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# Associations of novel dietary and lifestyle inflammation scores with all-cause, all-cancer, and all-cardiovascular disease mortality among older woman

By

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Master of Public Health

Epidemiology

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# Associations of novel dietary and lifestyle inflammation scores with all-cause, all-cancer, and all-cardiovascular disease mortality among older woman

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B.S.

Fudan University

2018

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An abstract of

A thesis submitted to the Faculty of the

Rollins School of Public Health of Emory University

in partial fulfillment of the requirements for the degree of

Master of Public Health

in Epidemiology

2020

# Abstract

Associations of novel dietary and lifestyle inflammation scores with all-cause, all-cancer, and all-cardiovascular disease mortality among older woman
By Zhuoyun Li

**Background:** Exogenous exposures that may contribute to chronic, low-grade inflammation collectively may increase chronic disease and mortality risks. We investigated associations of novel questionnaire-based dietary (DIS) and lifestyle (LIS) inflammation scores with all-cause, all-cancer, and cardiovascular disease (CVD) mortality in the prospective Iowa Women's Health Study (IWHS; 1986 – 2012; $n$ = 33,155, of whom 17,431 died during follow up).

**Methods:** The previously reported weights for the components of the 19-component DIS and 4-component LIS were calculated based on their strengths of associations with a panel of inflammation biomarkers in a diverse subset of participants in the Reasons for Geographic and Racial Differences in Stroke study (REGARDS). In the IWHS, we summed each study participant's weighted components to yield their inflammation scores; a higher score was considered more pro-inflammatory. We assessed DIS- and LIS-mortality associations using multivariable Cox proportional hazards regression.

**Results:** Among participants in the highest relative to the lowest DIS and LIS quintiles, the adjusted hazards ratios (HR) and their 95% confidence intervals [CI], were, respectively, for all-cause mortality, 1.11 (1.05-1.16;) and 1.59 (1.51-1.67); for all-cancer mortality, 1.06 (0.96-1.17) and 1.51 (1.37-1.66); and for CVD mortality, 1.11 (1.03-1.20) and 1.78 (1.65-1.93) (all $P_{trend}<0.01$). Among those in the highest relative to the lowest joint LIS/DIS quintile, the HRs (95% CIs) for all-cause, all-cancer, and all-CVD mortality were 1.88 (1.71-2.08; $P_{interaction}=0.02$), 1.83 (1.50-2.21; $P_{interaction}=0.97$), and 1.90 (1.63-2.22; $P_{interaction}=0.05$), respectively.

**Conclusions:** These results suggest that more pro-inflammatory diets and lifestyles may be associated with higher all-cause, all-cancer, and all-CVD mortality risks.

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**Contents**

## Introduction

Cancer and cardiovascular diseases (CVD) are the world's most common causes of death [1]. Chronic inflammation has been mechanistically linked and associated with the incidence of several chronic diseases, such as cancer and CVD, and with mortality [2-5]. Individual dietary and lifestyle factors have been linked to chronic inflammation [6,7], several chronic diseases [8,9], and mortality [8,9]. However, many of the associations of the individual factors, especially the dietary factors, with risk have been weak and/or inconsistent across studies. It was hypothesized that whereas the individual effects of many individual exposures with risk may be small, collectively they may be substantial [10]. To address this, dietary inflammation scores [11,12] were developed to reflect the collective inflammation-related effects of multiple dietary factors, and found to be associated with several chronic diseases [13-16] and mortality [17,18].

Previously reported dietary inflammation scores include the dietary inflammation index (DII) [11] and empirical dietary inflammatory index (EDII) [12], recently renamed the empirical dietary inflammatory pattern (EDIP) [16]. The DII is primarily nutrient based, and so may not account other known and unknown constituents of whole foods that may contribute to inflammation. The EDIP is whole-foods based, but it is a primarily data-driven score developed in the relatively demographically, occupationally homogeneous Nurses' Health Study cohort population, which may limit its applicability to other populations. Neither the DII nor the EDIP address lifestyle contributions to inflammation. To address these limitations, Byrd *et al.*, developed novel, food frequency questionnaire (FFQ)-based dietary (DIS) and lifestyle questionnaire-based lifestyle (LIS) inflammation scores [19]. Weights for the scores' components were developed in the Reasons for

Geographic and Racial Differences in Stroke (REGARDS) cohort, with representation from black and white men and women from the United States' 48 contiguous states. The weights were based on the associations of the scores' components with a panel of circulating biomarkers of inflammation. The weights were then applied to calculating scores composed of sums of the weighted components in three separate populations. In each population, the DIS was more strongly associated with biomarkers of inflammation than were the DII and EDIP, the LIS was more strongly associated with the biomarkers than were any of the dietary inflammation scores, and the strongest association was among those in the joint highest DIS and LIS category [19]. The same association patterns were found in relation to incident CRC in a fourth population [20]. However, separate and joint associations of the DIS and LIS with mortality have not been reported.

Accordingly, we investigated separate and joint associations of the DIS and LIS with all-cause, all-cancer, and all-CVD mortality in the prospective Iowa Women's Health Study (IWHS). We hypothesized that more pro- relative to more anti-inflammatory dietary and lifestyle exposures, separately and jointly, would be associated with higher all-cause and cause-specific mortality.

## Methods

### *Study population*

A detailed description of the Iowa Women's Health Study (IWHS) design was previously reported [21]. Briefly, the IWHS is a prospective cohort study of 41,836 55 – 69-year-old Iowa women. Participants self-reported information on demographics, diet, lifestyle, family history, medical and reproductive history, and anthropometrics at baseline via a

mailed questionnaire in 1986, and have been followed for cancer incidence and mortality through 2012. Follow-up questionnaires were mailed in 1987, 1989, 1992, 1997, and 2004. The study was approved by the Minnesota Institutional Review Board (IRB), and the current analysis was approved by the Emory University IRB.

*Data collection*

A 127-item Willett food frequency questionnaire (FFQ) [22], for which the validity and reliability in the study population was reported [23], was used to collect information on dietary and vitamin and mineral supplement intakes. Participants were asked to recall their usual food consumption over the past year. Nutrient and total energy intakes for each participant were calculated by summing all nutrients and energy from all food sources using Willett's nutrient database [22]. Physical activity was assessed based on two questions about participants' frequencies of moderate and vigorous activities [24]. The use of self-reported anthropometrics was validated in the study population [23]. Body mass index (BMI) was calculated as weight divided by height squared ($kg/m_2$). After baseline, diet and physical activity were comprehensively reassessed only in 2004 when only 68% of the participants remained alive; therefore, we used only baseline exposure information for the primary analyses, but included 2004 exposure information in one of two sensitivity analyses (described further below) that supported the validity of basing the primary analyses on only baseline exposure information.

Information on deaths was obtained from the State Health Registry of Iowa and the National Death Index. Cause of death was assigned and coded by state vital registries according to the International Classification of Diseases (ICD). CVD mortality was

defined using ICD-9 codes 390-459 and ICD-10 codes I00-I99; cancer mortality was defined using ICD-9 codes 140-239 and ICD-10 codes C00-D48.

*Summary of the development and validation of the dietary (DIS) and lifestyle (LIS) inflammation scores*

Byrd *et al.* [19] previously reported the development of novel dietary and lifestyle inflammation scores (DIS and LIS, respectively) from a diverse subset (*n*=639) of the Reasons for Geographic and Racial Differences in Stroke (REGARDS) cohort, a prospective cohort study of white and black men and women in the United States' 48 contiguous states. The validity of how the scores were constructed was validated in three other populations. Briefly, to compose the DIS and LIS, 19 food groups (18 whole foods and beverages, and one composite micronutrient supplement group) and 4 lifestyle characteristics (smoking status, alcohol intake, physical activity, and body mass index) were selected *a priori* (Supplemental Table 1) based on biological plausibility, previous literature, and consideration of reconstructing the groups with other commonly used FFQs. The DIS components (dietary and supplemental intakes) were acquired via a Block 98 FFQ, which was validated in various populations [25]. The LIS components were assessed via a 30 – 45-minute telephone interview, and anthropometrics were taken at an in-home visit by trained staff. The DIS and LIS components' weights were developed via assessing the strengths of the multivariable-adjusted associations of each individual component with a panel of circulating biomarkers of inflammation (comprising high sensitivity C-reactive protein, (hsCRP), interleukin (IL)-6, IL-8, and IL-10). An individual's DIS or LIS was then calculated as the sum of their weighted components. When the DIS scoring procedures and weights were applied in three different external

populations in which different FFQs were used (a Block 98 and two Willett FFQ versions), the DIS was more strongly directly associated with circulating biomarkers of inflammation than was the DII or EDIP [19]. The estimated DIS and LIS associations with inflammation biomarkers were similar across sex and race [19].

*Calculation of the DIS and LIS in the IWHS*

To calculate the DIS and LIS in the IWHS, we used the methods described by Byrd *et al*. [19]. For the 18 whole-foods group components of the DIS, we disaggregated mixed dishes into their components using the "My Pyramid Equivalents Database" [26] and then added the disaggregated components to their respective DIS food groups. For the nineteenth component of the DIS, we calculated a supplement score by ranking supplemental micronutrient intakes into tertiles, which we assigned values of 0 – 2; then multiplied the values by +1 or -1 for a micronutrient's hypothesized anti- or pro-inflammatory properties, respectively; and then summed the values for each participant. Then, the DIS for each participant was created by transforming each component's value (all values were continuous variables) by the natural logarithm, then standardizing each to a mean of 0 and a standard deviation of 1.0 based on the baseline distribution of intake among all participants, then multiplying the component's value by its respective weight (see Supplemental Table 1), and then summing the weighted components. A higher score indicated a higher balance of pro- to anti-inflammatory dietary exposures.

