> 7 drinks/wk for women, > 14 drinks/wk drinks for men) vs. non-drinker	1
Moderate drinker	Moderate (1 – 7 drinks/wk for women, 1 – 14 drinks/wk for men) vs. non-drinker	-1
Moderately physically active[e]	Exercises 1 – 3 times/wk vs. does not exercise	-1
Heavily physically active[e]	Exercises ≥ 4 times/wk vs. does not exercise	-2
Current smoker	Currently smokes tobacco vs. does not currently smoke tobacco	1

Overweight BMI	Overweight BMI vs. normal BMI	1
Obese BMI	Obese BMI vs. normal BMI	2

Abbreviations: BMI, body mass index; DIS, dietary inflammation score; LIS, lifestyle inflammation score

[a] All DIS and LIS components received equal weights; signs (+ or -) assigned *a priori* based on previous literature

[b] Dietary components were standardized to the case-cohort sample, by sex, to a mean of zero and standard deviation of 1

[c] 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)

[d] All lifestyle components were dummy variables, coded as '1' for the non-referent category and '0' for the referent category

[e] When calculating the LIS using lifestyle behavior measurement instruments where 'times physically active per week' cannot be derived, the given variables (e.g., METs/wk) were ranked into quantiles, which were taken to construct dummy variables, and the respective weights were similarly applied

Table A2.9. Associations of the equally weighted DIS and LIS with plasma concentrations of inflammation biomarkers[a] in the REGARDs cohort (N = 14,210), MAP (N = 433), and CECP (N = 173)

	Inflammation Scores[b]			
	DIS-equal weight[c]		LIS-equal weight[d]	
Populations	Adjusted OR (95% CI)	*p-trend*	Adjusted OR (95% CI)	*p-trend*
REGARDS				
Quintiles				
1	1.00		1.00	
2	1.19 (1.05, 1.35)		1.51 (1.31, 1.74)	
3	1.41 (1.25, 1.60)		2.09 (1.83, 2.38)	
4	1.57 (1.38, 1.78)		3.05 (2.66, 3.49)	
5	1.65 (1.45, 1.88)	*<0.001*	3.96 (3.41, 4.61)	*<0.001*
MAP				
Quartiles				
1	1.00		1.00	
2	1.52 (0.81, 2.85)		1.79 (1.02,3.14)	
3	2.01 (1.05, 3.82)		2.48 (1.40,4.38)	
4	1.71 (0.87, 3.33)	*0.14*	3.46 (1.79,6.72)	*<0.001*
CECP				
Quantiles				
1	1.00		1.00	
2	1.89 (0.95, 3.79)	*NA*	1.85 (0.96, 3.59)	*NA*

Abbreviations: CECP, Calcium and Colorectal Epithelial Cell Proliferation trial; CI, confidence interval; DIS, dietary inflammation score; hsCRP, high-sensitivity C-reactive protein; MAP (pooled MAP I and II), Markers of Adenomatous Polyps; OR, odds ratio; REGARDS, Reasons for Racial and Geographic Differences in Stroke

[a] In the REGARDS and pooled MAP studies, the outcome was hsCRP concentrations categorized as </≥ 3 mg/dL, and in the CECP trial, the outcome was the inflammation biomarker score (comprising IL-1β, IL-6, IL-8, IL-12p40, TNF-α, VEGF, and IL-10 [the latter with a negative sign]) dichotomized as </≥ 0 (based on the study population median); all associations assessed using multivariable logistic regression

[b] All DIS and LIS components received *a priori* equal weights

[c] For each study, covariates in the DIS-equal weight logistic regression models were:

REGARDS: age, sex, race (Black or White), education (less than high school and high school graduate or some college or more), region (Belt, Buckle, Other), comorbidity score (comprises a history of cancer, heart disease, diabetes mellitus, or chronic kidney disease), current hormone replacement therapy use (among women), smoking (current or former and never), body mass index (BMI; kg/m^2), alcohol intake (non-drinker, moderate-drinker, or heavy-drinker), physical activity level (exercises 0, 1-3, or ≥ 4 times/wk), total energy intake (kcal/day), season of baseline interview (Spring, Summer, Fall, or Winter), and regular use of aspirin, other NSAIDs, or lipid lowering medications (≥ twice/wk)

MAP: age, sex, education (less than high school and high school graduate or some college or more), current hormone replacement use (among women), smoking (current or former and never), BMI category (based on WHO BMI classifications), alcohol intake (non-drinker, moderate-drinker, or heavy-drinker), physical activity level (tertiles based on the distribution of weekly metabolic equivalents of task–min/wk expenditure in the study population), total energy intake (kcal/day), study (MAP I or MAP II), and regular aspirin or other NSAID use (≥ once/wk)

CECP: age, sex, a comorbidity score (comprising diabetes mellitus or heart disease), smoking (current or former and never), BMI (kg/m^2), alcohol intake (non-drinker, moderate-drinker, or heavy-drinker), physical activity level (tertiles based on the distribution of weekly minutes of physical activity in the study population), and total energy intake (kcal/day), and regular aspirin or other NSAID use (≥ once/wk)

[d] For each study, covariates in the LIS-equal weight logistic regression models were:

REGARDS: age, sex, race (Black or White), education (less than high school and high school graduate or some college or more), region (Belt, Buckle, Other), comorbidity score (comprises a history of cancer, heart disease, diabetes mellitus, or chronic kidney disease), current hormone replacement therapy use (among women), energy intake (kcal/day), season of baseline interview (Spring, Summer, Fall, or Winter), the DIS, and regular use of aspirin, other NSAIDs, or lipid lowering medications (≥ twice/wk)

MAP: age, sex, education (less than high school and high school graduate or some college or more), current hormone replacement use (among women), total energy intake (kcal/day), study (MAP I or MAP II), the DIS, and regular aspirin or other NSAID use (≥ once/wk)

CECP: age, sex, a comorbidity score (comprising diabetes mellitus or heart disease), total energy intake (kcal/day), the DIS, and regular aspirin or other NSAID use (≥ once/wk)

Table A2.10. Geometric mean inflammation marker plasma concentrations[a] and relative differences across quantiles of dietary and lifestyle inflammation scores in the REGARDs cohort (N = 14,210), MAP (N = 433), and CECP (N = 173) study

	Inflammation Scores[b]											
	DIS[c]		DIS - equal weight[c]		LIS [d]		LIS - equal weight[d]		DII[e]		EDII[e]	
	Adjusted mean (95% CI)	% diff.	Adjusted mean (95% CI)	% diff.	Adjusted mean (95% CI)	% diff.	Adjusted mean (95% CI)	% diff.	Adjusted mean (95% CI)	% diff.	Adjusted mean (95% CI)	% diff.
REGARDS												
Quintiles												
1	1.8 (1.8, 1.9)	ref	1.8 (1.7, 1.9)	ref	1.2 (1.2, 1.3)	ref	1.2 (1.2, 1.3)	ref	1.9 (1.8, 2.0)	ref	2.0 (1.9, 2.1)	ref
2	2.0 (1.9, 2.1)	11.1	2.0 (1.9, 2.1)	11.1	1.6 (1.5, 1.6)	33.3	1.6 (1.5, 1.7)	33.3	2.1 (2.0, 2.2)	10.5	2.2 (2.1, 2.2)	10.0
3	2.1 (2.0, 2.2)	16.7	2.2 (2.1, 2.3)	22.2	2.0 (1.9, 2.0)	66.7	1.9 (1.9, 2.0)	58.3	2.2 (2.1, 2.2)	15.8	2.2 (2.1, 2.3)	10.0
4	2.2 (2.1, 2.3)	22.2	2.2 (2.1, 2.3)	22.2	2.2 (2.1, 2.3)	83.3	2.4 (2.3, 2.4)	100	2.3 (2.2, 2.3)	21.1	2.2 (2.1, 2.3)	10.0
5	2.3 (2.2, 2.4)	27.8	2.3 (2.2, 2.4)	27.8	2.7 (2.6, 2.8)	125	2.7 (2.6, 2.8)	125	2.4 (2.3, 2.5)	26.3	2.3 (2.2, 2.4)	15.0
P-trend	*<0.001*		*<0.001*		*<0.001*		*<0.001*		*<0.001*		*<0.001*	
MAP												
Quartiles												
1	1.9 (1.5, 2.4)	ref	2.0 (1.6, 2.4)	ref	1.4 (1.2, 1.7)	ref	1.7 (1.4, 2.0)	ref	2.2 (1.8, 2.7)	ref	2.2 (1.8, 2.7)	ref
2	2.3 (1.8, 2.8)	21.1	2.2 (1.8, 2.7)	10.0	2.0 (1.7, 2.4)	42.9	2.2 (1.8, 2.6)	29.4	2.1 (1.8, 2.6)	-4.5	2.4 (2.0, 2.9)	9.1
3	2.3 (1.9, 2.8)	21.1	2.4 (1.9, 2.9)	20.0	2.3 (1.9, 2.8)	64.3	2.2 (1.9, 2.7)	29.4	2.5 (2.0, 2.9)	13.6	2.3 (1.9, 2.7)	4.5
4	2.5 (2.0, 3.1)	31.6	2.4 (2.0, 3.0)	20.0	3.2 (2.6, 3.8)	129	2.9 (2.3, 3.6)	70.6	2.6 (2.2, 3.2)	18.2	2.6 (2.1, 3.1)	18.2
P-trend	0.02		0.05		<0.001		<0.001		0.10		0.35	
CECP												
Quantiles												
1	-0.3 (-1.6, 1.1)	ref	-0.3 (-1.4, 0.9)	ref	0.5 (0.2, 1.2)	ref	0.6 (0.3, 1.2)	ref	-0.1 (-1.3, 1.1)	ref	-0.3 (-1.5, 0.8)	ref
2	0.3 (-1.0, 1.5)	215	0.3 (-0.8, 1.4)	210	2.5 (1.1, 5.6)	400	3.0 (1.2, 7.4)	400	-0.1 (-1.2, 0.9)	0.0	0.0 (-1.0, 1.0)	108

Abbreviations: CECP, Calcium and Colorectal Epithelial Cell Proliferation trial; CI, confidence interval; diff, difference; DII, dietary inflammatory index; DIS, dietary inflammation score; EDII, empirical dietary inflammation index; hsCRP, high-sensitivity C-reactive protein; MAP, Markers of Adenomatous Polyps; OR, odds ratio REGARDS, Reasons for Racial and Geographic Differences in Stroke Study

