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Associations of dietary and lifestyle inflammation scores with mortality due to CVD, cancer, and all causes among Black and White American men and women

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Abstract

One potential mechanism by which diet and lifestyle may affect chronic disease risk and subsequent mortality is through chronic systemic inflammation. In this study, we investigated whether the inflammatory potentials of diet and lifestyle, separately and combined, were associated with all-cause, all-CVD and all-cancer mortality risk. We analysed data on 18 484 (of whom 4103 died during follow-up) Black and White men and women aged ≥45 years from the prospective REasons for Geographic and Racial Differences in Stroke study. Using baseline (2003–2007) Block 98 FFQ and lifestyle questionnaire data, we constructed the previously validated inflammation biomarker panel-weighted, 19-component dietary inflammation score (DIS) and 4-component lifestyle inflammation score (LIS) to reflect the overall inflammatory potential of diet and lifestyle. From multivariable Cox proportional hazards models, the hazards ratios (HR) and their 95 % CI for the DIS–all-cause mortality and LIS–all-cause mortality risk associations were 1·32 (95 % CI (1·18, 1·47); $P_{\text{for trend}} < 0{\cdot}01$) and 1·25 (95 % CI (1·12, 1·38); $P_{\text{for trend}} < 0{\cdot}01$), respectively, among those in the highest relative to the lowest quintiles. The findings were similar by sex and race and for all-cancer mortality, but weaker for all-CVD mortality. The joint HR for all-cause mortality among those in the highest relative to the lowest quintiles of both the DIS and LIS was 1·91 (95 % CI 1·57, 2·33) ($P_{\text{for interaction}} < 0{\cdot}01$). Diet and lifestyle, via their contributions to systemic inflammation, separately, but perhaps especially jointly, may be associated with higher mortality risk among men and women.

Key words: **All-cause mortality: Cause-specific mortality: Diet: Inflammation: Lifestyle: Prospective studies**

CVD and cancer are among the leading causes of death globally[1]. Emerging evidence suggests that chronic low-grade systemic inflammation may be a unifying mechanism underlying the development and progression of CVD and cancer[2]. Circulating concentrations of inflammation biomarkers have been associated with higher risk for cancer[3], CVD[4,5] and mortality[6–8]. Diet and several lifestyle factors, including obesity, physical inactivity and alcohol and tobacco use are thought to contribute to inflammation[9]. While diet and lifestyle are accepted risk factors common to CVD, cancer and mortality risk[10,11], whether inflammation is the primary mechanism through which diet and lifestyle affect mortality risk remains unclear.

Most previous studies that reported associations of the inflammatory potential of diet with all-cause and cause-specific mortality risk assessed diet using the dietary inflammatory index (DII). The largely nutrient-based DII was developed *a priori* based on its individual components' reported effects on various inflammation biomarkers (mostly C-reactive protein) in *in vitro* and animal model studies and human trials, and associations with such biomarkers in human observational studies[12]. In a 2017 meta-analysis of prospective cohort studies, the DII was positively associated with all-cause (four studies), all-CVD (three studies) and all-cancer (four studies) mortality risk[13]. Studies published since also support these findings for all-cause[14–21] and all-CVD[15–21] mortality, though findings for all-cancer mortality were more mixed[15,16,18–21]. However, the largely nutrient rather than food-based nature of the DII may not fully account for all the dietary constituents that may act and interact amongst themselves to affect inflammation. Moreover, the inflammatory potential of other lifestyle factors, such as physical inactivity, obesity and tobacco use, together with diet, may act collectively to affect mortality risk.

We recently developed and validated two novel scores, an *a priori*, largely whole foods and beverages-based dietary inflammation score (DIS) and a lifestyle inflammation score (LIS),

Abbreviations: DII, dietary inflammatory index; DIS, dietary inflammation score; HR, hazard ratio; LIS, lifestyle inflammation score; NSAID, non-steroidal anti-inflammatory drug; REGARDS, REasons for Geographic and Racial Differences in Stroke.

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based on FFQ and lifestyle questionnaire responses, and weighted to reflect dietary and lifestyle contributions to inflammation[22]. The DIS was more strongly associated with high circulating concentrations of inflammation biomarkers than was the DII in three populations[22]. The DIS and LIS were also positively associated with all-cause, all-cancer and all-CVD mortality risk separately, and especially jointly, among older White women in Iowa[23]. However, DIS–mortality and LIS–mortality risk associations have not been investigated in a population comprising Black and White men and women. Accordingly, in the present study, we aimed to investigate the separate and combined associations of the DIS and LIS with all-cause, all-CVD and all-cancer mortality risk in a large, diverse cohort of US men and women. We hypothesised that the separate and, especially, the combined scores would be directly associated with all three mortality outcomes. We also compared associations of the weighted DIS and LIS (representing their components' inflammatory potential) with mortality to those for an equal-weight DIS and LIS (representing their components' overall mechanisms, not just inflammation-related ones) to explore the extent to which associations with risk may be inflammation-related.

