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Novel Dietary and Lifestyle Inflammation Scores Directly Associated with All-Cause, All-Cancer, and All-Cardiovascular Disease Mortality Risks Among Women

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ABSTRACT

Background: Exogenous exposures collectively may contribute to chronic, low-grade inflammation and increase risks for major chronic diseases and mortality. We previously developed, validated, and reported a novel, FFQ-based and lifestyle questionnaire–based, inflammation biomarker panel–weighted, predominantly whole foods–based 19-component dietary inflammation score (DIS) and 4-component lifestyle inflammation score (LIS; comprising physical activity, alcohol intake, BMI, and current smoking status). Both scores were more strongly associated with circulating biomarkers of inflammation in 3 populations than were previously reported dietary inflammation indices. Associations of the DIS and LIS with mortality risk have not been reported.

Objectives: To investigate separate and joint associations of the DIS and LIS with all-cause, all-cancer, and cardiovascular disease (CVD) mortality risks in the prospective Iowa Women's Health Study (1986–2012; $n = 33{,}155$ women, ages 55–69 years, of whom 17,431 died during follow-up, including 4379 from cancer and 6574 from CVD).

Methods: We summed each study participant's scores' components, weighted by their published weights, to yield the participant's inflammation score; 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 HRs for all-cause mortality were 1.11 (95% CI: 1.05–1.16) and 1.60 (95% CI: 1.53–1.68), respectively; for all-cancer mortality were 1.07 (95% CI: 0.97–1.17) and 1.51 (95% CI: 1.38–1.66), respectively; and for CVD mortality were 1.12 (95% CI: 1.03–1.21) and 1.79 (95% CI: 1.66–1.94), respectively (all P_{trend} values < 0.01). Among those in the highest relative to the lowest joint LIS/DIS quintiles, the HRs for all-cause, all-cancer, and all-CVD mortality were 1.88 (95% CI: 1.71–2.08), 1.82 (95% CI: 1.50–2.20), and 1.92 (95% CI: 1.64–2.24), respectively.

Conclusions: More pro-inflammatory diets and lifestyles, separately but especially jointly, may be associated with higher all-cause, all-cancer, and all-CVD mortality risks among women. *J Nutr* 2021;151:930–939.

Keywords: mortality, inflammation, diet, lifestyle, inflammation scores, cohort studies

Introduction

Cancer and cardiovascular diseases (CVDs) 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 risks (2–5). Individual dietary and lifestyle factors have been linked to chronic inflammation (6, 7), several chronic diseases (8, 9), and mortality risks (8, 9). However, many of the associations of the individual factors, especially the dietary factors, with these risks 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 were found to be associated with several chronic diseases (13–16) and mortality risks (17, 18).

Previously reported dietary inflammation scores, which include the dietary inflammatory index (DII) (11) and empirical

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dietary inflammatory index (12), recently renamed the empirical dietary inflammatory pattern (EDIP) (16), have important limitations. The DII is primarily nutrient based, and so may not account for 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 and occupationally homogeneous Nurses' Health Study (NHS) 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. (19) developed the novel, FFQ-based dietary inflammation score (DIS) and lifestyle questionnaire–based lifestyle inflammation score (LIS). 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 3 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 colorectal cancer (CRC) in a fourth population (20). However, separate and joint associations of the DIS and LIS with mortality risks 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 risks in the prospective Iowa Women's Health Study (IWHS). We hypothesized that more pro-inflammatory relative to more anti-inflammatory dietary and lifestyle exposures, separately and jointly, would be associated with higher all-cause and cause-specific mortality risks. We also investigated associations of unweighted DIS and LIS with mortality, and compared them with associations between the weighted scores and mortality to explore the extent to which associations of the components collectively with risk may be inflammation-related.