[a] In the REGARDS and MAP, the outcome was adjusted geometric mean hsCRP concentrations, and in CECP, the outcome was the inflammation biomarker score (comprising IL-1β, IL-6, IL-8, IL-12p40, TNF-α, VEGF, and IL-10 [the latter with a negative sign]); all associations assessed using multivariable general linear regression

[b] Weights for all dietary and lifestyle components in the DIS and LIS are equal to the maximum likelihood for the β coefficients obtained from multivariable linear regression models (dependent variable: summary inflammation biomarker z-score) in the REGARDS case-cohort sample; DIS-equal weight and LIS-equal weight: all DIS and LIS components received *a priori* equal weights; DII and EDII: weights and components derived from Shivappa, *et al* (1) and Tabung, *et al*(111), respectively

[c] For each study, covariates in the DIS and DIS-equal weight linear regression models were:

REGARDS: age, sex, race (Black or White), education (less than high school and high school graduate or some college or more), region (Belt, Buckle, Other), comorbidity score (comprises a history of cancer, heart disease, diabetes mellitus, or chronic kidney disease), current hormone replacement therapy use (among women), smoking (current or former and never), body mass index (BMI; kg/m^2), alcohol intake (non-drinker, moderate-drinker, or heavy-drinker), physical activity level (exercises 0, 1-3, or ≥ 4 times/wk), total energy intake (kcal/day), season of baseline interview (Spring, Summer, Fall, or Winter), and regular use of aspirin, other NSAIDs, or lipid lowering medications (≥ twice/wk)

MAP: age, sex, education (less than high school and high school graduate or some college or more), current hormone replacement use (among women), smoking (current or former and never), BMI category (based on WHO BMI classifications), alcohol intake (non-drinker, moderate-drinker, or heavy-drinker), physical activity level (tertiles based on the distribution of weekly metabolic equivalents of task–min/wk expenditure in the study population), total energy intake (kcal/day), study (MAP I or MAP II), and regular aspirin or other NSAID use (≥ once/wk)

CECP: age, sex, a comorbidity score (comprising diabetes mellitus or heart disease), smoking (current or former and never), BMI (kg/m^2), alcohol intake (non-drinker, moderate-drinker, or heavy-drinker), physical activity level (tertiles based on the distribution of weekly minutes of physical activity in the study population), and total energy intake (kcal/day), and regular aspirin or other NSAID use (≥ once/wk)

[d] For each study, covariates in the LIS and LIS-equal weight linear regression models were:

REGARDS: age, sex, race (Black or White), education (less than high school and high school graduate or some college or more), region (Belt, Buckle, Other), comorbidity score (comprises a history of cancer, heart disease, diabetes mellitus, or chronic kidney disease), current hormone replacement therapy use (among women), energy intake (kcal/day), season of baseline interview (Spring, Summer, Fall, or Winter), the DIS, and regular use of aspirin, other NSAIDs, or lipid lowering medications (≥ twice/wk)

MAP: age, sex, education (less than high school and high school graduate or some college or more), current hormone replacement use (among women), total energy intake (kcal/day), study (MAP I or MAP II), the DIS, and regular aspirin or other NSAID use (≥ once/wk)

CECP: age, sex, a comorbidity score (comprising diabetes mellitus or heart disease), total energy intake (kcal/day), the DIS, and regular aspirin or other NSAID use (≥ once/wk)

[e] For each study, covariates in DII and EDII linear regression models included those listed in footnote 'c', except for alcohol intake

Table A2.11. Conventional and MCM/bootstrap-technique associations of DIS and LIS with plasma concentrations of inflammation biomarkers[a] in REGARDs cohort (N = 14,210), MAP (N = 433), and the CECP trial (N = 173)

	Conventional Results[b]		**MCM/Bootstrapped Results[d]**
	Adjusted OR (95% CI)	*p-trend*[c]	Adjusted OR (95% CI)[e]
REGARDS			
Quintiles of DIS[f]			
1	1.00		1.00
2	1.25 (1.10, 1.41)		1.18 (1.00, 1.38)
3	1.38 (1.22, 1.56)		1.27 (1.09, 1.54)
4	1.50 (1.32, 1.70)		1.38 (1.19, 1.57)
5	1.66 (1.46, 1.90)	<0.001	1.50 (1.23, 1.71)
Quintiles of LIS[g]			
1	1.00		1.00
2	1.58 (1.38, 1.82)		1.78 (1.25, 2.36)
3	2.31 (2.05, 2.61)		2.30 (1.75, 3.09)
4	2.74 (2.42, 3.12)		3.20 (2.34, 4.16)
5	4.29 (3.79, 4.87)	<0.001	4.26 (3.26, 5.32)
MAP			
Quartiles of DIS[f]			
1	1.00		1.00
2	1.66 (0.89, 3.12)		1.57 (0.79, 3.24)
3	1.33 (0.70, 2.53)		1.62 (0.80, 3.63)
4	1.94 (1.00, 3.79)	0.12	1.58 (0.76, 3.58)
Quartiles of LIS[g]			
1	1.00		1.00
2	2.39 (1.28, 4.46)		3.08 (1.41, 6.16)
3	2.53 (1.35, 4.72)		3.40 (1.73, 7.04)
4	7.24 (3.70, 14.17)	<0.001	7.38 (3.36, 15.64)
CECP			
Quantiles of DIS[f]			
1	1.00		1.00
2	1.42 (0.71, 2.82)	0.91	1.45 (0.58, 3.88)
Quantiles of LIS[g]			
1	1.00		1.00
2	1.56 (0.82, 2.97)	0.09	1.75 (0.88, 3.63)

Abbreviations: CECP, Calcium and Colorectal Epithelial Cell Proliferation trial; CI, confidence interval; DIS, dietary inflammation score; hsCRP, high-sensitivity C-reactive protein; LIS, lifestyle inflammation score; MAPs, Markers of Adenomatous Polyps; MCM, Monte Carlo Methods; OR, odds ratio; REGARDS, Reasons for Racial and Geographic Differences in Stroke Study

[a] In the REGARDS and MAPs studies, the outcome was hsCRP concentrations categorized as </≥ 3 mg/dL, and in the CECP trial, the outcome was the inflammation biomarker score (comprising IL-1β, IL-6, IL-8, IL-12p40, TNF-α, VEGF, and IL-10 [the latter with a negative sign]) dichotomized as </≥ 0 (based on the study population median); all associations assessed using multivariable logistic regression

[b] Weights for all dietary and lifestyle components in the conventional DIS and LIS are equal to the maximum likelihood for the β coefficients obtained from multivariable linear regression models (dependent variable: summary inflammation biomarker z-score) in the REGARDS case-cohort sample

[c] Calculated by entering sex- and study-specific median of each DIS and LIS quantile assigned to each participant into multivariable logistic regression models

[d] Weights for all dietary and lifestyle components in the DIS and LIS are equal to the maximum likelihood for the β coefficients obtained from multivariable linear regression models (dependent variable: summary inflammation z-score), plus a randomly sampled standard normal deviate, over ~ 1,000,000/N iterations, multiplied by the standard error matrix obtained from the regression models in the REGARDS case-cohort sample. Each population (REGARDS, MAP, and CECP) was subsequently bootstrapped so that the confidence intervals contain all random error from the DIS/LIS weights and the odds ratio estimate

[e] The lower confidence limit, odd ratio estimate, and upper confidence limits are the 2.5, 50, and 97.5 percentiles over all iterations of the MCM/bootstrap DIS and LIS

[f] For each study, covariates in the DIS logistic regression models were:

REGARDS: age, sex, race (Black or White), education (less than high school and high school graduate or some college or more), region (Belt, Buckle, Other), comorbidity score (comprises a history of cancer, heart disease, diabetes mellitus, or chronic kidney disease), current hormone replacement therapy use (among women), smoking (current or former and never), body mass index (BMI; kg/m^2), alcohol intake (non-drinker, moderate-drinker, or heavy-drinker), physical activity level (exercises 0, 1-3, or ≥ 4 times/wk), total energy intake (kcal/day), season of baseline interview (Spring, Summer, Fall, or Winter), and regular use of aspirin, other NSAIDs, or lipid lowering medications (≥ twice/wk)

MAP: age, sex, education (less than high school and high school graduate or some college or more), current hormone replacement use (among women), smoking (current or former and never), BMI category (based on WHO BMI classifications), alcohol intake (non-drinker, moderate-drinker, or heavy-drinker), physical activity level (tertiles based on the distribution of weekly metabolic equivalents of task–min/wk expenditure in the study population), total energy intake (kcal/day), study (MAP I or MAP II), and regular aspirin or other NSAID use (≥ once/wk)

CECP: age, sex, a comorbidity score (comprising diabetes mellitus or heart disease), regular aspirin or other NSAID use (≥ once/wk), smoking (current or former and never), BMI (kg/m^2), alcohol intake (non-drinker, moderate-drinker, or heavy-drinker), physical activity level (tertiles based on the distribution of weekly minutes of physical activity in the study population), and total energy intake (kcal/day), and regular aspirin or other NSAID use (≥ once/wk)

[g] For each study, covariates in the LIS logistic regression models were:

REGARDS: age, sex, race (Black or White), education (less than high school and high school graduate or some college or more), region (Belt, Buckle, Other), comorbidity score (comprises a history of cancer, heart disease, diabetes mellitus, or chronic kidney disease), current hormone replacement therapy use (among women), energy intake (kcal/day), season of baseline interview (Spring, Summer, Fall, or Winter), the DIS, and regular use of aspirin, other NSAIDs, or lipid lowering medications (≥ twice/wk)

MAP: age, sex, education (less than high school and high school graduate or some college or more), current hormone replacement use (among women), total energy intake (kcal/day), study (MAP I or MAP II), the DIS, and regular aspirin or other NSAID use (≥ once/wk)

CECP: age, sex, a comorbidity score (comprising diabetes mellitus or heart disease), total energy intake (kcal/day), the DIS, and regular aspirin or other NSAID use (≥ once/wk)

Table A2.12. Joint/combined associations of the MCM/bootstrap technique DIS and LIS with plasma hsCRP concentrations[a] in the REGARDS cohort (N = 14,210)