Methods

Study population and data collection

We analysed data from 30 183 participants in a previously described prospective cohort study, REasons for Geographic and Racial Differences in Stroke (REGARDS)[24]. Briefly, adults ≥45 years old were enrolled in REGARDS January 2003–October 2007 using a random sampling design within race-sex-geographic strata to recruit White and Black American men and women in both 'stroke belt' and non-stroke belt regions of the contiguous forty-eight states of the USA. REGARDS was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving human subjects/patients were approved by the University of Alabama-Birmingham Institutional Review Board (approval # IRB-020925004). Written informed consent was obtained from all study participants at enrolment. After enrolment, participants completed a telephone interview to collect information on demographics, medical conditions, lifestyle and other factors, followed by an in-home physical exam to obtain anthropometrics, including BMI. Dietary and alcohol data were derived from a previously validated[25], self-administered 110-item Block 98 FFQ, which was given to participants during the in-home visit to complete and return by mail. Physical activity was assessed via an open-ended question regarding the frequency in which the participant engaged in 'intense physical activity, enough to work up a sweat'. Smoking status was derived from two questions regarding: (1) whether the participant smoked ≥100 cigarettes in their lifetime and (2) whether they currently smoked. Individuals who smoked <100 cigarettes were classified as never smokers. Individuals who smoked ≥100 cigarettes were classified as former smokers if they did not currently smoke, and current smokers if they did. We excluded participants according to criteria as shown in Fig. 1, yielding an analytic sample of 18 484.

Exposure assessment

We created the exposures of interest, the DIS and LIS, to be mechanistic exposure scores (as opposed to diet or lifestyle 'quality' scores) to reflect the overall inflammatory potential of diet and lifestyle, respectively, and calculated them exactly as previously described[22]. Accordingly, both scores comprised sums of components weighted according to their strengths of associations with a panel of systemic biomarkers of inflammation in a diverse population[22].

Briefly, the 19-component DIS comprises eighteen food (whole foods and beverages) groups (leafy greens and cruciferous vegetables; tomatoes; apples and berries; deep-yellow or orange fruits and vegetables; other fruits and real fruit juices; other vegetables; legumes; fish; poultry; red and organ meats; processed meats; added sugars; high-fat dairy products; low-fat dairy products; coffee and tea; nuts; other fats; refined grains and starchy vegetables) and one vitamin/mineral supplement score (Table 1). For the supplement score, first, we categorised individuals according to sex-specific tertiles of the distribution for each of the seventeen supplemental micronutrients considered (listed below). We assigned individuals in the lowest, middle and highest intake tertiles values of 0, 1 and 2, respectively. Then, we multiplied the tertile values for the hypothesised anti-inflammatory micronutrients (vitamins A, B_{12}, B_6, C, D and E; and β-carotene, folate, niacin, riboflavin, Ca, Mg, Se, thiamin and Zn) by +1, and the values for hypothesised pro-inflammatory micronutrients (Cu and Fe) by −1. We then summed the values to yield the supplement score. We standardised each of the eighteen food groups (g/d) and the supplement score to a mean of 0 and a SD of 1 based on the distribution in the analytic population. We then multiplied the resultant values for the nineteen DIS components by their respective weights (Table 1) and summed them to yield the DIS.

For the LIS, we categorised each component as follows: alcohol (non-drinkers (0 drinks/d), moderate drinkers (>0–≤1 drink/d for women and >0–≤2 drinks/d for men) and heavy drinkers (>1 drink/d for women and >2 drinks/d for men)); physical activity (inactive (0 times/week), moderately active (1–3 times/week) and heavily active (≥4 times/week)); BMI (normal (<25 kg/m^2), overweight (25–<30 kg/m^2) and obese (≥30 kg/m^2)); and smoking (current and not current). We created dummy variables for each of the components and multiplied them by their assigned weights (Table 1) and summed them to yield the LIS.