The LIS comprised four 3-category components: alcohol consumption, physical activity, smoking status, and BMI. Heavy alcohol consumption was defined as >7 drinks/week, and moderate alcohol consumption as >0 to ≤7 drinks/week. Physical activity was categorized as heavy (defined as vigorous activity twice a week or moderate activity >4

times/week), moderate (vigorous activity once a week and moderate activity once a week, or moderate activity 2 – 4 times/week), or low. Baseline smoking status was categorized as "current" or "former and never". Baseline BMI was categorized as normal (18.5 – 24.99 kg/$m_2$), overweight (25 – 29.99 kg/$m_2$), or obese (≥30 kg/$m_2$). The categories for each variable were initially assigned values of 0 – 2, then the value of each LIS component was multiplied by its respective weight (see Supplemental Table 1), and the weighted values were summed. A higher score indicated a higher balance of pro- to anti-inflammatory lifestyle exposures.

*Statistical analyses*

Prior to calculating the scores and beginning the analyses, we excluded participants who left >10% of their FFQ questions blank (n=159) or reported unreasonable energy intakes (<600 or >5,000 kcal/day; n=490), leaving an analytic cohort of 33,155 participants. We calculated follow-up time as the time from the date of completing the baseline questionnaire to the date of death or the end of follow up (December 31, 2012), whichever was first [27]. We assessed correlation between the DIS and LIS using a Pearson correlation coefficient.

Participants' selected characteristics, by score quintiles, were summarized and compared using the $\chi_2$ test for categorical variables and one-way analysis of variance for continuous variables (transformed by the natural logarithm, when indicated, to meet normality assumptions). To estimate associations of the inflammation scores with all-cause, all-cancer, and all-CVD mortality, we calculated hazards ratios (HR) and their 95% confidence intervals (CI) using multivariable Cox proportional hazards regression models. The DIS and LIS were analyzed as both continuous and categorical variables

(according to quintiles of the distributions among all participants at baseline). The median values of each score quintile were used to calculate tests for trend.

Based on previous relevant literature and biological plausibility, the following variables were *a priori* included as model covariates: age (years, continuous), hormone replacement therapy use (never, past, current), comorbidity scores (0 – 3; includes 0/1 sum of yes/no for diabetes, heart disease, and cirrhosis), total energy intake (kcal/day; continuous), education level ( ≤ high school, > high school and < college, ≥ college) and marital status (currently married or not). For the DIS model, we also included physical activity (low, medium, high), smoking status (never, former, and current smoker), alcohol use (drinks/week; continuous), and BMI (kg/$m_2$; continuous) as model covariates. For the LIS model, we also included an equally-weighted dietary inflammation score (to capture the inflammation as well as other potential effects of the components) as a covariate. The proportional hazards assumption was tested for all model covariates using Schoenfeld residuals.

To assess potential interaction between the DIS and LIS in relation to mortality, we performed joint/combined (cross-classification) analyses in which the reference group was participants in the first quintiles of both of scores. $P_{interaction}$ was assessed by including a DIS*LIS interaction term in the multivariable Cox proportional hazards regression models in which the scores were analyzed as continuous variables.

To assess whether associations differed by categories of *a priori*-selected participant characteristics, we conducted separate analyses within each category of age (≤/> median age of 61 years), HRT use (current/past or never), and comorbidity status (having one or more chronic diseases [diabetes, heart disease, or cirrhosis] or not).

To assess the sensitivity of the associations to various considerations, we repeated the analyses with these variations: (i) since comprehensive data on diet and physical activity during follow up were not collected until 2004 and some participants could have changed their exposures somewhat during follow up, we assessed DIS-and LIS-mortality associations after 5, 10, 15, 20, and 25 years of follow up; (ii) assessed associations of unweighted DIS and LIS with mortality, and (iii) excluded participants who died within 1 year of follow-up (to rule out reverse causality within the first year substantially affecting the estimated associations).

All analyses were conducted using SAS statistical software, version 9.4 (SAS Institute, Cary, NC). All *P*-values were two-sided. *P*-values ≤0.05 or 95% CIs that excluded 1.0 were considered statistically significant.

**Results**

Of the 33,155 cancer-free women included in the analytic cohort, over a mean/median 22.0/26.2 person-years of follow up, 17,431 died (4,379 from cancer, and 6,574 from CVD). The Pearson correlation between the DIS and LIS was $r = 0.11$.

The baseline characteristics of the study participants according to DIS and LIS quintiles are summarized in Table 1. Participants in the highest relative to the lowest quintiles of both scores were less likely to have more than a high school education, take HRT, take a multivitamin, or have a high level of physical activity. Exclusive of components in the DIS, participants in the higher DIS quintiles also were more likely to be a current smoker,

and as would be expected from how the DIS was constructed, on average, had lower total calcium, total vitamin E, and dietary fiber intakes, and higher saturated fat intakes. Exclusive of components in the LIS, participants in the higher LIS quintiles also were more likely to have a chronic disease and, on average, had lower vitamin E intakes.

Associations of the DIS and LIS with all-cause and cause-specific mortality are shown in Table 2. Multivariable adjustment modestly attenuated all estimated associations, multivariable-adjusted associations of any given score with mortality were similar across mortality categories, and the LIS-mortality associations were stronger than the DIS-mortality associations. When the scores were analyzed as continuous variables, they were statistically significantly directly associated with risk for all mortality types; for each one point increase in the DIS, there was a 2 – 3% increase in risk for all mortality types, and for each one point increase in the LIS, there were 10%, 11%, and 14% increases in risk for all-cancer, all-cause, and all-CVD mortality, respectively. When the scores were analyzed according to quintiles, for the LIS, there were statistically significant patterns of increasing mortality risk with an increasing score, and among those in the highest relative to the lowest LIS quintiles, risk was statistically significantly 59%, 51%, and 78% higher for all-cause, all-cancer, and all-CVD mortality, respectively. For the DIS, there were statistically significant increases in mortality risk with an increasing score for all-cause and all-CVD mortality, and among those in the highest relative to the lowest DIS quintiles, risk was statistically significantly 11% higher for both all-cause and all-CVD mortality, whereas it was estimated to be non-statistically significantly 6% higher for all-cancer mortality.

The multivariable-adjusted joint/combined (cross-classification) associations of the DIS and LIS with mortality are shown in Table 3. For all mortality types, the highest risk

tended to be among participants in the highest relative to the joint DIS/LIS quintile, and were statistically significantly 88%, 85% and 90% higher for all-cause, all-cancer, and all-CVD mortality, respectively ($P_{interaction}$=0.02, 0.97, and 0.05, respectively).

As shown in Supplemental Table 2, there were no clear patterns of differences in multivariable-adjusted associations of the DIS with all-cause or cause-specific mortality according to age, HRT use, or baseline chronic disease status, or of the LIS with all-cause or cause-specific mortality according to comorbidity status. However, the association of the LIS with all-cause and CVD mortality tended to be more strongly direct among participants who were younger (≤ the median age of 61 yrs.) at baseline.

In the sensitivity analyses, for each mortality type, the estimated DIS-and LIS-mortality associations after 5, 10, 15, 20, and 25 years of follow up (Supplemental Table 3) were similar to each other and to those from the primary analyses. The direct associations of the equally-weighted DIS with all-cause and cause-specific mortality were similar to, but generally a little stronger than, those for the weighted DIS (Supplemental Table 4). Exclusion of participants who died within 1 or 2 years of follow-up (Supplement Table 5) had no appreciable impact on the associations of the DIS and LIS with all-cause mortality shown in Table 2. Finally, removal of the vitamin/mineral supplement score from the DIS yielded negligible change in the estimated associations of the DIS with all-cause or cause-specific mortality (Supplemental Table 6).

**Discussion**

Our results suggest that more pro-inflammatory diets and lifestyles, separately, but perhaps especially jointly, may be associated with higher all-cause, all-cancer, and all-CVD mortality risks. Our results also suggest that a more pro-inflammatory lifestyle may contribute more to higher mortality risk than does a more pro-inflammatory diet, and that more pro-inflammatory diets and lifestyles may be more strongly associated with all-CVD mortality than with all-cancer mortality.

Chronically higher systemic inflammation has been consistently, strongly linked to multiple chronic diseases that are major causes of premature mortality, as well as with all-cause and cause-specific mortality. In general populations, circulating biomarkers of inflammation were strongly, statistically significantly, directly associated with risk of heart disease [28-30] and type II diabetes mellitus [31,32] in large prospective studies, and with hypertension in a cross-sectional study [33]. Also, in general populations, circulating inflammation biomarkers were strongly, statistically significantly, directly associated with all-cause mortality in two prospective studies [34,35] and one case-control study [36]; with CVD mortality in a prospective study [34]; and all-cancer mortality in two prospective studies [34,37].