	LIS quintiles[b,c]									
	1		**2**		**3**		**4**		**5**	
DIS quintiles[b,c]	*n*	OR (95% CI)	*n*	OR (95% CI)	*n*	OR (95% CI)	*n*	OR (95% CI)	*n*	OR (95% CI)
1	938	1.00 (ref)	461	1.73 (1.08, 2.29)	649	2.23 (1.55, 2.83)	410	3.16 (2.13, 4.16)	385	4.13 (2.99, 5.27)
2	782	1.18 (1.00, 1.39)	464	2.01 (1.23, 2.84)	680	2.63 (1.80, 3.50)	465	3.71 (2.42, 5.16)	451	4.86 (3.37, 6.39)
3	573	1.32 (1.11, 1.57)	469	2.25 (1.37, 3.17)	664	2.93 (2.03, 3.99)	512	4.12 (2.74, 5.78)	624	5.43 (3.75, 7.22)
4	497	1.43 (1.18, 1.70)	423	2.42 (1.49, 3.53)	653	3.19 (2.13, 4.34)	572	4.47 (2.94, 6.23)	697	5.88 (4.09, 7.91)
5	359	1.55 (1.25, 1.88)	409	2.62 (1.58, 3.84)	617	3.41 (2.28, 4.74)	623	4.83 (3.18, 6.90)	833	6.32 (4.30, 8.62)

Abbreviations: CI, confidence interval; DIS, dietary inflammation score; hsCRP, high-sensitivity C-reactive protein; MCM, Monte Carlo Methods; OR, odds ratio; REGARDS, Reasons for Racial and Geographic Differences in Stroke study

[a] The outcome was hsCRP concentrations categorized as ≤/> 3 mg/dL; all associations assessed using multivariable logistic regression

[b] Weights for all dietary and lifestyle components in the DIS and LIS are equal to the maximum likelihood for the β coefficients obtained from multivariable linear regression models (dependent variable: summary inflammation z-score), plus a randomly sampled standard normal deviate, over ~ 1,000,000/N iterations, multiplied by the standard error matrix obtained from the regression models in the REGARDS case-cohort sample. Each population (REGARDS, MAP, and CECP) was subsequently bootstrapped so that the confidence intervals contain all random error from the DIS/LIS weights and the odds ratio estimate. The lower confidence limit, odd ratio estimate, and upper confidence limits are the 2.5, 50, and 97.5 percentiles over all iterations of the MCM/bootstrap DIS and LIS.

[c] Covariates in logistic regression model: age, sex, race (Black or White), education (less than high school and high school graduate or some college or more), region (Belt, Buckle, Other), comorbidity score (comprises a history of cancer, heart disease, diabetes mellitus, or chronic kidney disease), current hormone replacement therapy use (among women), energy intake (kcal/day), season of baseline interview (Spring, Summer, Fall, or Winter), and self-reported regular use of aspirin, other NSAIDs, or lipid lowering medications (≥ twice/wk)

Table A2.13. Associations of the MCM/bootstrap technique DIS and LIS with hsCRP plasma concentrations[a] by selected characteristics in REGARDS cohort (N = 14,210)

Characteristic	*n*	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
DIS[b,c]						
Age, y						
< 65	8,567	1.00	1.17 (0.94, 1.49)	1.34 (1.07, 1.63)	1.44 (1.15, 1.81)	1.53 (1.22, 1.93)
≥ 65	5,528	1.00	1.14 (0.88, 1.48)	1.23 (0.96, 1.60)	1.31 (1.00, 1.67)	1.44 (1.12, 1.88)
Sex						
Male	6,325	1.00	1.16 (0.94, 1.40)	1.21 (0.95, 1.50)	1.36 (1.03, 1.59)	1.50 (1.20, 1.88)
Female	7,770	1.00	1.19 (0.98, 1.44)	1.32 (1.09, 1.57)	1.41 (1.14, 1.67)	1.48 (1.15, 1.79)
Race						
White	9,506	1.00	1.21 (1.01, 1.42)	1.31 (1.09, 1.56)	1.39 (1.11, 1.65)	1.52 (1.19, 1.83)
Black	4,589	1.00	1.10 (0.80, 1.53)	1.22 (0.83, 1.70)	1.31 (1.02, 1.83)	1.43 (0.93, 1.82)
Has a comorbidity[d]						
No	8,316	1.00	1.14 (0.91, 1.38)	1.22 (1.03, 1.51)	1.31 (1.14, 1.60)	1.44 (1.21, 1.83)
Yes	5,779	1.00	1.21 (0.97, 1.72)	1.33 (1.02, 1.80)	1.46 (1.17, 1.86)	1.48 (1.19, 2.01)
Non-aspirin NSAID use						
Takes NSAID < twice/wk	11,911	1.00	1.17 (1.01, 1.41)	1.29 (1.07, 1.53)	1.39 (1.21, 1.59)	1.50 (1.21, 1.76)
Takes NSAID ≥ twice/wk	2,165	1.00	1.15 (0.75, 1.63)	1.20 (0.84, 1.82)	1.29 (0.85, 2.15)	1.36 (0.94, 2.17)
Aspirin use						
Takes aspirin < twice/wk	8,027	1.00	1.22 (1.00, 1.47)	1.33 (1.07, 1.71)	1.47 (1.22, 1.67)	1.53 (1.22, 1.82)
Takes aspirin ≥ twice/wk	6,066	1.00	1.10 (0.90, 1.50)	1.20 (0.92, 1.61)	1.26 (1.03, 1.56)	1.47 (1.16, 2.05)
Tobacco use						
Former or non-smoker	12,038	1.00	1.18 (0.97, 1.38)	1.28 (1.09, 1.57)	1.38 (1.15, 1.60)	1.46 (1.19, 1.71)
Current smoker	2,057	1.00	1.22 (0.67, 1.82)	1.27 (0.81, 2.00)	1.46 (0.91, 2.49)	1.66 (1.00, 2.62)
BMI, kg/m^2						
18.5 – 24.99	3,387	1.00	1.21 (0.86, 1.85)	1.39 (0.88, 2.09)	1.59 (0.88, 2.29)	1.64 (1.18, 2.48)
25 – 29.99	5,463	1.00	1.13 (0.89, 1.47)	1.26 (0.89, 1.65)	1.36 (1.08, 1.76)	1.49 (1.10, 2.13)
≥ 30	5,102	1.00	1.14 (0.89, 1.46)	1.21 (0.95, 1.58)	1.25 (0.98, 1.48)	1.31 (1.08, 1.71)
Alcohol use[e]						
Non-drinker	8,109	1.00	1.18 (0.95, 1.50)	1.29 (1.04, 1.61)	1.38 (1.18, 1.67)	1.52 (1.27, 1.82)
Moderate drinker	5,322	1.00	1.14 (0.95, 1.57)	1.25 (0.98, 1.58)	1.38 (1.04, 1.74)	1.47 (1.14, 1.99)
Heavy drinker	664	1.00	1.13 (0.49, 2.06)	1.08 (0.42, 2.93)	1.09 (0.47, 2.69)	1.14 (0.35, 3.33)
Physical activity						
No exercise/wk	4,135	1.00	1.19 (0.87, 1.89)	1.22 (0.91, 1.99)	1.31 (0.89, 1.70)	1.43 (1.12, 1.96)
Exercises 1-3 times/wk	5,468	1.00	1.12 (0.89, 1.48)	1.23 (0.97, 1.56)	1.42 (1.04, 1.80)	1.60 (1.16, 2.06)

Exercises ≥ 4 times/wk	4,492	1.00	1.17 (0.89, 1.54)	1.34 (1.06, 1.81)	1.38 (0.96, 1.83)	1.44 (1.09, 1.85)
LIS[b,f]						
Age, y						
< 65	8,567	1.00	1.75 (1.10, 2.46)	2.53 (1.70, 3.41)	3.59 (2.41, 4.90)	4.73 (3.36, 6.35)
≥ 65	5,528	1.00	1.68 (0.93, 2.31)	1.90 (1.28, 2.46)	2.61 (1.70, 3.53)	3.29 (2.28, 4.60)
Sex						
Male	6,325	1.00	1.60 (1.17, 2.01)	1.86 (1.41, 2.39)	2.56 (1.76, 3.28)	3.34 (2.40, 4.38)
Female	7,770	1.00	1.92 (1.20, 2.78)	2.64 (1.89, 3.74)	3.71 (2.70, 5.06)	4.96 (3.71, 6.27)
Comorbidity[d]						
No	8,316	1.00	1.88 (1.28, 2.54)	2.49 (1.85, 3.50)	3.56 (2.48, 4.66)	4.85 (3.75, 6.21)
Yes	5,779	1.00	1.56 (1.07, 2.22)	1.95 (1.42, 2.64)	2.62 (1.85, 3.61)	3.39 (2.51, 4.43)
Race						
White	9,506	1.00	1.84 (1.18, 2.54)	2.47 (1.84, 3.44)	3.39 (2.48, 4.49)	4.29 (3.40, 5.17)
Black	4,589	1.00	1.56 (0.84, 2.61)	1.95 (1.33, 2.80)	2.72 (1.63, 4.20)	3.90 (2.57, 6.03)
Non-aspirin NSAID use						
Takes NSAID < twice/wk	11,911	1.00	1.78 (1.18, 2.47)	2.22 (1.70, 3.06)	3.16 (2.21, 4.02)	4.18 (3.17, 5.22)
Takes NSAID ≥ twice/wk	2,165	1.00	1.68 (1.03, 2.86)	2.57 (1.67, 3.88)	3.39 (2.25, 5.21)	4.37 (2.88, 6.40)
Aspirin use						
Takes aspirin < twice/wk	8,027	1.00	1.99 (1.28, 2.75)	2.62 (1.85, 3.55)	3.80 (2.55, 5.21)	5.28 (3.91, 6.91)
Takes aspirin ≥ twice/wk	6,066	1.00	1.49 (1.11, 2.13)	1.82 (1.44, 2.41)	2.44 (1.87, 2.98)	3.08 (2.41, 3.94)

Abbreviations: BMI, body mass index; CI, confidence interval; DIS, dietary inflammation score; hsCRP, high-sensitivity C-reactive protein; MCM, Monte Carlo Methods; OR, odds ratio; NSAID, nonsteroidal anti-inflammatory drug; REGARDS, Reasons for Racial and Geographic Differences in Stroke Study

[a] The outcome was hsCRP concentrations categorized as ≤/> 3 mg/dL; all associations assessed using multivariable logistic regression

[b] Weights for all dietary and lifestyle components in the DIS and LIS are equal to the maximum likelihood for the β coefficients obtained from multivariable linear regression models (dependent variable: summary z-score), plus a randomly sampled standard normal deviate, over ~ 1,000,000/N iterations, multiplied by the standard error matrix obtained from the regression models in the REGARDS case-cohort sample. Each population (REGARDS, MAP, and CECP) was subsequently bootstrapped so that the confidence intervals contain all random error from the DIS/LIS weights and the odds ratio estimate. The lower confidence limit, odd ratio estimate, and upper confidence limits are the 2.5, 50, and 97.5 percentiles over all iterations of the MCM/bootstrap DIS and LIS.