Outcome assessment

REGARDS participants or their designated proxies were contacted by study staff every 6 months to ascertain deaths. If a death was reported, all associated records were collected, including medical records and the death certificate, and cause of death (through December 2016) was adjudicated by a committee of trained adjudicators[26]. Our primary outcome of interest was all-cause mortality, defined as deaths due to any cause. Secondary outcomes of interest included all-CVD mortality, defined as deaths due to myocardial infarction, stroke, sudden death, heart failure, pulmonary embolism, other cardiac causes of death (e.g. myocarditis) and non-cardiac but other CVD

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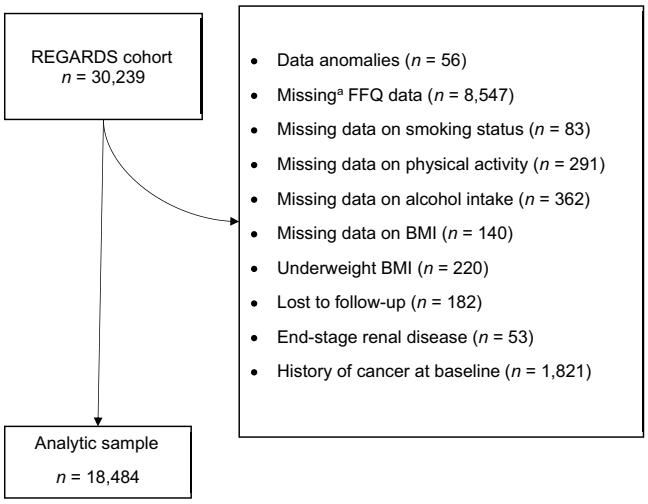

Fig. 1. Exclusion flow chart among participants in the REGARDS study. REGARDS, REasons for Geographic and Racial Differences in Stroke. [a]Those who did not return the FFQ, returned a blank FFQ or those who skipped >15 % of the FFQ.

deaths (e.g. ruptured aortic aneurysm), and all-cancer mortality, defined as deaths due to any type of cancer.

Statistical analyses

We summarised the participants' baseline characteristics overall and within quintiles of the DIS and LIS distributions among all participants in the analytic cohort. We produced cumulative incidence functions for all-cause, all-CVD and all-cancer mortality within strata of the DIS and LIS quintiles. To estimate associations of DIS and LIS quintiles with mortality outcomes, we used multivariable Cox proportional hazards regression models to calculate cause-specific hazards ratios (HR) and their 95 % CI. To assess potential interaction between the DIS and LIS, we conducted joint/combined analyses to estimate the separate and combined associations of the DIS and LIS with all-cause, all-CVD and all-cancer mortality risk. For all analyses, follow-up began on the date of baseline questionnaire completion and ended at death or 31 December 2016, whichever was earliest. We assessed proportional hazards assumptions using likelihood ratio tests to compare models with and without a survival time exposure of interest interaction term; we observed no violations.

We identified and selected covariates as potential confounders based on biological plausibility and previous literature[15–18,20,21,27–29]. In all multivariable models, we adjusted for age (years), sex/current hormone therapy use (male, female-hormone therapy and female-no hormone therapy), race (White and Black American), annual household income (<$20 k, 20–34 k, 35–74 k, ≥75 k and missing), education (<high school, high school graduate, some college and college graduate or more), marital status (married, single and other), health insurance (yes and no), region of residence (stroke belt and non-stroke belt), regular (≥twice/week) non-aspirin non-steroidal anti-inflammatory drug (NSAID) or aspirin use (yes and no), regular statin use (yes and no), total energy intake (kcal/d), and co-morbid conditions (diabetes, heart disease (surgery or procedure on arteries, angioplasty or stenting of coronary arteries, repair of an aortic aneurism, self-reported myocardial infarction or evidence of a myocardial infarction via electrocardiogram) or kidney disease (based on glomerular filtration rate >60 ml/min/1·73 m^2 or a urinary albumin:creatinine ratio >30 mg/g)) at baseline; scored 0–3). Multivariable models for the DIS additionally included all LIS components individually (for this purpose, we operationalised smoking as smoking pack-years). LIS models additionally included an equal-weight DIS and former smoking.