A substantial literature supports the plausibility of multiple individual dietary and lifestyle exposures contributing to chronic inflammation (a summary of the biological plausibility for the DIS and LIS components in relation to inflammation is provided in Supplemental Table 7 [includes references]). As summarized in Supplemental Table 7, multiple plant foods, such as vegetables, fruits, and nuts, contain a variety of constituents that have direct and/or indirect anti-inflammatory properties. A prominent indirect anti-inflammatory property is antioxidant effects. Pro-oxidant effects from dietary exposures, such as fats from meats, damage tissues, which provokes an inflammatory response.

Many antioxidants, such as vitamins C and vitamin E, counter direct and indirect pro-oxidant exposures. Certain lifestyle-related exposures may especially affect inflammation. As summarized in Supplemental Table 7, heavy alcohol intake, obesity, and smoking increase systemic inflammation, and moderate alcohol intake and physical activity reduce systemic inflammation.

Recent evidence suggests that, although the contributions of individual dietary or lifestyle exposures to inflammation may be relatively small, collectively they may be substantial. To address this, various dietary indices or scores to represent the collective effects of dietary components on inflammation were reported. These include the DII [11], the EDIP [12], and more recently, the DIS [19] reported herein. The DII and EDIP have several limitations. The DII is primarily nutrient-based [11], and so may not fully account for the various non-included known and unknown nutrients and non-nutrients in whole foods that may affect inflammation. The EDIP was developed as a primarily data-driven score among Nurses' Health Study (NHS) participants [12], an occupationally and demographically relatively homogeneous group, which may limit its applicability/generalizability to other populations. The novel inflammation biomarker panel-weighted DIS was developed to address the above limitations and the need for characterizing the collective effects of whole food/beverages/supplements to inflammation [19]. After the weights for the DIS components were developed in a subset of the REGARDS population, they were used to calculate the DIS and compare its associations with various inflammation biomarkers to those of the DII and EDIP in three other populations: the portion of the REGARDS population that was not included in developing the score (n = 14,210 with hsCRP measurements), the Markers of Adenomatous Polyps (n = 423 with hsCRP measurements), and the Calcium and Colorectal Epithelial Cell Proliferation study (n = 173 with a panel of eight inflammation

biomarkers) [19]. The associations of the DIS with circulating inflammation biomarker concentrations were stronger than those of DII and EDIP. Only one lifestyle inflammation score, the LIS, has been reported. In the same inflammation score development paper summarized above, the LIS was more strongly associated with inflammation biomarkers than were any of the dietary inflammation scores in all three study populations [19]. Furthermore, the strongest associations found in the three study populations were for participants in the highest relative to the lowest joint quintile of the DIS and LIS.

Dietary inflammation scores have been investigated in relation to chronic disease and mortality outcomes. A higher (more pro-inflammatory) DII was strongly, directly associated with incident Type II diabetes mellitus [13], CVD [14], and several cancers [15,38], including CRC [38] and prostate cancer [15]. In large prospective cohort studies, the DII was statistically significantly, directly associated with all-cause mortality in five of five [17,18,39-41], with CVD mortality in three of three [17,40,41], and with all-cancer mortality in two of two [17,40]. A higher (more pro-inflammatory) EDIP, which was developed using a primarily data-driven approach in the Nurses' Health Study (NHS), was associated with higher risk for colon and rectal cancer in the NHS and the Health Professionals Follow-up Study [42], but not with ovarian cancer incidence [43] or multiple myeloma-specific mortality [44] in the NHS. It was directly associated with CVD mortality in a small cohort study [45], and modestly directly associated with all-cause mortality in a case-control study among African-American women with ovarian cancer [46]. The DIS was statistically significantly, directly associated with incident colorectal cancer in the large, prospective NIH-AARP Diet and Health Study; the associations of the DIS with CRC were stronger than those of the DII and EDIP [20].

As noted above, although our LIS is the first reported lifestyle score designed to reflect the collective contributions of lifestyle to inflammation, components in the LIS have been combined in various ways before, and associations of the combinations, or scores, with chronic disease and mortality outcomes were reported from 14 prospective studies (includes four that involved the NHS). Score components commonly included across the studies were smoking, alcohol intake, physical activity, BMI, and diet (e.g., adherence to a Mediterranean diet score, intakes of fruit and vegetables) [47-60]. In 13 of the 14 studies, the scores were calculated such that a higher score would reflect a healthier lifestyle (i.e., the opposite direction from the LIS) [47-59]. In the seven cohort studies, the combined lifestyle score was statistically significantly associated with higher risk for coronary heart disease [47], Type 2 diabetes mellitus [48], hypertension [49], all-cancer incidence [52], incident stomach cancer [53], and incident colon and rectal cancer [50,51]. Seven studies reported strong, statistically significant associations in the hypothesized directions with all-cause mortality [54-60]. Of these studies, all four that reported associations with CVD and all-cancer mortality, found strong, statistically significant associations in the hypothesized directions [54,55,58,60].

Our study has several strengths. First, it includes a large sample size and number of deaths, and our findings were robust to multiple sensitivity analyses. Second, our DIS and LIS were validated via comparing their associations with circulating inflammation biomarkers in three study populations [19]. In that study, the DIS was more strongly associated with circulating inflammation biomarkers than was the DII and EDIP, and the LIS was more strongly associated with the inflammation biomarkers than were any of the dietary scores. Third, to our knowledge, this study is the first reported investigation of a joint association of a dietary inflammation score and a lifestyle inflammation score, with all-cause and cause-specific mortality.

Our study also has several limitations. Key exposure data were collected only at baseline (1986) and 2004, and some participants' exposures may have changed over time. Since participants do not know their outcomes at baseline, error due to this would be considered non-differential, and so would tend to attenuate the results. One cohort study reported that participants' quantile rankings on dietary intakes assessed via and FFQ were relatively stable over time [61]. Moreover, in our study, we found that, for each mortality type, DIS- and LIS-mortality associations were similar after 5, 10, 15, 20, and 25 years of follow up. Other limitations include the general limitations of food frequency questionnaires (e.g., recall error and limited food choices); however, these types of error are considered non-differential in a prospective study. Finally, all study participants were women in Iowa, 99% of whom were white, which may limit the generalizability of our findings.

In conclusion, our findings, along with previous literature, suggest that a higher balance of pro-inflammatory to anti-inflammatory diet and lifestyle exposures, alone or in interaction, may be associated with higher risk for all-cause, all-cancer, and all-CVD mortality.

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## Tables

**Table 1.** Selected baseline characteristics of participants according to quintiles of the dietary (DIS) and lifestyle (LIS) inflammation scores in the Iowa Women's Health Study (*n* = 33,155), 1986 – 2012

| Characteristics[c] | Dietary inflammation score (DIS)[a] quintiles | | | | Lifestyle inflammation score (LIS)[b] quintiles | | | |
|---|---|---|---|---|---|---|---|---|
| | 1 (N = 6,606) | 3 (N = 6,634) | 5 (N = 6,621) | *P*[d] | 1 (N = 6,602) | 3 (N = 5,617) | 5 (N = 6,634) | *P*[d] |
| Age, years | 61.4 (4.2) | 61.5 (4.2) | 61.4 (4.2) | 0.26 | 61.3 (4.2) | 61.4 (4.2) | 61.4 (4.2) | 0.07 |
| White race, % | 99.2 | 99.5 | 99.0 | <0.01 | 99.5 | 99.3 | 98.8 | <0.01 |
| > High school education, % | 50.2 | 40.9 | 28.8 | <0.01 | 48.8 | 40.3 | 33.9 | <0.01 |
| Currently married, % | 76.8 | 77.7 | 76.2 | 0.13 | 77.9 | 76.7 | 75.2 | <0.01 |
| Current or past HRT use, % | 43.0 | 38.4 | 34.5 | <0.01 | 41.9 | 39.5 | 34.2 | <0.01 |
| Take multivitamin, % | 59.5 | 30.9 | 12.3 | <0.01 | 37.4 | 34.9 | 28.8 | <0.01 |
| Have comorbidity[e], % | 16.1 | 13.8 | 13.7 | 0.01 | 9.5 | 13.2 | 22.2 | <0.01 |
| Current smoker, % | 11.0 | 13.8 | 20.6 | <0.01 | 8.6 | 25.9 | 21.7 | <0.01 |
| Past smoker, % | 23.2 | 19.0 | 16.6 | <0.01 | 23.3 | 19.6 | 16.8 | <0.01 |
| Drink alcohol, % | 49.7 | 45.6 | 40.2 | <0.01 | 75.5 | 55.6 | 17.2 | <0.01 |
| High physical activity[f], % | 38.5 | 23.6 | 13.9 | <0.01 | 50.9 | 40.4 | 13.9 | <0.01 |
| Body mass index, kg/m$^2$ | 26.8 (4.8) | 26.8 (4.9) | 27.0 (5.2) | 0.01 | 22.7 (1.7) | 26.0 (3.4) | 33.3 (4.7) | <0.01 |
| Waist:hip ratio | 0.827 (0.083) | 0.835 (0.083) | 0.848 (0.088) | <0.01 | 0.792 (0.071) | 0.834 (0.078) | 0.886 (0.081) | <0.01 |
| Total vegetables, servings/wk | 36.8 (19.4) | 24.5 (11.8) | 17.4 (8.9) | <0.01 | 26.7 (14.8) | 25.9 (15.2) | 25.7 (15.0) | <0.01 |
| Total fruit, servings/wk | 25.5 (13.1) | 18.3 (9.8) | 12.0 (8.1) | <0.01 | 19.8 (10.9) | 18.1 (11.3) | 17.6 (11.0) | <0.01 |
| Red & processed meats, servings/wk | 5.6 (3.9) | 6.7 (4.3) | 7.6 (4.9) | <0.01 | 6.1 (4.1) | 6.6 (4.2) | 7.2 (4.7) | <0.01 |
| Total energy intake, kcal/day | 1,814 (610) | 1,782 (604) | 1,825 (621) | <0.01 | 1,801 (581) | 1,807 (619) | 1,797 (620) | 0.09 |
| Total calcium intake[g], mg/1,000 kcal/day | 1,361 (598) | 1,075 (524) | 868 (458) | <0.01 | 1,186 (562) | 1,093 (562) | 1,031 (542) | <0.01 |
| Total vitamin E, mg/1,000 kcal/day | 123.0 (198.7) | 57.5 (136.3) | 27.7 (91.0) | <0.01 | 75.1 (157.8) | 65.9 (149.0) | 60.7 (146.4) | <0.01 |
| Total fat intake, g/1,000 kcal/day | 63.9 (26.0) | 68.1 (27.5) | 73.9 (29.1) | <0.01 | 67.1 (26.5) | 68.5 (27.9) | 69.6 (28.2) | <0.01 |
| Saturated fat intake, g/1,000 kcal/day | 22.1 (9.6) | 23.9 (10.3) | 26.2 (11.2) | <0.01 | 23.4 (10.1) | 24.1 (10.7) | 24.5 (10.6) | <0.01 |
| Protein intake, g/1,000 kcal/day | 88.7 (32.2) | 79.7 (29.2) | 75.3 (28.2) | <0.01 | 80.4 (28.2) | 80.9 (30.0) | 82.1 (31.2) | <0.01 |
| Carbohydrates intake, g/1,000 kcal/day | 226.6 (84.2) | 216.3 (78.2) | 216.8 (82.0) | <0.01 | 224.6 (78.3) | 217.2 (83.5) | 212.5 (79.8) | <0.01 |
| Dietary fiber intake, g/1,000 kcal/day | 24.2 (9.2) | 19.3 (7.1) | 16.2 (6.5) | <0.01 | 20.9 (8.2) | 19.5 (8.0) | 18.9 (7.8) | <0.01 |