[c] Covariates in the DIS logistic regression models were: age, sex, race (Black or White), education (less than high school and high school graduate or some college or more), region (Belt, Buckle, Other), comorbidity score (comprises a history of cancer, heart disease, diabetes mellitus, or chronic kidney disease), current hormone replacement therapy use (among women), smoking (current or former and never), body mass index (BMI) (in kg/m^2), alcohol intake (non-drinker, moderate-drinker, or heavy-drinker), physical activity level (exercises 0, 1-3, or ≥ 4 times/wk), total energy intake (kcal/day), season of baseline interview (Spring, Summer, Fall, or Winter), and self-reported regular use of aspirin, other NSAIDs, or lipid lowering medications (≥ twice/wk)

[d] Comorbidities include a history of cancer, heart disease, diabetes mellitus, or chronic kidney disease

[e] Heavy drinker defined as > 7 drinks/wk for women and > 14 drinks/wk drinks for men; moderate drinker defined as 1 – 7 drinks/wk for women, 1 – 14 drinks/wk for men

[f] Covariates in the LIS logistic regression models: age, sex, race (Black or White), education (less than high school and high school graduate or some college or more), region (Belt, Buckle, Other), comorbidity score (comprises a history of cancer, heart disease, diabetes mellitus, or chronic kidney disease), current

hormone replacement therapy use (among women), energy intake (kcal/day), season of baseline interview (Spring, Summer, Fall, or Winter), the DIS, and self-reported regular use of aspirin, other NSAIDs, or lipid lowering medications (≥ twice/wk)

Appendix 3. Chapter 3 Supplemental Tables

Table A3.1. Components of the dietary (DIS) and lifestyle (LIS) inflammation scores, their general descriptions, rationales for inclusion, and assigned weights

Components	General descriptions	Rationales for inclusion	Weights[a]
DIS components			
Added sugars	Sugar-sweetened soda, punch, lemonade, fruit drinks, chocolate candy bars, other mixed candy bars, candy without chocolate, jams, jellies, preserves, syrup or honey, dried or canned fruit	Induce postprandial hyperglycemia, which act as stressful stimuli through subsequent repeated mild postprandial hypoglycemia[94] and reduce nitric oxide availability (play role in regulation of inflammatory response[95]); elevate pro-inflammatory free fatty acid levels[88]; produce oxidative stress through oxidation of membrane lipids, proteins, lipoproteins, and DNA[96]	0.56
Apples and berries	Fresh apples, pears, apple juice or cider, strawberries, blueberries, raspberries, cherries	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[70–72]	-0.65
Coffee and tea	Coffee (decaffeinated and regular), herbal and non-herbal tea	Tea contains flavonoids and antioxidants (e.g., epicatechin and quercetin)[100]; 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[82,101]	-0.25
Deep yellow or orange vegetables and fruit	Cantaloupe, peaches, carrots, dark yellow or orange squash, figs	Contain pro-vitamin A carotenoids (e.g., β-carotene and α-carotene), which have a conjugated double-bond structure making them strong antioxidants[73]	-0.57
Fats	Mayonnaise, margarine, butter, vegetable oil	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[84–86]; contain saturated fats that mimic lipopolysaccharide (LPS), a pro-inflammatory stimulant, in the gut; increase cytotoxic, pro-oxidant, and pro-inflammatory bile acids in the colon[84,87]	0.31
Fish	Tuna fish, salmon, other light and dark meat fish, breaded fish cakes or fish sticks	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 [88–90]	-0.08

High-fat dairy	Whole milk, 2% milk, cream, high-fat ice cream, high-fat yogurt, cream cheese, other high-fat cheeses	Contain 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 conjugated linoleic acids (CLA), *cis*- and *trans*-palmitoleic acid, butyric acid, phytanic acid, and alpha-linolenic acid[97–99]	-0.14
Leafy greens and cruciferous vegetables	Kale, spinach, lettuce (iceberg, head, romaine, or leaf), broccoli, Brussels sprouts, cabbage, cauliflower, parsley, watercress	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, Nuclear factor-erythroid 2 (NF-E2)-related factor 2 (Nrf2), which plays a key role in cellular protection against oxidative stress and inflammation[55–65]	-0.14
Legumes	String beans, peas, lima beans, lentils, and beans (excluding soybeans)	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[58,82,83]	-0.04
Low-fat dairy	Skim milk, 1% milk, low-fat yogurt, low-fat ice cream, low-fat cottage or ricotta cheese, low-fat cheeses	Similar mechanisms to high-fat dairy (see mechanisms above), with lower fat content	-0.12
Nuts	Peanut butter, peanuts, other nuts	Contain Ω -3 fatty acids[88,89,102,103] (mechanisms similar to those described above in 'Fish') and contain *l*-arginine, which improves endothelium-dependent dilation (precursor of the endogenous vasodilator nitric oxide) and decreases platelet aggregation and monocyte adhesion[58]	-0.44
Other fruits and real fruit juices	Other fresh fruits than those listed above (e.g., pineapples, honeydew, grapes, kiwi, watermelon, lemon, grapefruit, and oranges), orange juice, grapefruit juice, apple juice, grape juice, and other real fruit juice	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[59,74–81]	-0.16
Other vegetables	Other vegetables than those listed above (e.g., okra, green peppers, onions, zucchini, and eggplant)	Contain antioxidants and polyphenols with similar mechanisms to those described above	-0.16
Poultry	Chicken or turkey with and without skin	Inversely associated with inflammation markers[91], contain low amounts of saturated fat[92], and contain *l*-arginine (see mechanisms in 'Nuts')	-0.45

Processed meats	Bacon, beef or pork hotdogs, chicken or turkey hot dogs, salami, bologna, other processed meats	Contain heme iron, which increases the bioavailability of iron, which in turn increases oxidative stress; contain higher saturated fat contents, Ω-6 fatty acids (see 'Fats'), and additives, such as nitrites, with suspected pro-inflammatory properties[91,93]	0.68
Red and organ meats	Hamburger, beef, pork, lamb, liver, gizzards, other organ meats	Contain heme iron (see above); contain Ω-6 fatty acids and saturated fat (see mechanisms in 'Fats' above)	0.02
Refined grains and starchy vegetables	Cold and cooked breakfast cereal, white or dark bread, bagels, English muffins, rolls, corn bread, white rice, pasta, pancakes, waffles, potatoes (French fried, scalloped, baked, boiled or mashed), sweet potato/yams, potato chips, crackers, tortillas, popcorn, pretzels, cookies, brownies, doughnuts, cake, pie, sweet rolls, coffee cakes, granola bars	Sparse in nutrients; some processed grains contain emulsifiers, which potentially break down mucin in the gut leading to inflammation[104]; and induce hyperglycemia (mechanisms described similar to those described above in 'Added Sugars')	0.72
Tomatoes	Tomatoes, tomato juice, tomato sauce, salsa	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[66–69]	-0.78
Supplement score[c]	Ranked score of supplements, including: vitamins A, B_1, B_{12}, B_6, C, D, and E; and β-carotene, folate, niacin, riboflavin, calcium, copper, iron, magnesium, selenium, and zinc	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)	-0.80
LIS components			
Overweight BMI	Overweight BMI vs. normal BMI	Adipose tissue synthesizes and releases pro-inflammatory adipokines, such as plasminogen activator inhibitor–1 (PA1) and TNF-α [43,105]	0.89
Obese BMI	Obese BMI vs. normal BMI	Mechanisms similar to those described above	1.57
Heavy drinker	Heavy (> 7 drinks/wk for women, > 14 drinks/wk drinks for men) vs. non-drinker	Heavy alcohol intake results in oxidative stress via oxidation of ethanol to acetaldehyde[36,37]	0.30
Moderate drinker	Moderate (1 – 7 drinks/wk for women, 1 – 14 drinks/wk for men) vs. non-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)[38] and inhibits IL-6 production and activity[39]	-0.66

Moderately physically active	Individuals in the middle tertile of MET-hours per week	Physical activity improves systemic plasma antioxidant capacity (increases adaptive responses to oxidative stress), increases concentrations of anti-inflammatory cytokines, and lowers vascular wall inflammation[41,105]	-0.18
Heavily physically active	Individuals in the highest tertile of MET-hours per week	Mechanisms similar to those described above	-0.41
Current smoker	Currently smokes tobacco vs. does not currently smoke tobacco	Toxins injure tissues, upregulating cytokines and acute phase reactants[42]	0.50

Abbreviations: BMI, body mass index; DIS, dietary inflammation score; LIS, lifestyle inflammation score; MET, metabolic equivalents of task

[a] Weights are β coefficients from multivariable linear regression models conducted in the REGARDS case-cohort sample (N =639), representing the average change in a summary inflammation biomarker z-score (sum of z-scores for high sensitivity C-reactive protein, interleukin-6, interleukin-8, interleukin-10 [the latter with a negative sign]) per one standard deviation increase in a dietary component or the presence of lifestyle component. Covariates in the final model 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; In the case-control studies, all dietary components were standardized based on the distribution among the controls, by sex, to a mean of zero and standard deviation of 1, and all lifestyle components were dummy variables

[b] 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)

Table A3.2. Multivariable-adjusted associations of the DIS and LIS with incident, sporadic colorectal adenomas in three pooled case-control studies (CPRU Study, 1991–1994; MAP I Study, 1994–1997; and MAP II Study, 2002), according to selected adenoma characteristics