We also conducted several supplemental (secondary and sensitivity) analyses. First, to assess potential effect modification, we investigated potential interactions of the DIS and LIS with selected participant characteristics (sex, age, race, region, non-aspirin NSAID use, aspirin use, statin use, co-morbidities at baseline and tobacco use). Second, we calculated and investigated associations of equal-weight DIS and LIS (all components multiplied by 1 or −1 and summed) with mortality risk. We did this because the inflammation biomarker-weighted DIS and LIS were intended to be mechanistic (as opposed to 'diet quality') scores to represent the *inflammatory* potential of diet and lifestyle (i.e. each component's contribution to the score is constrained by its strength of association with a panel of systemic biomarkers of inflammation and thus likely does not capture other potential mechanistic effects the components may have on disease or mortality risk). So, the equal-weight DIS and LIS were intended to represent the scores' *overall* potential (inflammation-related plus other disease risk mechanisms). We hypothesised that, since inflammation is unlikely to be the only mechanism through which diet and lifestyle affect mortality risk, the equal-weight scores would be more strongly associated with mortality risk than would the weighted scores. Third, to compare DIS–mortality and DII–mortality associations, we calculated the DII[12], the most commonly reported index for assessing the inflammatory potential of diet, exactly as previously described[22], based on thirty-four of the forty-five components available in REGARDS. For all DII components, we calculated *Z*-scores using the

Table 1. Components and construction of the DIS and the LIS in the REGARDS study

Scores' components	Description	Weight
DIS components*		
Leafy greens and cruciferous vegetables	Mustard greens, turnip greens and collards; spinach; green salad; broccoli; coleslaw and cabbage	–0·14
Tomatoes	Catsup, salsa or chili pepper; raw tomatoes, including in salad; tomato juice or v-8 juice; tomato from mixed dishes†	–0·78
Apples and berries	Apples or pears; strawberries	–0·65
Deep-yellow or orange fruits or vegetables	Raw peaches, apricots, nectarines in season; cantaloupe, in season; carrots, or mixed vegetables or stews containing carrots	–0·57
Other fruits and real fruit juices	Watermelon; any other fruit in season like grapes, honey-dew, pineapple and kiwi; oranges or tangerines; grapefruit; real 100 % orange juice or grapefruit juice, including fresh, frozen or boiled; other real fruit juices like apple juice, prune juice and lemonade	–0·16
Other vegetables	Any other vegetable, like okra, squash and cooked green peppers	–0·16
Legumes	Green beans or green peas; split pea, bean or lentil stew; baked beans, black-eyed peas, pintos and other dried bean; legumes from mixed dishes†	–0·04
Fish	Tuna, tuna salad and tuna casserole; fried fish or fish sandwich, at home or in a restaurant; other fish and not fried	–0·08
Poultry	Mixed dishes with chicken, like chicken casserole, chicken and noodles, pot pie or in stir fry; fried chicken at home or in a restaurant; chicken or turkey not fried, such as baked, grilled or on sandwiches	–0·45
Red and organ meats	Hamburgers, cheeseburgers, meat loaf, at home in or in a restaurant; tacos, burritos, enchiladas, tamales, etc., with meat or chicken; beef steaks, roasts, pot roast, or in frozen dinners or sandwiches; pork chops, pork roasts, or dinner ham; veal, lamb or deer meat; ribs, spareribs; liver, including chicken livers or liverwurst; gizzard, pork neckbones, chitlins, pigs feet, etc.; mixed dishes with beef or pork, like stew, corned beef hash, stuffed cabbage and meat dish with noodles; red meat from mixed dishes†	0·02
Processed meats	Bacon; breakfast sausage, including sausage biscuits; hot dogs, or sausage like Polish, Italian or chorizo; boloney, sliced ham, turkey lunch meat and other lunch meat; processed meat from mixed dishes†	0·68
Added sugars	Chocolate candy, candy bars; other candy, not chocolate, like hard candy, caramel, jelly beans; Kool-Aid, Hi-C or other drinks with added vitamin C; drinks with some juice in them, like Sunny Delight or Juice Squeeze; sugar or honey added to coffee or tea; canned fruit like apple sauce, fruit cocktail or dried fruit like raisins; jelly, jam or syrup; mustard, soya sauce, steak sauce, barbecue sauce and other sauces	.056
High-fat dairy products	Regular-fat cheese, sliced cheese or cheese spread, including on sandwiches; cream or half and half added; whole milk; reduced-fat 2 % milk; regular ice cream, ice milk and ice cream bars; high-fat dairy products from mixed dishes†	–0·14
Low-fat dairy products	Low-fat cheese, sliced cheese or cheese spread, including on sandwiches; non-fat milk; low-fat 1 % milk; low-fat ice cream, ice milk and ice cream bars; yogurt or frozen yogurt	–0·12
Coffee and tea	Coffee, regular or decaf; tea or iced tea (not herb teas)	–0·25
Nuts	Peanut butter; peanuts, other nuts or seeds	–0·44
Other fats	Oils or fats used in cooking; mayonnaise and sandwich spreads; butter or margarine on bread or on potatoes or vegetables, etc.	0·31
Refined grains and starchy vegetables	Sweet potatoes and yams (not in pie); pancakes, waffles, French toast, Pop-Tarts; breakfast bars, granola bars and power bars; cooked cereals like oatmeal, cream of wheat or grits; high-fibre cereals like All Bran, Raisin Bran and Fruit-n-Fiber; Product 19, Just Right or Total cereal; any other cold cereal like Corn Flakes, Cheerios and Special K; noodles, macaroni and pasta salad; crackers; doughnuts and Danish pastry; cake, sweet rolls and coffee cake; cookies; pumpkin pie and sweet potato pie; any other pie or cobbler; biscuits or muffins; rolls, hamburger buns, English muffins, bagels; dark bread like rye or whole wheat, including in sandwiches; white bread or toast, including French, Italian or in sandwiches; corn bread and corn muffins; tortillas; rice, or dishes made with rice; French fries, fried potatoes or hash browns white potatoes not fried, including boiled, baked, mashed and potato salad; grains from mixed dishes†	0·72
Supplements‡	Vitamins A, B_{12}, B_6, C, D and E; and β-carotene, folate, niacin, riboflavin, Ca, Mg, Se, thiamin, Zn, Fe and Cu	–0·80
LIS components		
Heavy drinker	> 1 drink (> 14 g ethanol)/d for women; > 2 drinks (> 28 g ethanol)/d for men	0·30
Moderate drinker	> 0–1 drink (14 g ethanol)/d for women; > 0–2 drinks (28 g ethanol)/d for men	–0·66
Moderately physically active	Exercise 1–3 times/week	–0·18
Heavily physically active	Exercise ≥ 4 times/week	–0·41
Current smoker	Self-reported current smoker at baseline	0·50
Overweight BMI	25–<30 kg/m^2	0·89
Obese BMI	≥ 30 kg/m^2	1·57