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Supplemental Tables 1–8 are available from the "Supplementary data" link in the online posting of the article and from the same link in the table of contents at http://academic.oup.com/jn.
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Abbreviations used: CRC, colorectal cancer; CVD, cardiovascular disease; DII, dietary inflammation index; DIS, dietary inflammation score; EDIP, empirical dietary inflammatory pattern; hsCRP, high-sensitivity C-reactive protein; HRT, hormone replacement therapy; ICD-9, International Classification of Diseases, Ninth Edition; ICD-10, International Classification of Diseases, Tenth Edition; IRB, Institutional Review Board; IWHS, Iowa Women's Health Study; LIS, lifestyle inflammation score; NHS, Nurses' Health Study; REGARDS, Reasons for Geographic and Racial Differences in Stroke.

Methods

Study population

A detailed description of the IWHS design was previously reported (21). Briefly, the IWHS is a prospective cohort study of 41,836 Iowa women 55–69 years old. Participants were identified through the 1985 Iowa Department of Transportation's current drivers list, of whom half with valid Iowa mailing addresses were mailed a questionnaire. Of these prospective participants, 41,836 (42.6%) completed the questionnaire and were eligible for study enrollment. 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 incidences 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 FFQ (22), for which the validity and reliability in the study population were 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 2 questions about participants' frequencies of moderate and vigorous activities (24). The use of self-reported anthropometrics was validated in the study population (23). 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 the 2004 exposure information in 1 of 2 sets of 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, Ninth and Tenth Editions (ICD-9 and ICD-10). 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 DIS and LIS

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 participants in the REGARDS study, a prospective cohort study of white and black men and women in the United States' 48 contiguous states. Briefly, to compose the DIS and LIS, 19 food groups (18 whole foods and beverages and 1 composite micronutrient supplement group) and 4 lifestyle characteristics (smoking status, alcohol intake, physical activity, and BMI) were selected a priori (**Supplemental Table 1**) based on biological plausibility, previous literature, and consideration of reconstructing the groups with commonly used FFQs and lifestyle questionnaires. 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- to 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), IL-6, IL-8, and IL-10]. An individual's DIS or LIS was then calculated as the sum of their weighted components. Importantly, when the DIS scoring procedures and weights were applied in 3 different external populations in which different FFQs were used [a Block98 and 2 Willett FFQ versions (22, 25–28)], 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

We calculated the DIS and LIS in the IWHS using the methods described by Byrd et al. (19). Briefly, for the 18 whole-foods group components of the DIS, we disaggregated mixed dishes into their components using the "My Pyramid Equivalents Database" (29) and then added the disaggregated components to their respective DIS food groups. For the nineteenth DIS component, we calculated a supplement score by ranking supplemental micronutrient intakes into tertiles, to which we assigned values of 0–2. We then multiplied the values by +1 or −1 for a micronutrient's hypothesized anti- or pro-inflammatory properties, respectively, and summed the values for each participant. We created the DIS for each participant by transforming each component's value (all values were continuous variables) by the natural logarithm, standardizing each to a mean of 0 and a standard deviation of 1.0 based on the baseline distribution of intake among all participants, 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 4 categorical components: alcohol consumption, physical activity, smoking status, and BMI. We defined the components' categories so as to correspond with those from the score development/validation study. Alcohol consumption was defined as heavy (>7 drinks/week; 98 g/week), moderate (>0 to ≤7 drinks/week; 98 g/week), or none. 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" (former and never were combined because former smoking was not considered to be contributing to current inflammation). Baseline BMI was categorized as normal/underweight (<25 kg/m^2; inclusion/exclusion of underweight with normal weight made no difference in the development/validation study or the present study), 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 had a history of cancer (other than nonmelanoma skin cancer) at baseline (n = 3830), left >10% of their FFQ questions blank (n = 3519), reported unreasonable energy intakes (<600 or >5000 kcal/d; n = 270), were missing data on any LIS component (n = 881), or had other invalid data or were missing key covariates (n = 181), 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 (31 December 2012), whichever was first (30). We assessed correlation between the DIS and LIS using a Spearman correlation coefficient.