Abbreviations: HRT, hormone replacement therapy; servings/wk, servings/week.
a For score construction, see text and Supplemental Table 1; a higher score indicates a more pro-inflammatory diet.
b For score construction, see text and Supplemental Table 1; a higher score indicates a more pro-inflammatory lifestyle.
c Continuous variables presented as mean (standard deviation), and categorical variables as percentages.
d P values from the $\chi 2$ test for categorical variables and one-way analysis of variance (ANOVA) for continuous variables.
e Self-reported history of diabetes mellitus, heart disease, and/or cirrhosis.
f Physical activity level derived from two questions regarding the frequency of moderate and vigorous physical activity (15), and categorized as high (vigorous activity twice a week or moderate activity > 4 times/week), medium (vigorous activity once a week plus moderate activity once a week, or moderate activity 2 – 4 times/week), and low.
g Total = diet + supplements.

**Table 2.** Associations[a] of the dietary (DIS) and lifestyle (LIS) inflammation scores with all-cause, all-cancer, and all-cardiovascular disease mortality in the Iowa Women's Health Study (n = 33,155), 1986 – 2012

| Mortality type/ score variable form | Inflammation scores | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Dietary[b] | | | | Lifestyle[c] | | | |
| | Minimally-adjusted model[d] | | Fully-adjusted model[e] | | Minimally-adjusted model[d] | | Fully-adjusted model[f] | |
| | HR | 95% CI | HR | 95% CI | HR | 95% CI | HR | 95% CI |
| All causes | | | | | | | | |
| Continuous | 1.05 | 1.04-1.06 | 1.03 | 1.02-1.04 | 1.14 | 1.13-1.15 | 1.11 | 1.10-1.12 |
| Quintiles | | | | | | | | |
| 1 | 1.00 | (ref) | 1.00 | (ref) | 1.00 | (ref) | 1.00 | (ref) |
| 2 | 1.01 | 0.97-1.06 | 1.00 | 0.95-1.05 | 1.14 | 1.09-1.20 | 1.10 | 1.05-1.16 |
| 3 | 1.04 | 0.99-1.09 | 1.03 | 0.98-1.08 | 1.35 | 1.28-1.42 | 1.29 | 1.22-1.35 |
| 4 | 1.12 | 1.07-1.17 | 1.07 | 1.02-1.12 | 1.28 | 1.23-1.35 | 1.20 | 1.14-1.26 |
| 5 | 1.22 | 1.16-1.28 | 1.11 | 1.05-1.16 | 1.79 | 1.70-1.87 | 1.59 | 1.51-1.67 |
| $P_{trend}$ | *<0.01* | | *<0.01* | | *<0.01* | | *<0.01* | |
| Cancer | | | | | | | | |
| Continuous | 1.05 | 1.02-1.07 | 1.02 | 1.00-1.04 | 1.11 | 1.09-1.14 | 1.10 | 1.08-1.12 |
| Quintiles | | | | | | | | |
| 1 | 1.00 | (ref) | 1.00 | (ref) | 1.00 | (ref) | 1.00 | (ref) |
| 2 | 1.00 | 0.91-1.10 | 0.98 | 0.89-1.08 | 1.05 | 0.95-1.16 | 1.03 | 0.93-1.14 |
| 3 | 0.97 | 0.88-1.07 | 0.95 | 0.86-1.05 | 1.34 | 1.21-1.48 | 1.31 | 1.19-1.45 |
| 4 | 1.12 | 1.02-1.22 | 1.06 | 0.96-1.17 | 1.21 | 1.10-1.33 | 1.17 | 1.06-1.29 |
| 5 | 1.18 | 1.07-1.29 | 1.06 | 0.96-1.17 | 1.60 | 1.46-1.76 | 1.51 | 1.37-1.66 |
| $P_{trend}$ | *<0.01* | | *0.11* | | *<0.01* | | *<0.01* | |
| CVD | | | | | | | | |
| Continuous | 1.05 | 1.03-1.06 | 1.03 | 1.01-1.05 | 1.18 | 1.16-1.20 | 1.14 | 1.12-1.16 |
| Quintiles | | | | | | | | |
| 1 | 1.00 | (ref) | 1.00 | (ref) | 1.00 | (ref) | 1.00 | (ref) |
| 2 | 0.99 | 0.92-1.07 | 0.99 | 0.92-1.07 | 1.18 | 1.09-1.28 | 1.13 | 1.05-1.23 |
| 3 | 1.03 | 0.95-1.11 | 1.03 | 0.95-1.11 | 1.31 | 1.21-1.43 | 1.24 | 1.14-1.36 |
| 4 | 1.07 | 0.99-1.16 | 1.04 | 0.96-1.12 | 1.40 | 1.30-1.52 | 1.29 | 1.19-1.40 |
| 5 | 1.20 | 1.11-1.29 | 1.11 | 1.03-1.20 | 2.10 | 1.94-2.27 | 1.78 | 1.65-1.93 |
| $P_{trend}$ | *<0.01* | | *<0.01* | | *<0.01* | | *<0.01* | |

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; DIS, dietary inflammation score; HR, hazards ratio; LIS, lifestyle inflammation score; ref, reference.

a HRs and 95% CIs from Cox proportional hazards models.

b For score construction, see text and Supplemental Table 1; a higher score indicates a more pro-inflammatory diet.

c Includes smoking, physical activity, alcohol use, and body mass index; for score construction, see text; a higher score indicates a more pro-inflammatory lifestyle.

d Covariates included age (years; continuous) and total energy intake (kcal/day; continuous).

e Covariates for DIS model included age (years; continuous), total energy intake (kcal/day; continuous); education (< high school, high school, > high school and < college, ≥ college), marital status (yes/no), smoking status (current, past, never smoker), alcohol use (servings/week; continuous), comorbidity score (includes sum of yes/no for diabetes, heart disease, and cirrhosis), hormone replacement therapy use (current, past, never), physical activity (low, medium, high), and body mass index (weight [kg]/height $[m]_2$; continuous).

f Covariates for LIS model included age (years; continuous), total energy intake (kcal/day; continuous), education (< high school, high school, > high school and < college, ≥ college), marital status (yes/no), comorbidity score (includes sum of yes/no for diabetes, heart disease, or cirrhosis), hormone replacement therapy use (current, past, never use), and equally-weighted DIS.