DIS, dietary inflammation score; LIS, lifestyle inflammation score; REGARDS, REasons for Geographic and Racial Differences in Stroke.

* Dietary components were standardised to the sample at baseline, by sex, to a mean of 0 and a SD of 1.

† Disaggregated from the following FFQ line items: refried beans or bean burritos; chili with beans (with or without meat); vegetable stew; vegetable soup, vegetable beef, chicken vegetable or tomato soup; any other soup, like chicken noodle, chowder, mushroom and instant soups; spaghetti, lasagna or other pasta with tomato sauce; cheese dishes without tomato sauce like macaroni and cheese; pizza, including carry-out; tacos, burritos, enchiladas, tamales, etc., with meat or chicken.

‡ Vitamin and mineral supplemental intakes (self-reported by the participant from multivitamin/mineral and individual supplements) were ranked into tertiles of intake and assigned a value from 0 (low or no intake) to 2 (highest intake) for hypothesised anti-inflammatory micronutrients (all listed micronutrients except for Fe and Cu) or from 0 (low or no intake) to –2 (highest intake) for hypothesised pro-inflammatory micronutrients (Fe and Cu).

published global means and standard deviations, which we then converted to normalised percentiles, centred and multiplied by their respective weights. Based on previous findings that the DIS was more strongly associated with inflammation biomarkers than was the DII in three populations[22], we hypothesised that the DIS–mortality associations would be stronger than the DII–mortality associations. Fourth, we assessed the effects on our estimated associations of excluding 'co-morbidities' as a model

covariate, because it may be a mediating factor (e.g. if individuals consume similar diets over time, a pro-inflammatory diet may increase the risk of co-morbidities present at baseline). Finally, because pharmalogical doses of β-carotene supplements may actually be pro-oxidant/pro-inflammatory and increase lung cancer and mortality risk among individuals at high risk for lung cancer[30], we assessed the effects on our estimated associations of excluding from analysis individuals with β-carotene supplement intakes above the study population's 95th percentile (≥4·2 mg).

We conducted our statistical analyses using SAS (version 9.4) and produced our graphs using R (R Foundation for Statistical Computing), version 3.5.2. All statistical tests were two-sided, and we considered $P \leq 0{\cdot}05$ or 95 % CI that excluded 1·0 to be statistically significant.