We summarized and compared participants' selected characteristics across score quintiles using the χ^2 test for categorical variables and 1-way ANOVA 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 risks, we calculated HRs and their 95% CIs using multivariable Cox proportional hazards regression models. We analyzed the DIS and LIS as both continuous and categorical variables (categorized according to quintiles of the distributions among all participants at baseline). We used the median values of the scores' quintiles to calculate tests for trend.

Based on previous relevant literature and biological plausibility, we included the following variables a priori as model covariates: age (years, continuous), hormone replacement therapy (HRT) use (never, past, current), a comorbidity score (0–3; includes 0/1 sums 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 (pack-years), alcohol use (drinks/week; continuous), and BMI (kg/m^2; continuous) as model covariates. For the LIS model, we also included as model covariates former smoking history (yes/no), since it is not included in the LIS but has been associated with higher mortality risk, and an unweighted dietary inflammation score (an unweighted score would capture both the inflammation and other potential effects of the components). We tested the proportional hazards assumption for all model covariates using Schoenfeld residuals.

To assess potential interactions between the DIS and LIS in relation to mortality risks, we performed joint/combined (cross-classification) analyses in which the reference group was participants in the first quintiles of both scores. We assessed $P_{interaction}$ 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 1 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 several variations. 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 *1*) assessed DIS and LIS mortality associations after 5, 10, 15, 20, and 25 years of follow-up; and *2*) incorporated exposure data from the 2004 follow-up questionnaire 2 ways. For the latter, among those who had not died prior to 2004, we assessed using both the mean of their baseline (1986) and 2004 follow-up DIS and LIS and only their 2004 DIS and LIS. We also assessed associations of an unweighted DIS and LIS with mortality risks. The weighted scores for our primary analyses are mechanistic scores designed to reflect the contributions of diet and lifestyle to systemic inflammation and, in turn, their inflammation-related associations with disease and mortality risks. The unweighted scores are not limited by the contributions of diet and lifestyle to inflammation, and were intended to more fully capture all mechanisms involved in the associations of their components with risk. Thus, we hypothesized that the unweighted scores would be more strongly associated with risk than would the weighted scores. In other sensitivity analyses, we excluded participants who died within the first 1 or 2 years of follow-up (to rule out reverse causality within early follow-up substantially affecting the estimated associations), and assessed the sensitivity of the DIS and mortality risk associations to removal of the supplement score component from the DIS.

We conducted all analyses using SAS statistical software, version 9.4 (SAS Institute). All P values were 2-sided. We considered P values ≤ 0.05 or 95% CIs that excluded 1.0 to be 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 (4379 from cancer, and 6574 from CVD). The Spearman 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. Participants in the higher DIS quintiles, aside from components in the DIS, also were more likely to

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

	DIS[1] quintiles				LIS[2] quintiles			
Characteristics	1 $n = 6608$	3 $n = 6632$	5 $n = 6622$	P[3]	1 $n = 6602$	3 $n = 5617$	5 $n = 6634$	P[3]
Age, y	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,[4] %	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,[5] %	38.5	23.6	13.9	<0.01	50.9	40.4	13.9	<0.01
BMI, 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/d	1814 ± 610	1782 ± 604	1825 ± 621	<0.01	1801 ± 581	1807 ± 619	1797 ± 620	0.09
Total calcium intake,[6] mg · (1000 kcal)$^{-1}$ · day^{-1}	1361 ± 598	1075 ± 524	868 ± 458	<0.01	1186 ± 562	1093 ± 562	1031 ± 542	<0.01
Total vitamin E,[6] mg · (1000 kcal)$^{-1}$· day^{-1}	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 · (1000 kcal)$^{-1}$ · day^{-1}	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 · (1000 kcal)$^{-1}$ · day^{-1}	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 · (1000 kcal)$^{-1}$ · day^{-1}	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 · (1000 kcal)$^{-1}$ · day^{-1}	226.6 ± 84.2	216.3 ± 78.2	216.8 ± 82.0	<0.01	2254.6 ± 78.3	217.2 ± 83.5	212.5 ± 79.8	<0.01
Dietary fiber intake, g · (1000 kcal)$^{-1}$ · day^{-1}	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