**Table 3.** Multivariable-adjusted joint/combined associations[a] of the dietary (DIS) and lifestyle (LIS) inflammation scores[b] with all-cause, all-cancer, and all-cardiovascular disease mortality; the Iowa Women's Health Study (*n* = 33,155), 1986 – 2012

| Mortality type/DIS quintiles | LIS quintiles | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | | 2 | | 3 | | 4 | | 5 | |
| | n | HR (95% CI) | n | HR (95% CI) | n | HR (95% CI) | n | HR (95% CI) | n | HR (95% CI) |
| All causes[c] | | | | | | | | | | |
| 1 | 1,677 | 1.00 (ref) | 1,410 | 1.08 (0.97-1.21) | 1,169 | 1.32 (1.18-1.47) | 1,183 | 1.25 (1.12-1.39) | 1,167 | 1.77 (1.60-1.96) |
| 2 | 1,424 | 1.05 (0.94-1.17) | 1,459 | 1.15 (1.03-1.27) | 1,151 | 1.33 (1.20-1.49) | 1,346 | 1.32 (1.20-1.47) | 1,255 | 1.60 (1.45-1.78) |
| 3 | 1,334 | 1.11 (0.91-1.23) | 1,476 | 1.15 (1.04-1.28) | 1,125 | 1.36 (1.22-1.52) | 1,419 | 1.31 (1.28-1.45) | 1,280 | 1.70 (1.53-1.88) |
| 4 | 1,181 | 1.13 (1.01-1.26) | 1,429 | 1.29 (1.16-1.43) | 1,073 | 1.44 (1.44-1.61) | 1,541 | 1.34 (1.36-1.48) | 1,435 | 1.82 (1.65-2.01) |
| 5 | 986 | 1.21 (1.07-1.35) | 1,381 | 1.40 (1.26-1.56) | 1,099 | 1.62 (1.62-1.81) | 1,658 | 1.42 (1.45-1.57) | 1,497 | 1.88 (1.71-2.08) |
| Cancer[d] | | | | | | | | | | |
| 1 | 1,677 | 1.00 (ref) | 1,410 | 1.09 (0.88-1.34) | 1,169 | 1.37 (1.11-1.69) | 1,183 | 1.31 (1.06-1.62) | 1,167 | 1.72 (1.40-2.11) |
| 2 | 1,424 | 1.17 (0.95-1.45) | 1,459 | 1.10 (0.89-1.36) | 1,151 | 1.44 (1.17-1.78) | 1,346 | 1.25 (1.01-1.54) | 1,255 | 1.37 (1.10-1.69) |
| 3 | 1,334 | 0.99 (0.79-1.23) | 1,476 | 1.09 (0.88-1.34) | 1,125 | 1.36 (1.10-1.69) | 1,419 | 1.21 (0.98-1.49) | 1,280 | 1.55 (1.26-1.90) |
| 4 | 1,181 | 1.10 (0.88-1.38) | 1,429 | 1.14 (0.92-1.41) | 1,073 | 1.54 (1.24-1.90) | 1,541 | 1.36 (1.11-1.66) | 1,435 | 1.88 (1.55-2.28) |
| 5 | 986 | 1.28 (1.02-1.60) | 1,381 | 1.29 (1.05-1.59) | 1,099 | 1.52 (1.23-1.89) | 1,658 | 1.37 (1.12-1.66) | 1,497 | 1.83 (1.50-2.21) |
| CVD[e] | | | | | | | | | | |
| 1 | 1,677 | 1.00 (ref) | 1,410 | 1.04 (0.87-1.23) | 1,169 | 1.25 (1.04-1.49) | 1,183 | 1.19 (1.00-1.42) | 1,167 | 1.81 (1.54-2.13) |
| 2 | 1,424 | 1.02 (0.86-1.22) | 1,459 | 1.07 (0.90-1.28) | 1,151 | 1.18 (0.98-1.41) | 1,346 | 1.30 (1.10-1.54) | 1,255 | 1.66 (1.41-1.96) |
| 3 | 1,334 | 1.02 (0.85-1.22) | 1,476 | 1.10 (0.93-1.31) | 1,125 | 1.23 (1.02-1.47) | 1,419 | 1.35 (1.15-1.59) | 1,280 | 1.75 (1.49-2.05) |
| 4 | 1,181 | 0.92 (0.76-1.11) | 1,429 | 1.19 (1.00-1.41) | 1,073 | 1.23 (1.02-1.48) | 1,541 | 1.31 (1.11-1.54) | 1,435 | 1.95 (1.67-2.28) |
| 5 | 986 | 1.08 (0.89-1.31) | 1,381 | 1.39 (1.18-1.64) | 1,099 | 1.44 (1.21-1.73) | 1,658 | 1.40 (1.20-1.65) | 1,497 | 1.90 (1.63-2.22) |

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; DIS, dietary inflammation score; HR, hazards ratio; LIS, lifestyle inflammation score; ref, reference.

a HRs and 95% CIs from Cox proportional hazards models; covariates included age (years; continuous), education (< high school, high school, > high school and < college, ≥ college), hormone replacement therapy use (current, past, never), marital status (yes, no), comorbidity scores (0-3) and total energy intake (kcal/day; continuous).

b For construction of scores, see text and Table 1; a higher score indicates a more pro-inflammatory diet/lifestyle.

c $P_{interaction}$ = 0.02; from Wald test

d $P_{interaction}$ = 0.97; from Wald test

c $P_{interaction}$ = 0.05; from Wald test

## Supplemental Tables

**Supplemental Table 1.** Components, descriptions, and weights of the components of the dietary (DIS) and lifestyle (LIS) inflammation scores in the Iowa Women's Health Study

| Components | Descriptions | Weights[a] |
|---|---|---|
| *DIS components* | | |
| Added sugars | Sweetened carbonated beverages, non-carbonated fruit drinks, candy bars, candy without chocolate, chocolate bars or pieces, dried fruits (apple, banana, papayas, peaches, pineapple, and mixed dried fruit), fruit cocktail, honey, jams, jellies, preserves, prunes, pudding, raisins or grapes, canned cherries, sweet pickles, and syrup | 0.56 |
| Apples and berries | Apple, apple juice or cider, strawberries, blueberries, apple sauce, fresh blackberries, fresh raspberries, and quince | -0.65 |
| Coffee and tea | Coffee (decaffeinated and caffeinated), and tea | -0.25 |
| Deep yellow or orange vegetables and fruit | Cantaloupe, peach, carrots, carrot juice, persimmons, and figs | -0.57 |
| Fats | Butter, gravy, margarine, and mayonnaise or other creamy dressing | 0.31 |
| Fish | Canned tuna fish, dark meat fish, and other fish | -0.08 |
| High-fat dairy | Cream, ice cream, sour cream, cream cheese, other high-fat cheese, cream sauce, sherbet or ice milk, whole milk, and yogurt | -0.14 |
| Leafy greens and cruciferous vegetables | Broccoli, cabbage or coleslaw, cauliflower, Brussels sprouts, cooked or raw spinach, kale, mustard, or chard greens, iceberg lettuce, romaine lettuce, endive, parsley, kohlrabi, and watercress | -0.14 |
| Legumes | Beans, fava beans, string beans, peas, peapods, alfalfa sprouts, and bean sprouts | -0.04 |
| Low-fat dairy | Low-fat cottage or ricotta cheese, and skim or low-fat milk | -0.12 |
| Nuts | Nuts, peanut butter, seeds, and water chestnuts | -0.44 |
| Other fruits and real fruit juices | Artichoke, Crenshaw melon, fresh coconut, fresh currants, dates, grapefruit, honeydew, apricot juice, grapefruit juice, mango juice, orange juice, other fruit juices, papaya juice, fresh pineapple or pineapple juice, prune juice, kiwi fruit, lemons, limes, mangos, nectarines, oranges, olives, papayas, tangerines, and watermelon | -0.16 |
| Other vegetables | Asparagus, beets, celery, celery juice, corn, daikon radish, eggplant, garlic, horseradish, Jerusalem artichokes, mixed vegetables, mushrooms, okra, parsnips, green or chili peppers, rutabaga, rhubarb, scallions, yellow squash, zucchini, or summer squash, turnips, and V8 juice | -0.16 |
| Poultry | Chicken with and without skin | -0.45 |
| Processed meats | Bacon, hotdogs, and processed meat | 0.68 |
| Red and organ meats | Hamburger, liver, beef, pork, and lamb as a main dish or stew, | 0.02 |
| Refined grains and starchy vegetables | Dark or white bread, brownies, home-baked or ready-made cakes, cold or other cooked breakfast cereal, cooked oatmeal, crackers, home-baked or ready-made cookies, doughnuts, granola bars or other granola, English muffin, bagels, rolls, muffins or biscuits, pancakes or waffles, pasta, home-baked or ready-made pastries, homemade or ready-made pie, popcorn, potatoes, French-fried potatoes, potato chips, brown rice, and yams | 0.72 |
| Supplement score[b] | Ranked score of supplements, including: b-carotene, B-complex vitamins, calcium, copper, folic acid, iodine, iron, magnesium, selenium, zinc, and vitamins A, C, D, and E | -0.80 |
| Tomatoes | Tomatoes, tomato juice, and tomato sauce | -0.78 |

Abbreviations: BMI, body mass index; DIS, dietary inflammation score; hsCRP, high sensitivity C-reactive protein; IL, interleukin; LIS, lifestyle inflammation score; FFQ, food frequency questionnaire; NSAID, nonsteroidal anti-inflammatory drug; REGARDS, Reasons for Geographical and Racial Differences in Stroke.

[a] Weights are β–estimates from multivariable linear regression models estimating associations of the dietary and lifestyle components with a summary inflammation biomarker score (a sum of standardized circulating hsCRP, IL-6, IL-8, and IL-10 concentrations [the latter with a negative sign] in a subset (N = 639) of the REGARDS cohort. Participants had ≤ 1 chronic disease, were < 75 years old, had plausible energy intake (500 – 6,000 kcal/day), answered ≥ 90% of FFQ questions, had hsCRP concentrations < 10 mg/L, and had non-outlying values for other inflammation biomarker concentrations. All weights are adjusted for sex, hormone replacement therapy (among women), race (Black or White), education (less than high school or high school graduate vs. some college or more), self-reported regular use of aspirin, NSAID, or lipid lowering medication (≥ 2 times/wk), region of residence in United States (Stroke Belt, Buckle, Other), season of baseline interview (Spring, Summer, Fall, or Winter), comorbidity (history of cancer, heart disease, diabetes, or chronic kidney disease), age (continuous), and total energy intake (kcal/day), and all dietary and lifestyle components in the DIS and LIS.