	Inflammation Score[a]					
	DIS[b]			LIS[c]		
Adenoma characteristics and inflammation score quintile	**No. Cases**	**Adjusted OR (95% CI)**	***p-trend***	**No. Cases**	**Adjusted OR (95% CI)**	***p-trend***
Adenoma subtype						
Tubular						
1	88	1.00		73	1.00	
2	127	1.37 (0.99, 1.91)		83	1.15 (0.80, 1.64)	
3	100	1.08 (0.77, 1.52)		122	1.46 (1.04, 2.04)	
4	105	1.21 (0.86, 1.71)		122	1.54 (1.10, 2.16)	
5	117	1.30 (0.93, 1.82)	0.28	137	1.97 (1.41, 2.75)	<0.001
Tubulovillous or villous						
1	39	1.00		30	1.00	
2	38	0.98 (0.60, 1.61)		33	1.15 (0.68, 1.95)	
3	36	0.87 (0.53, 1.42)		42	1.20 (0.73, 1.98)	
4	47	1.13 (0.70, 1.83)		58	1.65 (1.02, 2.65)	
5	64	1.57 (1.00, 2.47)	0.04	61	2.07 (1.29, 3.32)	<0.001
No. of adenomas						
1 adenoma						
1	91	1.00		72	1.00	
2	104	1.13 (0.82, 1.57)		72	1.05 (0.73, 1.51)	
3	95	0.99 (0.71, 1.39)		117	1.49 (1.07, 2.08)	
4	96	1.05 (0.75, 1.47)		132	1.72 (1.24, 2.39)	
5	125	1.33 (0.96, 1.84)	0.15	118	1.76 (1.26, 2.46)	<0.001
≥ 2 adenomas						
1	36	1.00		31	1.00	
2	62	1.64 (1.02, 2.63)		44	1.39 (0.84, 2.31)	
3	42	1.12 (0.68, 1.86)		48	1.21 (0.74, 1.99)	
4	56	1.53 (0.94, 2.49)		49	1.34 (0.82, 2.19)	
5	56	1.53 (0.94, 2.47)	0.18	80	2.63 (1.66, 4.18)	<0.001
Adenoma size						
< 1 cm						
1	74	1.00		66	1.00	
2	111	1.44 (1.02, 2.04)		74	1.13 (0.78, 1.65)	
3	84	1.10 (0.77, 1.59)		94	1.24 (0.86, 1.77)	
4	89	1.24 (0.86, 1.79)		114	1.56 (1.10, 2.21)	
5	103	1.39 (0.97, 1.99)	0.19	113	1.83 (1.28, 2.60)	<0.001
≥ 1 cm						
1	42	1.00		28	1.00	
2	40	0.95 (0.58, 1.53)		29	1.07 (0.61, 1.86)	
3	41	0.92 (0.57, 1.49)		56	1.70 (1.04, 2.77)	
4	56	1.22 (0.77, 1.93)		57	1.85 (1.14, 3.02)	
5	67	1.51 (0.97, 2.35)	0.04	76	2.70 (1.69, 4.32)	<0.001
Degree of atypia						
Mild						

1	57	1.00		47	1.00	
2	82	1.37 (0.93, 2.03)		48	0.95 (0.61, 1.49)	
3	63	1.06 (0.71, 1.60)		75	1.38 (0.92, 2.07)	
4	56	0.97 (0.64, 1.48)		78	1.47 (0.98, 2.20)	
5	72	1.23 (0.82, 1.83)	0.77	82	1.69 (1.13, 2.54)	0.0014
Moderate to severe						
1	70	1.00		56	1.00	
2	84	1.19 (0.82, 1.72)		68	1.34 (0.90, 1.99)	
3	74	1.02 (0.69, 1.48)		90	1.43 (0.98, 2.08)	
4	96	1.36 (0.94, 1.97)		103	1.70 (1.18, 2.46)	
5	109	1.54 (1.08, 2.21)	0.02	116	2.30 (1.60, 3.32)	<0.001

Abbreviations: BMI, body mass index; CI, confidence interval; CPRU, Cancer Prevention Research Unit; DIS, dietary inflammation score; LIS, lifestyle inflammation score; MAP, Markers of Adenomatous Polyps; MET, metabolic equivalents of task; OR, odds ratio

[a] For construction of inflammation score, see text and Table 1; higher scores indicate a higher balance of pro- versus anti-inflammatory exposures

[b] Covariates in the DIS unconditional logistic regression models were: age, sex, education (less than college graduate or college graduate or higher), takes NSAID/aspirin regularly (≥ once/week), hormone therapy use (among women), family history of colorectal cancer in a first degree relative (yes/no), smoking status (never, former, or current smoker), BMI (kg/m^2), alcohol intake (non-drinker, moderate drinker, or heavy drinker), physical activity (categorized into tertiles of MET-hours/wk), total energy intake (kcal/day), and study (MAP I, MAP II, or CPRU)

[c] Covariates in the LIS unconditional logistic regression models were: age, sex, takes NSAID/aspirin regularly (≥ once/week), hormone therapy use (among women), family history of colorectal cancer in a first degree relative (yes/no), former smoking status (former smoker or non-former smoker), total energy intake (kcal/day), study (MAP I, MAP II, or CPRU), and the equally-weighted DIS

Table A3.3. Multivariable-adjusted associations of the DIS and LIS with incident, sporadic colorectal adenoma in three pooled case-control studies (CPRU Study, 1991–1994; MAP I Study, 1994–1997; and MAP II Study, 2002), according to selected participant characteristics

Characteristic	No. of cases/controls	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	*p-trend*	*p-interaction*
DIS [a,b]								
Age, y								
< 57	318/1,091	1.00	1.24 (0.80, 1.92)	0.95 (0.60, 1.50)	1.00 (0.63, 1.57)	1.13 (0.72, 1.77)	*0.88*	
≥ 57	459/911	1.00	1.29 (0.88, 1.90)	1.03 (0.69, 1.53)	1.27 (0.85, 1.88)	1.58 (1.07, 2.33)	*0.04*	*0.83*
Sex								
Male	475/861	1.00	1.23 (0.83, 1.83)	1.23 (0.83, 1.83)	1.27 (0.85, 1.90)	1.69 (1.15, 2.49)	*0.01*	
Female	302/1,141	1.00	1.29 (0.84, 1.96)	0.76 (0.48, 1.21)	1.08 (0.70, 1.69)	1.05 (0.67, 1.64)	*0.93*	*0.25*
Aspirin or other NSAID use								
Takes aspirin or NSAID < once/week	501/1,167	1.00	1.17 (0.81, 1.69)	0.79 (0.54, 1.16)	1.06 (0.73, 1.55)	1.38 (0.96, 1.98)	*0.14*	
Take aspirin or NSAID ≥ once/week	276/835	1.00	1.49 (0.94, 2.38)	1.48 (0.91, 2.41)	1.31 (0.80, 2.13)	1.24 (0.76, 2.04)	*0.48*	*0.21*
Family history of CRC[c]								
No	646/1,646	1.00	1.20 (0.88, 1.65)	0.97 (0.70, 1.35)	1.11 (0.81, 1.54)	1.40 (1.02, 1.91)	*0.08*	
Yes	131/356	1.00	1.93 (0.88, 4.25)	1.24 (0.56, 2.76)	1.82 (0.82, 4.04)	1.24 (0.55, 2.80)	*0.83*	*0.55*
Tobacco use								
Non-smoker	236/920	1.00	1.76 (1.08, 2.86)	1.16 (0.69, 1.95)	1.27 (0.76, 2.12)	1.72 (1.04, 2.84)	*0.17*	
Former smoker	352/804	1.00	1.13 (0.75, 1.71)	1.03 (0.68, 1.56)	1.17 (0.76, 1.79)	1.28 (0.85, 1.95)	*0.26*	
Current smoker	189/278	1.00	0.82 (0.36, 1.86)	0.77 (0.34, 1.76)	1.08 (0.49, 2.38)	1.09 (0.50, 2.39)	*0.50*	*0.83*
BMI, kg/m^2								
18.5 – 24.99	256/819	1.00	0.77 (0.48, 1.24)	0.56 (0.34, 0.93)	0.70 (0.42, 1.17)	0.69 (0.41, 1.15)	*0.13*	
25 – 29.99	313/746	1.00	1.88 (1.18, 3.00)	1.44 (0.89, 2.34)	1.96 (1.21, 3.17)	2.27 (1.41, 3.67)	*0.002*	
≥ 30	208/437	1.00	1.55 (0.84, 2.86)	1.37 (0.73, 2.58)	1.17 (0.64, 2.14)	1.69 (0.96, 2.99)	*0.19*	*0.07*
Alcohol use[d]								
Non-drinker	284/673	1.00	1.12 (0.67, 1.86)	0.83 (0.48, 1.43)	1.28 (0.78, 2.09)	1.49 (0.93, 2.38)	*0.06*	
Moderate drinker	373/1,146	1.00	1.60 (1.08, 2.37)	1.18 (0.79, 1.78)	1.17 (0.76, 1.79)	1.48 (0.97, 2.26)	*0.31*	
Heavy drinker	120/183	1.00	0.73 (0.32, 1.67)	0.85 (0.37, 1.95)	1.04 (0.44, 2.49)	0.88 (0.38, 2.05)	*0.98*	*0.61*
Physical activity[e]								
Lowest tertile of physical activity	281/664	1.00	1.02 (0.61, 1.71)	0.78 (0.47, 1.32)	0.70 (0.41, 1.19)	1.13 (0.69, 1.86)	*0.88*	
Middle tertile of physical activity	235/664	1.00	1.63 (0.96, 2.79)	1.41 (0.81, 2.44)	1.71 (0.99, 2.93)	2.02 (1.17, 3.49)	*0.02*	
Highest tertile of physical activity	261/674	1.00	1.25 (0.77, 2.02)	0.93 (0.56, 1.55)	1.47 (0.89, 2.42)	1.16 (0.71, 1.89)	*0.47*	*0.28*
Study								
MAP I	176/173	1.00	1.46 (0.69, 3.09)	0.93 (0.41, 2.07)	1.33 (0.60, 2.94)	1.44 (0.65, 3.19)	*0.44*	
MAP II	47/119	1.00	1.38 (0.43, 4.41)	0.86 (0.23, 3.24)	1.12 (0.31, 4.03)	1.63 (0.48, 5.60)	*0.56*	
CPRU	554/1,710	1.00	1.25 (0.90, 1.74)	1.06 (0.75, 1.48)	1.21 (0.87, 1.69)	1.41 (1.02, 1.95)	*0.08*	*0.99*
LIS [a,f]								
Age, y								
< 57	318/1,091	1.00	0.97 (0.59, 1.61)	1.78 (1.16, 2.73)	1.81 (1.17, 2.80)	2.19 (1.43, 3.37)	*<0.001*	
≥ 57	459/911	1.00	1.21 (0.80, 1.82)	1.12 (0.75, 1.68)	1.38 (0.93, 2.05)	1.78 (1.19, 2.65)	*0.003*	*0.27*
Sex								
Male	475/861	1.00	1.38 (0.89, 2.16)	1.48 (0.97, 2.26)	1.55 (1.02, 2.36)	2.30 (1.51, 3.51)	*<0.001*	
Female	302/1,141	1.00	0.91 (0.57, 1.44)	1.45 (0.96, 2.20)	1.78 (1.19, 2.68)	1.76 (1.16, 2.66)	*<0.001*	*0.23*
Aspirin or other NSAID use								
Takes aspirin or NSAID <once/week	501/1,167	1.00	1.26 (0.85, 1.86)	1.50 (1.04, 2.16)	1.89 (1.32, 2.72)	2.09 (1.44, 3.03)	*<0.001*	
Take aspirin or NSAID ≥ once/week	276/835	1.00	0.94 (0.56, 1.60)	1.29 (0.79, 2.10)	1.13 (0.69, 1.85)	1.85 (1.16, 2.97)	*0.01*	*0.64*
Family history of CRC[c]								
No	646/1,646	1.00	1.18 (0.83, 1.67)	1.46 (1.05, 2.02)	1.64 (1.19, 2.26)	2.05 (1.49, 2.82)	*<0.001*	