Continuous variables are presented as means ± SDs and categorical variables as percentages. Abbreviations: DIS, dietary inflammation score; HRT, hormone replacement therapy; LIS, lifestyle inflammation score; wk, week.

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

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

[3] P values are from the χ^2 test for categorical variables and 1-way ANOVA for continuous variables (transformed by the natural logarithm when indicated to meet the normality assumption).

[4] Self-reported history of diabetes mellitus, heart disease, and/or cirrhosis.

[5] Physical activity level derived from 2 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/wk), medium (vigorous activity once a week plus moderate activity once a week, or moderate activity 2–4 times/wk), and low.

[6] Total = diet + supplements.

TABLE 2 Associations of the dietary and lifestyle inflammation scores with all-cause, all-cancer, and all-cardiovascular disease mortality risk in the Iowa Women's Health Study ($n = 33,155$), 1986–2012

	Inflammation scores					
	Dietary[1]			Lifestyle[2]		
Mortality type/score variable form	Case count	Minimally adjusted model[3] HR (95% CI)	Fully adjusted model[4] HR (95% CI)	Case count	Minimally adjusted model[3] HR (95% CI)	Fully adjusted model[5] 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	3298	1.00 (ref)	1.00 (ref)	2921	1.00 (ref)	1.00 (ref)
2	3370	1.01 (0.97–1.06)	1.00 (0.95–1.05)	3489	1.14 (1.09–1.20)	1.11 (1.05–1.16)
3	3444	1.04 (0.99–1.09)	1.02 (0.97–1.07)	3021	1.35 (1.28–1.42)	1.29 (1.23–1.36)
4	3579	1.12 (1.07–1.17)	1.08 (1.02–1.13)	3785	1.29 (1.22–1.35)	1.21 (1.15–1.27)
5	3740	1.22 (1.16–1.28)	1.11 (1.05–1.16)	4215	1.79 (1.70–1.87)	1.60 (1.53–1.68)
P_{trend}	—	<0.01	<0.01	—	<0.01	<0.01
Cancer						
Continuous	—	1.04 (1.02–1.07)	1.02 (1.00–1.04)	—	1.11 (1.09–1.14)	1.10 (1.08–1.13)
Quintiles						
1	846	1.00 (ref)	1.00 (ref)	764	1.00 (ref)	1.00 (ref)
2	850	1.00 (0.91–1.10)	0.98 (0.89–1.08)	839	1.05 (0.95–1.16)	1.03 (1.94–1.14)
3	822	0.97 (0.88–1.07)	0.96 (0.87–1.06)	804	1.33 (1.21–1.48)	1.31 (1.19–1.45)
4	921	1.12 (1.02–1.22)	1.07 (0.97–1.18)	944	1.21 (1.10–1.33)	1.18 (1.07–1.29)
5	940	1.18 (1.07–1.29)	1.07 (0.97–1.17)	1028	1.58 (1.44–1.74)	1.51 (1.38–1.66)
P_{trend}	—	<0.01	0.09	—	<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	1265	1.00 (ref)	1.00 (ref)	1038	1.00 (ref)	1.00 (ref)
2	1269	0.99 (0.92–1.07)	0.99 (0.91–1.07)	1292	1.18 (1.09–1.28)	1.14 (1.05–1.24)
3	1314	1.03 (0.95–1.11)	1.02 (0.94–1.10)	1046	1.31 (1.21–1.43)	1.25 (1.15–1.36)
4	1316	1.07 (0.99–1.16)	1.05 (0.97–1.13)	1469	1.40 (1.30–1.52)	1.30 (1.20–1.40)
5	1410	1.20 (1.11–1.29)	1.12 (1.03–1.21)	1729	2.07 (1.92–2.24)	1.79 (1.66–1.94)
P_{trend}	—	<0.01	<0.01	—	<0.01	<0.01

HRs and 95% CIs are from Cox proportional hazards models. Abbreviations: CVD, cardiovascular disease; DIS, dietary inflammation score; LIS, lifestyle inflammation score; ref, reference.