[b] All individual supplements were ranked into tertiles of intake and assigned values of 0, 1, or 2 for anti-inflammatory supplements and 0, -1, or -2 for pro-inflammatory supplements.

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

**Supplement Table 2.** Adjusted association[a] of the dietary (DIS) and lifestyle (LIS) inflammation scores with all-cause, all-cancer and all-CVD mortality, according to categories of risk factors; the Iowa Women's Health Study (n = 33,155), 1986-2012

| Stratification variables, score quintiles | Causes of death | | | | | |
|---|---|---|---|---|---|---|
| | All causes | | Cancer | | CVD | |
| | DIS[b] HR (95% CI) | LIS[c] HR (95% CI) | DIS HR (95% CI) | LIS HR (95% CI) | DIS HR (95%CI) | LIS HR (95% CI) |
| **Age, years** | | | | | | |
| **<=61 (n = 14,959)** | | | | | | |
| 1 | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) |
| 2 | 1.00 (0.92-1.09) | 1.11 (1.02-1.22) | 0.95 (0.82-1.10) | 0.96 (0.82-1.12) | 1.10 (0.95-1.28) | 1.19 (1.01-1.41) |
| 3 | 1.07 (0.98-1.17) | 1.39 (1.27-1.52) | 0.95 (0.82-1.11) | 1.34 (1.14-1.56) | 1.17 (0.01-1.37) | 1.35 (1.14-1.61) |
| 4 | 1.09 (1.09-1.19) | 1.27 (1.16-1.39) | 1.03 (0.89-1.20) | 1.18 (1.01-1.37) | 1.09 (0.94-1.27) | 1.40 (1.19-1.65) |
| 5 | 1.13 (1.04-1.23) | 1.85 (1.70-2.01) | 1.03 (0.88-1.19) | 1.65 (1.42-1.91) | 1.20 (1.03-1.40) | 2.20 (1.89-2.56) |
| $P_{trend}$ | *<0.01* | *<0.01* | *<0.01* | *<0.01* | *<0.01* | *<0.01* |
| **>61 (n = 18,196)** | | | | | | |
| 1 | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) |
| 2 | 1.00 (0.94-1.06) | 1.10 (1.03-1.16) | 1.00 (0.88-1.13) | 1.08 (0.95-1.22) | 0.96 (0.87-1.05) | 1.12 (1.02-1.23) |
| 3 | 1.01 (0.95-1.07) | 1.24 (1.17-1.32) | 0.95 (0.84-1.08) | 1.29 (1.13-1.47) | 0.98 (0.90-1.08) | 1.21 (1.09-1.33) |
| 4 | 1.05 (0.99-1.12) | 1.17 (1.11-1.24) | 1.08 (0.96-1.22) | 1.17 (1.03-1.32) | 1.02 (0.93-1.11) | 1.25 (1.14-1.37) |
| 5 | 1.09 (1.03-1.16) | 1.47 (1.39-1.56) | 1.08 (0.95-1.23) | 1.41 (1.24-1.59) | 1.08 (0.99-1.18) | 1.64 (1.49-1.79) |
| $P_{trend}$ | *<0.01* | *<0.01* | *<0.01* | *<0.01* | *<0.01* | *<0.01* |
| $P_{interaction}$[d] | *0.10* | *<0.01* | *0.91* | *0.03* | *0.17* | *<0.01* |
| **HRT use** | | | | | | |
| **No (n = 20,271)** | | | | | | |
| 1 | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) |
| 2 | 1.00 (0.94-1.06) | 1.10 (1.03-1.17) | 1.00 (0.88-1.13) | 1.00 (0.88-1.14) | 1.03 (0.93-1.14) | 1.14 (1.03-1.27) |
| 3 | 1.03 (0.97-1.09) | 1.25 (1.17-1.33) | 0.92 (0.81-1.04) | 1.26 (1.11-1.44) | 1.10 (0.99-1.21) | 1.22 (1.10-1.37) |
| 4 | 1.07 (1.00-1.14) | 1.17 (1.10-1.24) | 1.05 (0.93-1.19) | 1.20 (1.06-1.35) | 1.10 (0.99-1.21) | 1.21 (1.09-1.34) |
| 5 | 1.11 (1.05-1.19) | 1.56 (1.47-1.66) | 1.10 (0.97-1.24) | 1.57 (1.39-1.78) | 1.17 (1.06-1.29) | 1.68 (1.52-1.86) |
| P for trend | *<0.01* | *<0.01* | *<0.01* | *<0.01* | *<0.01* | *<0.01* |
| **Yes (n = 12,884)** | | | | | | |
| 1 | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) |
| 2 | 1.00 (0.93-1.08) | 1.11 (1.02-1.19) | 0.95 (0.82-1.10) | 1.07 (0.92-1.24) | 0.94 (0.84-1.07) | 1.12 (0.98-1.27) |
| 3 | 1.02 (0.94-1.10) | 1.34 (1.24-1.45) | 1.01 (0.87-1.17) | 1.38 (1.19-1.61) | 0.92 (0.82-1.05) | 1.27 (1.10-1.45) |
| 4 | 1.07 (0.99-1.15) | 1.24 (1.15-1.34) | 1.09 (0.94-1.26) | 1.13 (0.97-1.32) | 0.96 (0.85-1.09) | 1.42 (1.25-1.61) |
| 5 | 1.09 (1.01-1.18 | 1.65 (1.52-1.78) | 1.00 (0.85-1.17) | 1.38 (1.18-1.61) | 1.03 (0.91-1.17) | 1.94 (1.70-2.20) |
| $P_{trend}$ | *<0.01* | *<0.01* | *<0.01* | *<0.01* | *<0.01* | *<0.01* |
| $P_{interaction}$ | *0.30* | *<0.01* | *0.29* | *0.08* | *0.08* | *0.15* |
| **Comorbidity status** | | | | | | |
| **No (n = 28,394)** | | | | | | |
| 1 | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) |
| 2 | 0.98 (0.93-1.04) | 1.11 (1.05-1.17) | 0.96 (0.87-1.07) | 1.05 (0.95-1.16) | 0.98 (0.89-1.07) | 1.12 (1.02-1.23) |
| 3 | 1.02 (0.97-1.08) | 1.31 (1.24-1.38) | 0.94 (0.85-1.05) | 1.32 (1.19-1.47) | 1.03 (0.94-1.13) | 1.27 (1.15-1.40) |
| 4 | 1.07 (1.01-1.13) | 1.21 (1.14-1.27) | 1.07 (0.96-1.18) | 1.18 (1.07-1.31) | 1.01 (0.92-1.11) | 1.31 (1.20-1.44) |
| 5 | 1.11 (1.05-1.17) | 1.61 (1.52-1.70) | 1.07 (0.97-1.19) | 1.50 (1.36-1.67) | 1.11 (1.01-1.21) | 1.85 (1.69-2.02) |
| P for trend | *<0.01* | *<0.01* | *<0.01* | *<0.01* | *<0.01* | *<0.01* |
| **Yes (n = 4,761)** | | | | | | |
| 1 | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) |

Abbreviations: HR, hazards ratio; CI, confidence interval; HRT, hormone replacement therapy; DIS, dietary inflammation score; LIS, lifestyle inflammation score

a HRs and 95% CIs from Cox proportional hazards models.

b For score construction, see text and Table 1; covariates of adjusted model included age (years; continuous), education (< high school, high school, > high school and < college, ≥ college), marital status (yes/no), smoking status (current, past, never smoker), alcohol use (servings/week; continuous), comorbidity score (includes sum of yes/no for diabetes, heart disease, and cirrhosis), hormone replacement therapy use (current, past, never), physical activity (low, medium, high), body mass index (weight [kg]/height [m]$_2$; continuous), and total energy intake (kcal/day; continuous).

c Includes smoking, physical activity, alcohol use, and body mass index; for score construction, see text; a higher score indicates a more proinflammatory lifestyle; covariates of adjusted model included age (years; continuous), education (< high school, high school, > high school and < college, ≥ college), comorbidity score (includes sum of yes/no for diabetes, heart disease, and cirrhosis), hormone replacement therapy use (current, past, never use), total energy intake (kcal/day; continuous), and equally-weighted dietary inflammation score (DIS).

d *P* for interaction from stratified risk factor*score interaction term in Cox proportional hazards model.