	Yes	131/356	1.00	1.13 (0.54, 2.35)	1.29 (0.66, 2.54)	1.39 (0.69, 2.79)	1.92 (0.96, 3.85)	*0.06*	*1.00*
Study									
	MAP I	176/173	1.00	1.14 (0.51, 2.54)	1.50 (0.71, 3.15)	1.36 (0.61, 3.02)	2.14 (0.98, 4.65)	*0.05*	
	MAP II	47/119	1.00	1.02 (0.28, 3.76)	0.97 (0.33, 2.82)	1.32 (0.46, 3.79)	2.84 (0.84, 9.60)	*0.12*	
	CPRU	554/1,710	1.00	1.19 (0.84, 1.71)	1.45 (1.03, 2.03)	1.68 (1.21, 2.34)	1.98 (1.42, 2.75)	*<0.001*	*0.97*

Abbreviations: BMI, body mass index; CI, confidence interval; CPRU, Cancer Prevention Research Unit; CRC, colorectal cancer; DIS, dietary inflammation score; LIS, lifestyle inflammation score; MAP, Markers of Adenomatous Polyps; MET, metabolic equivalent of task; NSAID, non-steroidal anti-inflammatory drug; OR, odds ratio

[a] For inflammation score construction, see text and Table 1; higher scores indicate a higher balance of pro- versus anti-inflammatory exposures

[b] Covariates in the DIS unconditional logistic regression models were: age, sex, education (less than college graduate or college graduate or higher), regular use of NSAID/aspirin (≥ once/week), hormone therapy use (among women), family history of colorectal cancer in a first degree relative (yes/no), smoking status (never, former, or current smoker), BMI (kg/m^2), alcohol intake (non-drinker, moderate drinker, or heavy drinker), physical activity (categorized into tertiles of MET-hours/wk), total energy intake (kcal/day), and study (MAP I, MAP II, or CPRU)

[c] In a first degree relative

[d] Heavy drinker defined as > 7 drinks/wk for women and > 14 drinks/wk drinks for men; moderate drinker defined as 1 – 7 drinks/wk for women, 1 – 14 drinks/wk for men

[e] Participants categorized into tertiles of MET-hours of moderate and vigorous physical activity per week based on the distribution among the controls

[f] Covariates in the LIS unconditional logistic regression models were: age, sex, regular NSAID/aspirin use (≥ once/week), hormone therapy use (among women), family history of colorectal cancer in a first degree relative (yes/no), former smoking status (non-former smoker or former smoker), total energy intake (kcal/day), study (MAP I, MAP II, or CPRU), and the equally-weighted DIS

Table A3.4. Multivariable-adjusted associations of the equally-weighted DIS and LIS with incident, sporadic colorectal adenomas in three pooled case-control studies (CPRU Study, 1991–1994; MAP I Study, 1994–1997; and MAP II Study, 2002)

Equally weighted inflammation scores[a]			
DIS - equal weight[b]		LIS - equal weight[c]	
Adjusted OR (95% CI)	*p-trend*	Adjusted OR (95% CI)	*p-trend*
1.00		1.00	
1.04 (0.78, 1.40)		1.12 (0.87, 1.45)	
1.11 (0.83, 1.48)		1.58 (1.22, 2.06)	
1.05 (0.78, 1.41)		1.66 (1.25, 2.21)	
1.30 (0.97, 1.75)	0.10	1.96 (1.41, 2.72)	<0.001

Abbreviations: BMI, body mass index; CI, confidence interval; CPRU, Cancer Prevention Research Unit; DIS, dietary inflammation score; LIS, lifestyle inflammation score; MAP, Markers of Adenomatous Polyps; MET, metabolic equivalent of task; NSAID, non-steroidal anti-inflammatory drug; OR, odds ratio

[a] Dietary and lifestyle components of the equally weighted inflammation scores are the same as 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

[b] Covariates in the DIS-equal weight unconditional logistic regression models were: age, sex, education (less than college graduate or college graduate or higher), regular aspirin/other NSAID use (≥ once/week), hormone therapy use (among women), family history of colorectal cancer in a first degree relative (yes/no), smoking status (never, former, or current smoker), BMI (kg/m^2), alcohol intake (non-drinker, moderate drinker, or heavy drinker), physical activity (categorized into tertiles of MET-hours/wk), total energy intake (kcal/day), and study (MAP I, MAP II, or CPRU)

[c] Covariates in the LIS-equal weight unconditional logistic regression models were: age, sex, takes NSAIDs/aspirin regularly (≥ once/week), hormone therapy use (among women), family history of colorectal cancer in a first degree relative (yes/no), former smoking status (former smoker or non-former smoker), total energy intake (kcal/day), study (MAP I, MAP II, or CPRU), and the equally-weighted DIS

Table A3.5. Multivariable-adjusted associations of the DII and EDII with incident, sporadic colorectal adenomas in three pooled case-control studies (CPRU Study, 1991–1994; MAP I Study, 1994–1997; and MAP II Study, 2002), overall and by sex

		Inflammation score[a]					
			DII			EDII	
		No. of cases/ controls	Adjusted OR (95% CI)	*p-trend*	*No. of cases/ controls*	Adjusted OR (95% CI)	*p-trend*
Overall							
	Quintiles						
	1	144/404	1.00		167/404	1.00	
	2	151/399	1.11 (0.83, 1.48)		146/399	0.90 (0.68, 1.18)	
	3	169/402	1.28 (0.96, 1.71)		169/402	0.99 (0.75, 1.30)	
	4	150/399	1.13 (0.84, 1.52)		151/399	0.86 (0.65, 1.13)	
	5	163/398	1.26 (0.92, 1.72)	0.16	144/398	0.83 (0.62, 1.11)	0.23
Males							
	Quintiles						
	1	96/174	1.00		104/174	1.00	
	2	74/172	0.81 (0.54, 1.20)		84/172	0.84 (0.57, 1.22)	
	3	108/172	1.25 (0.86, 1.83)		98/172	0.93 (0.64, 1.34)	
	4	98/172	1.20 (0.82, 1.78)		87/172	0.78 (0.53, 1.14)	
	5	99/171	1.24 (0.83, 1.87)	0.10	102/171	0.88 (0.60, 1.29)	0.49
Females							
	Quintiles						
	1	48/230	1.00		63/230	1.00	
	2	77/227	1.54 (1.00, 2.38)		62/227	1.00 (0.66, 1.51)	
	3	61/230	1.29 (0.82, 2.03)		71/230	1.10 (0.73, 1.66)	
	4	52/227	1.01 (0.62, 1.65)		64/227	0.96 (0.63, 1.47)	
	5	64/227	1.24 (0.75, 2.05)	0.97	42/227	0.75 (0.47, 1.19)	0.25

Abbreviations: BMI, body mass index; CI, confidence interval; CPRU, Cancer Prevention Research Unit; DII, dietary inflammatory index; EDII, empirical dietary inflammatory index; MAP, Markers of Adenomatous Polyps; MET, metabolic equivalent of task; NSAID, non-steroidal anti-inflammatory drug; OR, odds ratio

[a] Weights and components for the DII and EDII are derived from Shivappa, *et al*(1) and Tabung, *et al*(2), respectively

[b] Covariates in the DII and EDII unconditional logistic regression models were: age, sex, education (less than college graduate or college graduate or higher), regular aspirin/other NSAID use (≥ once/week), hormone therapy use (among women), family history of colorectal cancer in a first degree relative (yes/no), smoking status (never, former, or current smoker), BMI (kg/m^2), physical activity (tertiles of MET-hours/wk), total energy intake (kcal/day), and study (MAP I, MAP II, or CPRU)

Table A3.6. Multivariable-adjusted associations of the MCM/Bootstrapped DIS and LIS with incident, sporadic colorectal adenomas in three pooled case-control studies (CPRU Study, 1991–1994; MAP I Study, 1994–1997; and MAP II Study, 2002)

	Inflammation score[a]	
	DIS[b]	**LIS[c]**
	Adjusted OR (95% CI)	Adjusted OR (95% CI)
Quintiles		
1	1.00	1.00
2	1.09 (0.76, 1.68)	1.16 (0.81, 1.59)
3	1.25 (0.85, 1.66)	1.39 (0.91, 1.93)
4	1.31 (0.91, 1.88)	1.66 (1.23, 2.40)
5	1.43 (0.93, 2.00)	1.95 (1.41, 2.69)

Abbreviations: BMI, body mass index; CI, confidence interval; CPRU, Cancer Prevention Research Unit; DIS, dietary inflammation score; LIS, lifestyle inflammation score; MAP, Markers of Adenomatous Polyps; MCM, Monte Carlo Method; MET, metabolic equivalent of task; NSAID, non-steroidal anti-inflammatory drug; OR, odds ratio; REGARDS, Reasons for Geographic and Racial Differences in Stroke Study

[a] Weights for all dietary and lifestyle components in the DIS and LIS are equal to the maximum likelihood for the β coefficients obtained from multivariable linear regression models (dependent variable: summary inflammation z-score), plus a randomly sampled standard normal deviate, over 360 iterations, multiplied by the standard error matrix obtained from the regression models in the REGARDS case-cohort sample. The case-control study was subsequently bootstrapped so that the confidence intervals contain all random error from the DIS/LIS weights and the odds ratio estimate.