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

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

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

[4] Covariates for DIS model included age (years; continuous), total energy intake (kcal/d; continuous); education (<high school, high school, >high school and <college, or ≥college), marital status (yes/no), smoking (pack-years), alcohol use (drinks/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 BMI [weight (kg)/height (m)^2; continuous].

[5] Covariates for LIS model included age (years; continuous), total energy intake (kcal/d; continuous), education (<high school, high school, >high school and <college, or ≥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), former smoker (yes/no), and unweighted DIS.

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. Participants in the higher LIS quintiles, aside from components in the LIS, 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 risks are shown in Table 2. Multivariable adjustment modestly attenuated all estimated associations, multivariable-adjusted associations of any given score with mortality risk were similar across mortality categories, and the LIS-mortality risk associations were stronger than the DIS-mortality risk associations. When we analyzed the scores as continuous variables, they were statistically significantly, directly associated with risk for all mortality types; for each 1 point increase in the DIS, there was a 2–3% higher risk for all mortality types, and for each 1 point increase in the LIS, the risks were 11%, 10%, and 14% higher for all-cause, all-cancer, and all-CVD mortality, respectively. When we analyzed the scores according to quintiles, for the DIS, there were statistically significant increases in mortality risks with increasing scores for all-cause and all-CVD mortality. Among those in the highest relative to the lowest DIS quintiles, the risks were statistically significantly 11% higher for all-cause mortality and 12% higher for all-CVD mortality, whereas the risk was estimated to be non–statistically significantly 7% higher for all-cancer mortality. 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, risks were statistically significantly 60%, 51%, and 79% higher for all-cause, all-cancer, and all-CVD mortality, respectively.

The multivariable-adjusted joint/combined (cross-classification) associations of the DIS and LIS with mortality