**Supplemental Table 3.** Multivariable-adjusted associations[a] of the dietary (DIS) and lifestyle (LIS) inflammation scores with all-cause, all-cancer, and all-cardiovascular disease mortality, when stopping follow-up at 5, 10, 15, 20, and 25 years; the Iowa Women's Health Study (n = 33,155), 1986 – 2012

| tion<br>ortality types | Follow-up intervals | | | | |
|---|---|---|---|---|---|
| | 5 years | 10 years | 15 years | 20 years | 25 years |
| mortality, 5th relative to 1st quintile | | | | | |
| No. of deaths | 947 | 2,676 | 5,441 | 9,629 | 15,237 |
| HR[d] | 1.05 | 1.10 | 1.12 | 1.11 | 1.09 |
| (95% CI) | (0.85-1.30) | (0.97, 1.24) | (1.03, 1.23) | (1.04, 1.19) | (1.04, 1.15) |
| $P_{trend}$ | *0.36* | *0.07* | *< 0.0001* | *< 0.0001* | *< 0.0001* |
| mortality, 5th relative to 1st quintile | | | | | |
| No. of deaths | 385 | 1,076 | 1,994 | 3,010 | 4,033 |
| HR[d] | 0.80 | 0.98 | 1.06 | 1.06 | 1.07 |
| (95% CI) | (0.57, 1.12) | (0.81, 1.19) | (0.92, 1.22) | (0.94, 1.19) | (0.97, 1.18) |
| $P_{trend}$ | *0.72* | *0.81* | *0.26* | *< 0.0001* | *0.08* |
| ıortality, 5th relative to 1st quintile | | | | | |
| No. of deaths | 355 | 983 | 2,008 | 3,636 | 5,745 |
| HR[d] | 1.18 | 1.18 | 1.16 | 1.13 | 1.10 |
| (95% CI) | (0.84, 1.67) | (0.96, 1.44) | (1.00, 1.33) | (1.02, 1.26) | (1.01, 1.20) |
| $P_{trend}$ | *0.49* | *0.10* | *< 0.001* | *< 0.01* | *< 0.01* |
| mortality, 5th relative to 1st quintile | | | | | |
| No. of deaths | 947 | 2,676 | 5,441 | 9,629 | 15,237 |
| HR[d] | 1.54 | 1.54 | 1.59 | 1.61 | 1.61 |
| (95% CI) | (1.24, 1.91) | (1.35, 1.75) | (1.46, 1.74) | (1.51, 1.72) | (1.52, 1.69) |
| $P_{trend}$ | *< 0.01* | *< 0.0001* | *0.006* | *0.01* | *0.06* |
| mortality, 5th relative to 1st quintile | | | | | |
| No. of deaths | 385 | 1,076 | 1,994 | 3,010 | 4,033 |
| HR[d] | 1.74 | 1.61 | 1.62 | 1.52 | 1.56 |
| (95% CI) | (1.25, 2.41) | (1.33, 1.96) | (1.41, 1.87) | (1.36, 1.71) | (1.41, 1.72) |
| $P_{trend}$ | *< 0.01* | *< 0.0001* | *< 0.0001* | *< 0.0001* | *< 0.0001* |
| ıortality, 5th relative to 1st quintile | | | | | |
| No. of deaths | 355 | 983 | 2,008 | 3,636 | 5,745 |
| HR[d] | 1.68 | 1.63 | 1.79 | 1.87 | 1.78 |
| (95% CI) | (1.16, 2.43) | (1.32, 2.02) | (1.54, 2.07) | (1.68, 2.09) | (1.64, 1.94) |
| $P_{trend}$ | *0.02* | *< 0.0001* | *< 0.0001* | *< 0.0001* | *< 0.0001* |

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; DIS, dietary inflammation score; HR, hazards ratio; LIS, lifestyle inflammation score.

[a] HRs and 95% CIs from Cox proportional hazards models.

[b] For score construction, see text and Supplemental Table 1; a higher score indicates a more pro-inflammatory diet.

[c] Includes smoking, physical activity, alcohol use, and body mass index; for score construction, see text; a higher score indicates a more pro-inflammatory lifestyle.

[d] Covariates for DIS model included age (years; continuous), total energy intake (kcal/day; continuous), education (< high school, high school, > high school and < college, ≥ college), marital status (yes/no), smoking status (current, past, never smoker), alcohol use

(servings/week; continuous), comorbidity score (includes sum of yes/no for diabetes, heart disease, and cirrhosis), hormone replacement therapy use (current, past, never), physical activity (low, medium, high), and body mass index (weight [kg]/height $[m]_2$; continuous). Covariates for LIS model included age (years; continuous), total energy intake (kcal/day; continuous), education (< high school, high school, > high school and < college, ≥ college), marital status (yes/no), comorbidity score (includes sum of yes/no for diabetes, heart disease, or cirrhosis), hormone replacement therapy use (current, past, never use), and equally-weighted DIS.

**Supplement Table 4.** Associations[a] of the equally-weighted dietary (DIS) and lifestyle (LIS) inflammation scores with all-cause, all-cancer and all-CVD mortality in the Iowa Women's Health Study (n = 33,155), 1986 – 2012

| | Inflammation scores | | | |
|---|---|---|---|---|
| **Cause of deaths, variable forms** | **Dietary[b]** | | **Lifestyle[c]** | |
| | Adjusted HR[d] | 95% CI | Adjusted HR[e] | 95% CI |
| All causes | | | | |
| Continuous | 1.04 | 1.03-1.05 | 1.15 | 1.14-1.17 |
| Quintiles | | | | |
| 1 | 1.00 (ref) | | 1.00 (ref) | |
| 2 | 1.01 | 0.96-1.06 | 1.15 | 1.10-1.21 |
| 3 | 1.05 | 1.00-1.10 | 1.29 | 1.23-1.36 |
| 4 | 1.07 | 1.02-1.12 | 1.43 | 1.36-1.50 |
| 5 | 1.17 | 1.11-1.22 | 1.85 | 1.76-1.96 |
| $P_{trend}$ | *<0.01* | | *<0.01* | |
| Cancer | | | | |
| Continuous | 1.03 | 1.01-1.05 | 1.15 | 1.12-1.18 |
| Quintiles | | | | |
| 1 | 1.00 (ref) | | 1.00 (ref) | |
| 2 | 0.92 | 0.83-1.01 | 1.05 | 0.95-1.16 |
| 3 | 1.01 | 0.92-1.11 | 1.22 | 1.11-1.34 |
| 4 | 1.04 | 0.94-1.14 | 1.35 | 1.22-1.50 |
| 5 | 1.09 | 0.99-1.20 | 1.75 | 1.57-1.95 |
| $P_{trend}$ | *0.01* | | *<0.01* | |
| CVD | | | | |
| Continuous | 1.03 | 1.01-1.05 | 1.17 | 1.14-1.19 |
| Quintiles | | | | |
| 1 | 1.00 (ref) | | 1.00 (ref) | |
| 2 | 1.06 | 0.98-1.14 | 1.20 | 1.11-1.31 |
| 3 | 1.01 | 0.93-1.10 | 1.36 | 1.25-1.47 |
| 4 | 1.06 | 0.98-1.14 | 1.47 | 1.35-1.60 |
| 5 | 1.17 | 1.08-1.26 | 1.97 | 1.80-2.15 |
| $P_{trend}$ | *<0.01* | | *<0.01* | |

Abbreviations: CI, confidence interval, DIS, dietary inflammation score; HR, hazards ratio; LIS, lifestyle inflammation score

a HRs from Cox proportional hazards models.

b For score construction, see text and Table 1; a higher score indicates a more proinflammatory diet.

c Includes smoking, physical activity, alcohol use, and body mass index; for score construction, see text; a higher score indicates a more proinflammatory lifestyle.

d Covariates for DIS model included age (years; continuous), education (< high school, high school, > high school and < college, ≥ college), marital status (yes, no), smoking status (current, past, never smoker), alcohol use (servings/week; continuous), comorbidity score (includes sum of yes/no for diabetes, heart disease, and cirrhosis), hormone replacement therapy use (current, past, never), physical activity (low, medium, high), body mass index (weight [kg]/height [m]$_2$; continuous), and total energy intake (kcal/day; continuous).

e Covariates for LIS model included age (years; continuous), education (< high school, high school, > high school and < college, ≥ college), comorbidity score (includes sum of yes/no for diabetes, heart disease, and cirrhosis), hormone replacement therapy use (current, past, never use), total energy intake (kcal/day; continuous), and equally-weighted DIS.

**Supplement Table 5.** Multivariable-adjusted associations[a] of the dietary (DIS) and lifestyle (LIS) inflammation scores with all-cause mortality after excluding study participants who died within one or two years of follow up; the Iowa Women's Health Study (n = 33,155), 1986 – 2012