[b] Covariates in the DIS unconditional logistic regression models were: age, sex, education (less than college graduate or college graduate or higher), regular aspirin/other NSAID use (≥ once/week), hormone therapy use (among women), family history of colorectal cancer in a first degree relative (yes/no), smoking status (never, former, or current smoker), BMI (kg/m^2), alcohol intake (non-drinker, moderate drinker, or heavy drinker), physical activity (tertiles of MET-hours/wk), total energy intake (kcal/day), and study (MAP I, MAP II, or CPRU)

[c] Covariates in the LIS unconditional logistic regression models were: age, sex, regular aspirin/other NSAID use (≥ once/week), hormone therapy use (among women), family history of colorectal cancer in a first degree relative (yes/no), former smoking status (former smoker or non-former smoker), total energy intake (kcal/day), study (MAP I, MAP II, or CPRU), and the equally-weighted DIS

Appendix 4. Chapter 4 Supplemental Tables

Table A4.1. Components of the dietary (DIS) and lifestyle (LIS) inflammation scores, their general descriptions, rationales for inclusion, and assigned weights

Components	Rationales for inclusion
LIS components	
Overweight BMI	Adipose tissue synthesizes and releases pro-inflammatory adipokines, such as plasminogen activator inhibitor–1 (PA1) and TNF-α [43,105]
Obese BMI	Mechanisms similar to those described above
Heavy drinker	Heavy alcohol intake results in oxidative stress via oxidation of ethanol to acetaldehyde[36,37]
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)[38] and inhibits IL-6 production and activity[39]
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[41,105]
Heavily physically active	Mechanisms similar to those described above
Current smoker	Toxins injure tissues, upregulating cytokines and acute phase reactants[42]
DIS components	
Added sugars	Induce postprandial hyperglycemia, which act as stressful stimuli through subsequent repeated mild postprandial hypoglycemia[94] and reduce nitric oxide availability (play role in regulation of inflammatory response[95]); elevate pro-inflammatory free fatty acid levels[88]; produce oxidative stress through oxidation of membrane lipids, proteins, lipoproteins, and DNA[96]
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[70–72]
Coffee and tea	Tea contains flavonoids and antioxidants (e.g., epicatechin and quercetin)[100]; 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[82,101]
Deep yellow or orange vegetables and fruits	Contain pro-vitamin A carotenoids (e.g., β-carotene and α-carotene), which have a conjugated double-bond structure making them strong antioxidants[73]
Fats	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[84–86]; contain saturated fats that mimic lipopolysaccharide (LPS), a pro-inflammatory stimulant, in the gut; increase cytotoxic, pro-oxidant, and pro-inflammatory bile acids in the colon[84,87]

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 [88–90]
High-fat dairy	Contain 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 conjugated linoleic acids (CLA), *cis*- and *trans*-palmitoleic acid, butyric acid, phytanic acid, and alpha-linolenic acid[97–99]
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, Nuclear factor-erythroid 2 (NF-E2)-related factor 2 (Nrf2), which plays a key role in cellular protection against oxidative stress and inflammation[55–65]
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[58,82,83]
Low-fat dairy	Similar mechanisms to high-fat dairy (see mechanisms above), with lower fat content
Nuts	Contain Ω -3 fatty acids[88,89,102,103] (mechanisms similar to those described above in 'Fish') and contain *l*-arginine, which improves endothelium-dependent dilation (precursor of the endogenous vasodilator nitric oxide) and decreases platelet aggregation and monocyte adhesion[58]
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[59,74–81]
Other vegetables	Contain antioxidants and polyphenols with similar mechanisms to those described above
Poultry	Inversely associated with inflammation markers[91], contain low amounts of saturated fat[92], and contain *l*-arginine (see mechanisms in 'Nuts')
Processed meats	Contain heme iron, which increases the bioavailability of iron, which in turn increases oxidative stress; contain higher saturated fat contents, Ω-6 fatty acids (see 'Fats'), and additives, such as nitrites, with suspected pro-inflammatory properties[91,93]
Red and organ meats	Contain heme iron (see above); contain Ω-6 fatty acids and saturated fat (see mechanisms in 'Fats' above)
Refined grains and starchy vegetables	Sparse in nutrients; some processed grains contain emulsifiers, which potentially break down mucin in the gut leading to inflammation[104]; and induce hyperglycemia (mechanisms described similar to those described above in 'Added Sugars')

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[66–69]
Supplement score[c]	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; DIS, dietary inflammation score; hsCRP, high sensitivity C-reactive protein; IL, interleukin; LIS, lifestyle inflammation score; MET, metabolic equivalents of task; REGARDS, Reasons for Geographic and Racial Differences in Stroke study

[a] 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.

[b] 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)

Table A4.2. Associations of the dietary (DIS) and lifestyle (LIS) inflammation scores[a] with incident colorectal cancer by selected characteristics; the NIH-AARP Diet and Health Study (N = 453,465)

Characteristics	No. cases	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	*p-trend*	*p-interaction*[b]
DIS[c]								
Age, y								
< 65	5,567	1.00	1.01 (0.92, 1.10)	1.04 (0.95, 1.14)	1.06 (0.97, 1.16)	1.24 (1.14, 1.36)	*<0.0001*	
≥ 65	4,769	1.00	1.01 (0.92, 1.12)	1.07 (0.98, 1.18)	1.17 (1.07, 1.29)	1.29 (1.18, 1.42)	*<0.0001*	*0.64*
HRT use and sex								
Male	6,905	1.00	1.04 (0.96, 1.12)	1.07 (0.99, 1.15)	1.10 (1.02, 1.19)	1.29 (1.19, 1.39)	*<0.0001*	
Female on HRT	1,197	1.00	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*	
Female not on HRT	2,234	1.00	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	1.01 (0.94, 1.08)	1.05 (0.98, 1.12)	1.10 (1.03, 1.17)	1.26 (1.18, 1.35)	*<0.0001*	
Black	396	1.00	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	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[d]								
No	7,047	1.00	1.05 (0.97, 1.13)	1.08 (1.00, 1.16)	1.14 (1.06, 1.24)	1.28 (1.19, 1.39)	*<0.0001*	
Yes	3,289	1.00	0.94 (0.83, 1.05)	1.02 (0.91, 1.15)	1.05 (0.94, 1.18)	1.21 (1.08, 1.36)	*0.0001*	*0.36*
Family history of CRC[e]								
No	8,868	1.00	1.01 (0.94, 1.08)	1.06 (0.99, 1.13)	1.12 (1.05, 1.20)	1.26 (1.18, 1.35)	*<0.0001*	
Yes	1,019	1.00	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	0.96 (0.86, 1.08)	1.03 (0.92, 1.15)	1.07 (0.96, 1.20)	1.20 (1.07, 1.34)	*0.0004*	
Former smoker	5,792	1.00	1.06 (0.98, 1.16)	1.09 (1.00, 1.19)	1.16 (1.07, 1.27)	1.37 (1.26, 1.49)	*<0.0001*	
Current smoker	1,293	1.00	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	1.07 (0.95, 1.19)	0.99 (0.88, 1.11)	1.11 (0.99, 1.25)	1.29 (1.15, 1.45)	*<0.0001*	
25 – 29.99	4,619	1.00	0.92 (0.84, 1.02)	1.07 (0.98, 1.18)	1.13 (1.03, 1.24)	1.25 (1.14, 1.37)	*<0.0001*	
≥ 30	2,515	1.00	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[f]								
Non-drinker	2,408	1.00	1.07 (0.92, 1.24)	1.00 (0.87, 1.16)	1.15 (1.00, 1.33)	1.30 (1.13, 1.49)	*<0.0001*	
Moderate drinker	6,907	1.00	1.01 (0.93, 1.09)	1.08 (1.00, 1.17)	1.08 (1.00, 1.17)	1.23 (1.14, 1.34)	*<0.0001*	
Heavy drinker	1,021	1.00	1.00 (0.80, 1.25)	1.00 (0.80, 1.25)	1.30 (1.05, 1.61)	1.48 (1.20, 1.83)	*<0.0001*	*0.21*
Physical activity								
Rarely or never exercises	2,069	1.00	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	1.01 (0.90, 1.14)	0.99 (0.89, 1.11)	1.08 (0.97, 1.21)	1.20 (1.07, 1.34)	*0.0002*	
Exercises ≥ 3 times/wk	4,550	1.00	1.06 (0.97, 1.16)	1.11 (1.01, 1.22)	1.17 (1.06, 1.28)	1.35 (1.22, 1.48)	*<0.0001*	*0.27*
Take aspirin ≥ once/wk[g]								
No	3,913	1.00	1.06 (0.95, 1.18)	1.07 (0.96, 1.20)	1.23 (1.11, 1.37)	1.34 (1.21, 1.49)	*<0.0001*	
Yes	2,541	1.00	1.06 (0.93, 1.20)	1.19 (1.05, 1.35)	1.12 (0.98, 1.28)	1.35 (1.18, 1.54)	*<0.0001*	*0.27*
Take NSAID ≥ once/wk[g]								
No	5,238	1.00	1.04 (0.95, 1.14)	1.09 (0.99, 1.19)	1.18 (1.08, 1.29)	1.35 (1.23, 1.48)	*<0.0001*	
Yes	1,204	1.00	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[g]								
Never had one	920	1.00	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	1.02 (0.92, 1.14)	1.04 (0.94, 1.16)	1.17 (1.05, 1.30)	1.32 (1.18, 1.47)	*<0.0001*	
≥ 5 years ago	485	1.00	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*	