TABLE 3 Multivariable-adjusted joint/combined associations of the dietary and lifestyle inflammation scores with all-cause, all-cancer, and all-cardiovascular disease mortality risks, 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[1]										
1	1677	1.00 (ref)	1410	1.07 (0.96–1.19)	1169	1.32 (1.18–1.47)	1183	1.25 (1.12–1.39)	1167	1.77 (1.59–1.96)
2	1424	1.05 (0.94–1.17)	1459	1.15 (1.04–1.28)	1151	1.33 (1.20–1.49)	1346	1.31 (1.18–1.45)	1255	1.60 (1.44–1.78)
3	1334	1.09 (0.98–1.21)	1476	1.16 (1.04–1.29)	1125	1.36 (1.22–1.52)	1419	1.31 (1.18–1.45)	1280	1.69 (1.53–1.87)
4	1181	1.13 (1.01–1.27)	1429	1.28 (1.15–1.42)	1073	1.44 (1.44–1.61)	1541	1.34 (1.36–1.48)	1435	1.83 (1.65–2.01)
5	986	1.21 (1.07–1.35)	1381	1.40 (1.26–1.56)	1099	1.63 (1.46–1.81)	1658	1.42 (1.45–1.57)	1497	1.88 (1.71–2.08)
Cancer[2]										
1	1677	1.00 (ref)	1410	1.07 (0.87–1.33)	1169	1.37 (1.11–1.69)	1183	1.31 (1.06–1.62)	1167	1.69 (1.38–2.08)
2	1424	1.16 (0.95–1.43)	1459	1.10 (0.89–1.36)	1151	1.44 (1.16–1.77)	1346	1.22 (1.01–1.51)	1255	1.38 (1.11–1.70)
3	1334	0.99 (0.79–1.23)	1476	1.09 (0.88–1.34)	1125	1.35 (1.09–1.68)	1419	1.22 (0.99–1.50)	1280	1.55 (1.26–1.90)
4	1181	1.10 (0.88–1.38)	1429	1.14 (0.92–1.41)	1073	1.54 (1.24–1.90)	1541	1.36 (1.11–1.66)	1435	1.87 (1.54–2.26)
5	986	1.27 (1.02–1.59)	1381	1.28 (1.04–1.57)	1099	1.52 (1.23–1.89)	1658	1.35 (1.11–1.63)	1497	1.82 (1.50–2.20)
CVD[3]										
1	1677	1.00 (ref)	1410	1.03 (0.87–1.23)	1169	1.27 (1.06–1.52)	1183	1.20 (1.01–1.43)	1167	1.83 (1.56–2.16)
2	1424	1.05 (0.88–1.25)	1459	1.09 (0.92–1.30)	1151	1.18 (0.98–1.41)	1346	1.30 (1.10–1.54)	1255	1.66 (1.41–1.95)
3	1334	1.00 (0.83–1.20)	1476	1.14 (0.96–1.35)	1125	1.22 (1.02–1.47)	1419	1.35 (1.14–1.59)	1280	1.77 (1.50–2.08)
4	1181	0.94 (0.77–1.14)	1429	1.19 (1.00–1.41)	1073	1.25 (1.03–1.50)	1541	1.32 (1.12–1.55)	1435	1.97(1.68–2.30)
5	986	1.09 (0.90–1.32)	1381	1.40 (1.19–1.66)	1099	1.46 (1.22–1.75)	1658	1.43 (1.22–1.68)	1497	1.92 (1.64–2.24)

HRs and 95% CIs are from Cox proportional hazards models; covariates included age (years; continuous), education (<high school, high school, >high school and <college, or ≥college), hormone replacement therapy use (current, past, never), marital status (yes/no), comorbidity score (includes sum of yes/no for diabetes, heart disease, or cirrhosis), and total energy intake (kcal/d; continuous). For construction of DIS and LIS, see text and Table 1; a higher score indicates a more pro-inflammatory diet/lifestyle. Abbreviations: CVD, cardiovascular disease; DIS, dietary inflammation score; LIS, lifestyle inflammation score; ref, reference.

[1] $P_{interaction} = 0.02$; from Wald test.

[2] $P_{interaction} = 0.99$; from Wald test.

[3] $P_{interaction} = 0.82$; from Wald test.

risks are shown in Table 3. For all mortality types, the highest risk tended to be among participants in the highest relative to the lowest joint DIS/LIS quintile, and risks were statistically significantly 88%, 82%, and 92% higher for all-cause, all-cancer, and all-CVD mortality, respectively ($P_{interaction}$ values = 0.02, 0.99, and 0.82, respectively).

There were no clear patterns of differences in multivariable-adjusted associations of the DIS with all-cause or cause-specific mortality risks according to age, HRT use, or baseline chronic disease status, or of the LIS with all-cause or cause-specific mortality risks according to comorbidity status (**Supplemental Table 2**). However, the estimated direct associations of the LIS with all-cause and CVD mortality risks tended to be stronger among participants who were younger (≤ the median age of 61 years) at baseline.