| | Inflammation scores | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Dietary[b] | | | | Lifestyle[c] | | | |
| | Minimally adjusted model[d] | | Fully adjusted model[e] | | Minimally adjusted model[d] | | Fully adjusted model[f] | |
| | HR | 95% CI | HR | 95% CI | HR | 95% CI | HR | 95% CI |
| **Excluding** | | | | | | | | |
| **1 year (n = 33,053)** | | | | | | | | |
| Continuous | 1.05 | 1.04-1.06 | 1.03 | 1.02-1.04 | 1.14 | 1.13-1.15 | 1.11 | 1.1-1.12 |
| Quintiles | | | | | | | | |
| 1 | 1.00 (ref) | | 1.00 (ref) | | 1.00 (ref) | | 1.00 (ref) | |
| 2 | 1.01 | 0.97-1.06 | 1.00 | 0.95-1.05 | 1.14 | 1.08-1.19 | 1.10 | 1.05-1.15 |
| 3 | 1.04 | 0.99-1.09 | 1.03 | 0.98-1.08 | 1.34 | 1.28-1.42 | 1.29 | 1.22-1.35 |
| 4 | 1.11 | 1.06-1.17 | 1.06 | 1.01-1.12 | 1.28 | 1.22-1.35 | 1.20 | 1.14-1.26 |
| 5 | 1.22 | 1.16-1.27 | 1.10 | 1.05-1.16 | 1.79 | 1.70-1.87 | 1.59 | 1.52-1.67 |
| $P_{trend}$ | *<0.01* | | *<0.01* | | *<0.01* | | *<0.01* | |
| **2 years (n = 32,891)** | | | | | | | | |
| Continuous | 1.05 | 1.04-1.06 | 1.03 | 1.02-1.04 | 1.14 | 1.13-1.15 | 1.11 | 1.1-1.12 |
| Quintiles | | | | | | | | |
| 1 | 1.00 (ref) | | 1.00 (ref) | | 1.00 (ref) | | 1.00 (ref) | |
| 2 | 1.01 | 0.96-1.06 | 0.99 | 0.95-1.04 | 1.13 | 1.08-1.19 | 1.10 | 1.04-1.15 |
| 3 | 1.04 | 0.99-1.09 | 1.02 | 0.98-1.07 | 1.34 | 1.27-1.41 | 1.28 | 1.22-1.35 |
| 4 | 1.11 | 1.06-1.17 | 1.06 | 1.01-1.12 | 1.28 | 1.22-1.35 | 1.20 | 1.14-1.26 |
| 5 | 1.21 | 1.16-1.27 | 1.10 | 1.05-1.16 | 1.78 | 1.70-1.87 | 1.59 | 1.52-1.67 |
| $P_{trend}$ | *<0.01* | | *<0.01* | | *<0.01* | | *<0.01* | |

Abbreviations: CI, confidence interval, DIS, dietary inflammation score; HR, hazards ratio; LIS, lifestyle inflammation score

a HRs from Cox proportional hazards models.

b For score construction, see text and Table 1; a higher score indicates a more proinflammatory diet.

c Includes smoking, physical activity, alcohol use, and body mass index; for score construction, see text.

d Covariates included age (years; continuous) and total energy intake (kcal/day; continuous).

e Covariates for DIS model included age (years; continuous), education (< high school, high school, > high school and < college, ≥ college), marital status (yes, not), smoking status (current, past, never smoker), alcohol use (servings/week; continuous), comorbidity score (includes sum of yes/no for diabetes, heart disease, and cirrhosis), hormone replacement therapy use (current, past, never), physical activity (low, medium, high), body mass index (weight [kg]/height $[m]_2$; continuous), and total energy intake (kcal/day; continuous).

f Covariates for LIS model included age (years; continuous), education (< high school, high school, > high school and < college, ≥ college), family history of colorectal cancer in a first-degree relative (yes/no), comorbidity score (includes sum of yes/no for diabetes, heart disease, and cirrhosis), hormone replacement therapy use (current, past, never use), total energy intake (kcal/day; continuous), and equally-weighted DIS.

**Supplement Table 6.** Fully-adjusted associations[a] of the dietary inflammation score (DIS),[b] minus the supplemental vitamin/mineral component, with all-cause, all-cancer and all-CVD mortality in the Iowa Women's Health Study (n = 33,155), 1986 – 2012

| DIS variable forms | Causes of death | | | | | |
|---|---|---|---|---|---|---|
| | All cause | | All cancer | | CVD | |
| | HR | 95% CI | HR | 95% CI | HR | 95% CI |
| Continuous | 1.03 | (1.02-1.04) | 1.01 | (0.99-1.03) | 1.03 | (1.01-1.05) |
| Quintiles | | | | | | |
| 1 | 1.00 | (ref) | 1.00 | (ref) | 1.00 | (ref) |
| 2 | 1.02 | (0.97-1.07) | 0.96 | (0.87-1.05) | 1.00 | (0.93-1.09) |
| 3 | 1.04 | (0.99-1.09) | 0.98 | (0.89-1.07) | 1.01 | (0.93-1.09) |
| 4 | 1.07 | (1.02-1.13) | 0.96 | (0.87-1.06) | 1.05 | (0.97-1.13) |
| 5 | 1.13 | (1.08-1.19) | 1.04 | (0.95-1.15) | 1.12 | (1.04-1.21) |
| *Ptrend* | *<0.01* | | *<0.01* | | *<0.01* | |

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; DIS, dietary inflammation score; HR, hazards ratio; LIS, lifestyle inflammation score.

[a] From Cox proportional hazards regression; covariates included age (years; continuous), total energy intake (kcal/day; continuous); education (< high school, high school, > high school and < college, ≥ college), marital status (yes/no), smoking status (current, past, never smoker), alcohol use (servings/week; continuous), comorbidity score (includes sum of yes/no for diabetes, heart disease, and cirrhosis), hormone replacement therapy use (current, past, never), physical activity (low, medium, high), and body mass index (weight [kg]/height $[m]_2$; continuous).

[b] For score construction, see text and Supplemental Table 1; for this table, we excluded the supplemental vitamin/mineral component, and re-calculated the DIS; a higher score indicates a more pro-inflammatory diet.

**Supplemental Table 7.** DIS and LIS components and rationales for inclusion

| Components | Mechanisms involved in anti-/pro-inflammation |
|---|---|
| **DIS components** | |
| *Anti-inflammation* | |
| Apples and berries | Contain flavonoids and other antioxidants, which decrease oxidative stress and inflammation [1-3] |
| Coffee and tea | Tea contains phenolic compounds, which have antioxidant properties and reduce hepatic triglyceride accumulation [4]; coffee contains multiple anti-oxidants [5,6]; tea and coffee contain caffeine, which inhibits IL-1β production [7] |
| Deep yellow or orange vegetables and fruits | Contain provitamin A (β-carotene, β-cryptoxanthin, and α-carotene) carotenoids, which are known antioxidants [8,9] |
| Fish | Contain long-chain n-3 PUFAs (omega-3 fatty acids), which increase production of prostaglandin E3, and decrease the production of thromboxane A2 and leukotriene B4 formation (an inducer of inflammation) [10-12] |
| High-/low-fat dairy | Contain calcium and bioactive proteins, which decrease oxidative damage in the gut by binding bile acids and free fatty acids [13-15] |
| Leafy greens and cruciferous vegetables | Contain antioxidants (such as β-carotene, folacin, magnesium, calcium, lutein and glucosinolates), which have direct antioxidant effects or are essential components of antioxidant enzymes [16-22] |
| Legumes | A rich source of fermentable dietary fibers that are precursors of luminal butyrate, which has well-known anti-inflammatory properties in the colon [23,24] |
| Nuts | Contain *l*-arginine, which decreases platelet aggregation and monocyte adhesion and improves endothelium-dependent dilation (a precursor of the endogenous vasodilator nitric oxide); Contain n-3 PUFAs [25-28]; |
| Other fruits and real fruit juices | Contain flavonoids and other antioxidants (such as vitamin C, limonene, and neohesperidin) with mechanisms similar to those described above [29 33] |
| Other vegetables | Contain antioxidants and polyphenols with mechanisms similar to those described above [33-36] |
| Poultry | Contain *l*-arginine (mechanisms similar to those described in "Nuts" [37]; Inversely associated with inflammation; pro-inflammatory saturated fat content low [38] |
| Supplement score | Contains vitamins and minerals that are either direct anti- or pro-oxidants c are essential components of antioxidant enzymes, and are associated with biomarkers of inflammation (CRP and IL-6) and oxidative stress (F2-isoprostanes) [14,34,37,39-45] |
| Tomatoes | Contain lycopene, which is a potent singlet oxygen quencher and a powerful antioxidant [41,46-48] |
| *Pro-inflammation* | |
| Added sugar | Increases oxidative stress through oxidation of membrane lipids, proteins, lipoproteins, and DNA [49] |

| | |
|---|---|
| Other fats | Contain saturated fatty acids (SFA), which stimulate inflammatory respons via a pathway involving Toll-like receptors (TLR) [50]; contain polyunsaturated fatty acids (PUFA), which can be converted into arachidonic acid (the major substrate for production of eicosanoids, which play an important role in activating inflammatory responses) [51] |
| Processed meats | Contain saturated fats (see above); contain heme iron, which increases the bioavailability of iron, and in turn increases oxidative stress; contain nitrate and nitrite, with suspected proinflammatory properties [37,52] |
| Red and organ meat | Contain saturated fats and heme iron [37,38,53]; mechanisms described above |
| Refined grains and starchy vegetables | Contain emulsifiers, which increase inflammation when broken down in the gut [54] |
| **LIS components** | |
| *Anti-inflammation* | |
| Moderate alcohol intake | Increases concentrations of HDL cholesterol and apolipoprotein A1, which inhibit production of IL-6 or its action on hepatocytes [55] |
| Physical activity | Produces episodic elevations in skeletal muscle-derived IL-6, which trigger an anti-inflammatory cascade via inhibiting the production of pro-inflammatory cytokines (TNF-α and IL-1β) via stimulation of their antagonistic receptors [56,57] |
| *Pro-inflammation* | |
| Current smoker | Tobacco smoke contains multiple toxicants and pro-oxidants that harm tissues, upregulating cytokines and acute-phase reactants [58] |
| Heavy alcohol intake | Alcohol directly induces oxidative stress, through oxidation of ethanol to acetaldehyde [59,60] |
| Obesity and overweight | Accumulation of lipids in adipose tissue leads to initiation of an inflammatory process through the production of proinflammatory cytokines and chemokines, including TNF-α, IL-6, leptin, MCP-1, and PAI-1, by the adipocytes [61-63] |

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