LIS[f]								
Age, y								
< 65	5,567	1.00	1.21 (1.10, 1.33)	1.29 (1.18, 1.41)	1.34 (1.22, 1.46)	1.50 (1.37, 1.64)	*<0.0001*	
≥ 65	4,769	1.00	1.05 (0.96, 1.15)	1.14 (1.04, 1.25)	1.11 (1.01, 1.22)	1.28 (1.16, 1.41)	*<0.0001*	*0.07*
HRT use and sex								
Male	6,905	1.00	1.15 (1.06, 1.24)	1.29 (1.19, 1.39)	1.26 (1.16, 1.36)	1.49 (1.37, 1.62)	*<0.0001*	
Female on HRT	1,197	1.00	1.11 (0.92, 1.34)	1.21 (1.03, 1.44)	1.40 (1.17, 1.67)	1.39 (1.16, 1.67)	*<0.0001*	
Female not on HRT	2,234	1.00	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	1.13 (1.06, 1.21)	1.22 (1.15, 1.31)	1.24 (1.16, 1.32)	1.40 (1.31, 1.50)	*<0.0001*	
Black	396	1.00	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	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[d]								
No	7,047	1.00	1.15 (1.06, 1.24)	1.21 (1.13, 1.31)	1.25 (1.16, 1.35)	1.44 (1.33, 1.56)	*<0.0001*	
Yes	3,289	1.00	1.05 (0.93, 1.20)	1.19 (1.05, 1.35)	1.13 (1.00, 1.27)	1.26 (1.12, 1.42)	*<0.0001*	*0.18*
Family history of CRC[e]								
No	8,868	1.00	1.12 (1.05, 1.21)	1.19 (1.11, 1.28)	1.21 (1.13, 1.29)	1.38 (1.29, 1.49)	*<0.0001*	
Yes	1,019	1.00	1.03 (0.83, 1.26)	1.22 (1.00, 1.49)	1.19 (0.98, 1.45)	1.30 (1.05, 1.60)	*<0.0001*	*0.43*
Take aspirin ≥ once/wk[g]								
No	3,913	1.00	1.07 (0.97, 1.19)	1.19 (1.08, 1.32)	1.17 (1.05, 1.29)	1.29 (1.16, 1.43)	*<0.0001*	
Yes	2,541	1.00	1.23 (1.08, 1.40)	1.32 (1.16, 1.51)	1.34 (1.18, 1.53)	1.42 (1.24, 1.63)	*<0.0001*	*0.40*
Takes NSAID ≥ once/wk[g]								
No	5,238	1.00	1.11 (1.01, 1.21)	1.22 (1.12, 1.33)	1.24 (1.13, 1.35)	1.38 (1.26, 1.51)	*<0.0001*	
Yes	1,204	1.00	1.24 (1.02, 1.51)	1.32 (1.09, 1.60)	1.26 (1.04, 1.52)	1.29 (1.06, 1.57)	*<0.0001*	*0.32*
Colonoscopy post baseline[h]								
No	920	1.00	1.22 (0.97, 1.53)	1.36 (1.09, 1.70)	1.42 (1.15, 1.76)	1.35 (1.07, 1.70)	*<0.0001*	
< 5 years ago	3,713	1.00	1.18 (1.06, 1.30)	1.25 (1.13, 1.39)	1.26 (1.13, 1.39)	1.35 (1.21, 1.51)	*<0.0001*	
≥ 5 years ago	485	1.00	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 Institute of Health-American Association for Retired Persons

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

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

[c] 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)

[d] Self-reported heart disease, diabetes mellitus, gallstone or gallbladder disease, or emphysema at baseline

[e] In a first degree relative

[f] Covariates in the LIS Cox proportional hazards models were: age (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 or no), and the equally-weighted DIS

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

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

Table A4.3. Associations of the equally-weighted DIS[a] and LIS[a] with incident colorectal cancer in the NIH-AARP Diet and Health Study (N = 453,465)

	Overall		Men		Women	
	DIS-equal weight[b] Adjusted HR (95% CI)	**LIS-equal weight[c] Adjusted HR (95% CI)**	**DIS-equal weight[b] Adjusted HR (95% CI)**	**LIS-equal weight[c] Adjusted HR (95% CI)**	**DIS-equal weight[b] Adjusted HR (95% CI)**	**LIS-equal weight[c] Adjusted HR (95% CI)**
Quintiles						
1	1.00	1.00	1.00	1.00	1.00	1.00
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 Institute of Health-American Association for Retired Persons

[a] 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

[b] 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)

[c] Covariates in the LIS-weight Cox proportional hazards models were: age (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 or no), and the equally-weighted DIS

Table A4.4. Associations of the MCM/bootstrap-technique DIS and LIS with incident colorectal cancer overall in the NIH-AARP Diet and Health Study (N = 453,465)

	Inflammation score[a]	
	DIS[b] Adjusted HR (95% CI)	**LIS[c] Adjusted HR (95% CI)**
Quintiles		
1	1.00	1.00
2	1.00 (0.94, 1.10)	1.15 (1.08, 1.18)
3	1.05 (0.95, 1.17)	1.19 (1.13, 1.29)
4	1.11 (0.99, 1.28)	1.26 (1.21, 1.31)
5	1.21 (1.09, 1.40)	1.35 (1.26, 1.43)

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 Institute of Health-American Association for Retired Persons

[a] Weights for all dietary and lifestyle components in the DIS and LIS are equal to the maximum likelihood for the β coefficients obtained from multivariable linear regression models (dependent variable: summary inflammation z-score), plus a randomly sampled standard normal deviate, over 10 iterations, multiplied by the standard error matrix obtained from the regression models in the REGARDS case-cohort sample. The NIH AARP study was subsequently bootstrapped so that the confidence intervals contain all random error from the DIS/LIS weights and the hazards ratio estimate.

[b] 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)

[c] Covariates in the LIS Cox proportional hazards models were: age (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 or no), and the equally-weighted DIS

Table A4.5. Associations of the HEI[a] and the EDII[a] with incident colorectal cancer overall, and by sex; the NIH-AARP Diet and Health Study (N = 453,465)

	Overall		Males		Females	
	HEI-2015[b] Adjusted HR (95% CI)	**EDII[c] Adjusted HR (95% CI)**	**HEI-2015[b] Adjusted HR (95% CI)**	**EDII[c] Adjusted HR (95% CI)**	**HEI-2015[b] Adjusted HR (95% CI)**	**EDII[c] Adjusted HR (95% CI)**
Quintiles						
1	1.00	1.00	1.00	1.00	1.00	1.00
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; EDII, empirical dietary inflammation index; HEI, Healthy Eating Index 2015; HR, hazards ratio; LIS, lifestyle inflammation score; NIH-AARP, National Institute of Health-American Association for Retired Persons

[a] The HEI was constructed as described by Krebs-Smith et al.(162), but the scoring was reversed such that a lower score was considered potentially higher risk; the EDII was constructed as described by Tabung et al.(111)

[b] 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/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)

[c] Covariates in the EDII Cox proportional hazards models included those described in footnote 'b', except for alcohol intake

Table A4.6. 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 (N = 453,465)

	Overall	Men	Women
Lifestyle factor[a]	**Adjusted HR (95% CI)**	**Adjusted HR (95% CI)**	**Adjusted HR (95% CI)**
Body mass index[b]			
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[c]			
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 Institute of Health-American Association for Retired Persons

[a] All lifestyle components were included in the Cox proportional hazards models and additionally included: age (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), and the equally-weighted DIS

[b] Normal BMI: 18.5—24.99 kg/m^2; Overweight BMI: 25 – 29.99 kg/m^2; Obese BMI: ≥ 30 kg/m^2

[c] 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

Table A4.7. Sensitivity analyses for the associations of the DIS and LIS with incident colorectal cancer in the NIH-AARP Diet and Health Study (N = 453,465)

Sensitivity analysis	Inflammation score[a]	
	DIS[b] Adjusted HR (95% CI)	LIS[c] Adjusted HR (95% CI)
Exclude those who died or were diagnosed with CRC		
Within 1 year from baseline		
Continuous	1.04 (1.03, 1.05)	1.16 (1.13, 1.19)
Quintiles		
1	1.00	1.00
2	1.01 (0.95, 1.08)	1.12 (1.05, 1.20)
3	1.05 (0.99, 1.12)	1.20 (1.12, 1.28)
4	1.12 (1.05, 1.20)	1.22 (1.14, 1.30)
5	1.26 (1.18, 1.35)	1.38 (1.29, 1.48)
Within 2 years from baseline		
Continuous	1.04 (1.03, 1.05)	1.16 (1.12, 1.19)
Quintiles		
1	1.00	1.00
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)
Censor when reach age 75 during follow-up		
Continuous	1.04 (1.03, 1.05)	1.16 (1.13, 1.19)
Quintiles		
1	1.00	1.00
2	1.01 (0.95, 1.08)	1.13 (1.05, 1.20)
3	1.06 (0.99, 1.13)	1.21 (1.14, 1.29)
4	1.11 (1.05, 1.19)	1.22 (1.15, 1.30)
5	1.27 (1.19, 1.35)	1.38 (1.30, 1.48)

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

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

[b] 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)

[c] Covariates in the LIS Cox proportional Hazards models were: age (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 or no), and the equally-weighted DIS

Table A4.8. Adjusted associations of the dietary (DIS) and lifestyle (LIS) inflammation scores[a] with incident colorectal cancer, using date of any first cancer diagnoses as the censor date; the NIH-AARP Diet and Health Study (N = 453,465)

	Overall		Men		Women	
	DIS[b]	LIS[c]	DIS[b]	LIS[c]	DIS[b]	LIS[c]
	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)
Continuous	1.04 (1.03,1.05)	1.16 (1.13,1.19)	1.04 (1.03,1.05)	1.19 (1.15,1.23)	1.03 (1.02,1.05)	1.11 (1.06,1.16)
Quintiles						
1	1.00	1.00	1.00	1.00	1.00	1.00
2	1.01 (0.95,1.08)	1.13 (1.06,1.21)	1.03 (0.95,1.12)	1.15 (1.06,1.25)	0.96 (0.85,1.07)	1.12 (1.00,1.25)
3	1.06 (0.99,1.13)	1.21 (1.14,1.29)	1.07 (0.99,1.15)	1.29 (1.19,1.40)	1.04 (0.93,1.16)	1.08 (0.97,1.21)
4	1.12 (1.05,1.19)	1.23 (1.15,1.31)	1.10 (1.02,1.19)	1.26 (1.16,1.36)	1.13 (1.01,1.26)	1.18 (1.06,1.32)
5	1.27 (1.19,1.35)	1.39 (1.30,1.48)	1.29 (1.20,1.40)	1.48 (1.36,1.61)	1.21 (1.08,1.35)	1.25 (1.12,1.39)

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

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

[b] 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)

[c] Covariates in the LIS Cox proportional hazards models were: age (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 or no), and the equally-weighted DIS