In the sensitivity analyses, for each mortality type, the estimated DIS and LIS associations with mortality risk 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. When we used the mean of the baseline (1986) and 2004 follow-up exposure data among those who had not died prior to 2004 (**Supplemental Table 4**), it had negligible impacts on the estimated DIS and LIS associations with mortality. Similarly, when we used only the 2004 exposure data among those who had not died prior to 2004 (Supplemental Table 4), there was a negligible impact on the estimated direct DIS and mortality associations; the direct LIS and mortality associations were modestly weaker but remained statistically significant, and the 95% CIs for their HRs overlapped with the corresponding ones from the primary analysis. As we hypothesized, the direct associations of the unweighted DIS and LIS with all-cause and cause-specific mortality risks were generally a little stronger than those for the weighted DIS and LIS (**Supplemental Table 5**). The exclusion of participants who died within 1 or 2 years of follow-up (**Supplemental Table 6**) had no appreciable impact on the associations of the DIS and LIS with all-cause mortality risk shown in Table 2. Finally, removal of the vitamin/mineral supplement score from the DIS yielded negligible changes in the estimated associations of the DIS with all-cause and cause-specific mortality risks (**Supplemental Table 7**).

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 among women. Our results also suggest that a more pro-inflammatory lifestyle may contribute more to a 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 risk than with all-cancer mortality risk among women.

Chronically higher systemic inflammation has been consistently, strongly linked to multiple chronic diseases that are major causes of premature mortality, as well as all-cause and cause-specific mortality. In general populations, circulating biomarkers of inflammation were strongly, statistically significantly, directly associated with risks of heart disease (31–33) and type 2 diabetes mellitus (34, 35) in large, prospective studies and with hypertension in a cross-sectional study (36). Also, in general populations, circulating inflammation biomarkers were strongly, statistically significantly, directly associated with all-cause mortality risk in 2 prospective studies (37, 38) and

1 case-control study (39); with CVD mortality risk in a prospective study (37); and with all-cancer mortality risk in 2 prospective studies (37, 40).

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, with 63 references, is provided in **Supplemental Table 8**). As summarized in Supplemental Table 8, 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 E, counter direct and indirect pro-oxidant exposures. That supplemental antioxidant vitamins did not reduce risks for neoplasms or other chronic diseases in clinical trials does not negate their antioxidant/anti-inflammatory effects, nor the rationale for including them in the DIS. As reviewed elsewhere (41), issues with the antioxidant vitamin trials included the use of pharmacologic doses (which can yield pro-oxidant and/or other adverse effects) of 1 or a few agents for short durations among high-risk individuals already well along carcinogenesis pathways. Certain lifestyle-related exposures may especially affect inflammation. As summarized in Supplemental Table 8, 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 nonincluded known and unknown nutrients and nonnutrients in whole foods that may affect inflammation. The EDIP was developed as a primarily data-driven score among NHS participants (12), a relatively occupationally and demographically 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, as well as the need to characterize the collective effects of whole food/beverages/supplements on 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 3 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 studies (n = 423 with hsCRP measurements), and the Calcium and Colorectal Epithelial Cell Proliferation study (n = 173 with a panel of 8 inflammation biomarkers) (19). The associations of the DIS with circulating inflammation biomarker concentrations were stronger than those of the DII and EDIP. Only 1 lifestyle inflammation score, the LIS, has been reported (19). 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 3 study populations (19). Furthermore, the strongest associations found in the 3 study populations were for participants in the highest relative to the lowest joint quantile 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 2 diabetes mellitus (13), CVD (14), and several cancers (15, 42), including CRC (42) and prostate cancer (15). In large, prospective cohort studies, the DII was statistically significantly, directly associated with all-cause mortality risks in 5 of 5 studies (17, 18, 43–45), with CVD mortality risks in 3 of 3 studies (17, 44, 45), and with all-cancer mortality risks in 2 of 2 studies (17, 44). The EDIP was developed using a primarily data-driven approach in the NHS and was found to be comparably associated with inflammation biomarkers in the second NHS and the Health Professionals Follow-Up Study cohort of male health-care professionals (12). A higher (more pro-inflammatory) EDIP was associated with higher risks for colon and rectal cancer in the NHS and the Health Professionals Follow-up Study (46), but not with ovarian cancer incidence (47) or multiple myeloma–specific mortality risk (48) in the NHS. It was directly associated with CVD mortality risk in a small cohort study (49) and was modestly directly associated with all-cause mortality in a case-control study among African-American women with ovarian cancer (50). 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 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 were combined in various ways before, and associations of the combinations, or scores, with chronic disease and mortality outcomes were reported from 14 prospective studies (including 4 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). In addition to differences in score compositions, previous lifestyle scores were not weighted based on their associations with inflammation biomarkers, making them somewhat more similar to our unweighted LIS (51–64). 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) (51–63). In the 7 cohort studies, the combined lifestyle score was statistically significantly associated with lower risks for coronary heart disease (51), type 2 diabetes mellitus (52), hypertension (53), all-cancer incidence (56), incident stomach cancer (57), and incident colon and rectal cancer (54, 55). The 7 studies reported strong, statistically significant associations in the hypothesized directions with all-cause mortality risk (58–64). Of these studies, all 4 that reported associations with CVD and all-cancer mortality risks found strong, statistically significant associations in the hypothesized directions (58, 59, 62, 64).

In our study, we noted that, as hypothesized, the estimated direct associations of our unweighted DIS and LIS with mortality risks tended to be stronger than were those for the inflammation biomarker–weighted DIS and LIS, suggesting that a substantial amount of the collective contributions of diet and lifestyle—especially diet—to mortality risks may involve inflammation-related mechanisms. In support of this, in the IWHS, associations of the unweighted scores with mortality risks were also more similar to those for our previously

reported 14-component evolutionary concordance diet score, 9-component Mediterranean diet score, and 3-component evolutionary concordance lifestyle score (comprising BMI, physical activity, and smoking, weighted by their meta-analysis–derived strengths of associations with mortality) (65). The inverse of the HRs (to put them in the same risk rank directions as the DIS and LIS) for the associations of the evolutionary-concordance diet score, Mediterranean diet score, and evolutionary-concordance lifestyle score with all-cause mortality, among those in the highest relative to the lowest score quintiles, were 1.05, 1.18, and 1.92, respectively.

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 3 study populations (19). In Byrd et al.'s study (19), the DIS was more strongly associated with circulating inflammation biomarkers than were 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 risks.

Our study also has several limitations. Key exposure data were collected only at baseline (1986) and 2004, and some participants' exposures may have changed somewhat over time. However, since participants do not know their outcomes at baseline, error due to this would likely be nondifferential, and so would tend to attenuate the results. Also, 1 cohort study reported that participants' quantile rankings on dietary intakes assessed via FFQ were relatively stable over time (66). Moreover, in our study, we found that, for each mortality type, DIS and LIS associations with mortality risks were similar *1*) after 5, 10, 15, 20, and 25 years of follow-up; and *2*) after incorporating 2004 exposure data 2 different ways. We do note that when, among those still alive in 2004, we substituted the 2004 exposure data for the 1986 data, the LIS and mortality associations became modestly weaker, although they remained statistically significant and the 95% CIs for the corresponding HRs overlapped with those from the primary analysis. Possible reasons for the modestly weaker estimated associations include chance and that lifestyle habits earlier relative to those in later life may have played a stronger role in mortality risks. FFQs have known limitations, such as recall error and limited food choices; however, these types of error are considered nondifferential in a prospective study, and our FFQ was validated against 24-hour food recalls and performed reasonably well (23). The physical activity assessment in the IWHS was based on only 2 questions; however, physical activity alone was previously reported to be statistically significantly inversely associated with mortality risk (24) and other outcomes in the IWHS (67, 68). Furthermore, imprecisely measured exposures in cohort studies generally yield nondifferential exposure misclassification errors, which tend to attenuate associations. Although we included as covariates in our models all known and suspected risk factors for premature mortality ascertained in the IWHS that were not already contained in the scores, residual confounding is possible. 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 risks for all-cause, all-cancer, and all-CVD mortality.

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