Results

Over a median of 10·3 years of follow-up (range: 0·1–13·9), 4103 partipants died (1287 from CVD and 1072 from cancer). Participants in the highest relative to the lowest DIS quintile were more likely to be Black American, live in the US 'stroke belt' region, have lower household incomes and have less formal education (Table 2). Similar trends were observed across LIS quintiles.

The 12-year cumulative incidences of all-cause, all-CVD and all-cancer mortality were higher among participants in the highest DIS quintile (33·8 %, 10·1 % and 8·8 %, respectively) than in the lowest (21·8 %, 7·3 % and 5·4 %, respectively) (Fig. 2, online Supplemental Table 1). The 12-year cumulative incidences of all-cause, all-CVD and all-cancer mortality were higher among participants in the highest LIS quintile (31·4 %, 10·3 % and 7·9 %, respectively) than in the lowest (23·9 %, 6·9 % and 6·2 %, respectively) (Fig. 3, online Supplemental Table 2).

In multivariable models, the DIS was positively associated with all-cause and all-cancer mortality risk ($P_{\text{for trend}} < 0{\cdot}01$) (Table 3). For example, individuals in the highest relative to the lowest DIS quintile had statistically significant 32 % higher hazards of all-cause mortality (95 % CI (18, 47)) and statistically significant 39 % higher hazards of all-cancer mortality (95 % CI (11, 73)). The DIS association with all-CVD mortality was less clear. The LIS was postively associated with all three mortality outcomes (all $P_{\text{for trend}} \leq 0{\cdot}03$). For example, individuals in the highest relative to the lowest LIS quintile had statistically significant 25 % (95 % CI (12, 38)), 26 % (95 % CI (5, 52)) and 33 % (95 % CI (9, 63)) higher hazards of all-cause, all-CVD and all-cancer mortality, respectively.

In our joint/combined analyses, the highest hazards for all-cause mortality risk was among those in the highest joint DIS and LIS quintile relative to those in the joint lowest (Table 4); risk was statistically significantly 91 % higher (95 % CI (57, 133)) (P for multiplicative interaction < 0·01). This compares to statistically significant 46 % higher hazards among those in the lowest LIS quintile who were in the highest relative to the lowest DIS quintile, and statistically significant 48 % higher hazards among those in the lowest DIS quintile who were in the highest relative to the lowest LIS quintile. The sample sizes for joint/combined analyes for CVD and cancer mortality risk were more limited, and no $P_{\text{for interaction}}$ from these analyses was statistically significant. However, the findings for all-cancer mortality risk were very similar to those for all-cause mortality, for example, the highest HR was among those in the highest joint DIS and LIS quintile relative to those in the joint lowest (HR 2·17; 95 % CI (1·57, 3·01)) (online Supplemental Table 3). On the other hand, there was no clear pattern for joint/combined DIS and LIS analysis findings in relation to CVD mortality (online Supplemental Table 4).

There were no clear differences in the estimated DIS–all-cause mortality association across the strata of various other risk factors. However, there were suggestions that the estimated associations were stronger among those who were younger (<65 years) or formerly or currently smoked (online Supplemental Table 5). The LIS–all-cause mortality association was stronger among those who were younger (<65 years) (online Supplemental Table 6). The samples sizes for stratified analyses for CVD and all-cancer mortality were limited and the findings were too unstable for meaningful interpretation (online Supplemental Tables 7–10). However, there were suggestions that the DIS–all-CVD mortality association was stronger among women, younger participants and those without baseline co-morbidities.

The equal-weight DIS–mortality associations were minimally stronger and the equal-weight LIS–mortality associations were substantially stronger than those for their respective inflammation biomarker-weighted scores (online Supplemental Table 11). As examples, the HR for all-cause mortality risk among those in the highest relative to the lowest weighted and equal-weight DIS quintles were 1·32 and 1·38, respectively, and the corresponding values for the weighted and equal-weight LIS were 1·25 and 1·66, respectively.

Multivariable-adjusted DII–mortality associations were weaker than the corresponding DIS–mortality associations (online Supplemental Table 12). After excluding co-morbidities as a covariate from models, DIS–mortality associations were nearly identical, while LIS–mortality associations appeared stronger (online Supplemental Table 13). Results excluding participants with extreme β-carotene supplement intakes (online Supplemental Table 14) were similar, albeit slightly stronger, to those when those participants were included.

Discussion

Our results suggest that diets and lifestyles with greater inflammatory potentials, separately, but perhaps especially jointly, may be associated with higher mortality risk due to all causes, cancer and CVD. Our results also suggest that, although dietary and lifestyle contributions to mortality risk via inflammation may be substantial, for diet, inflammation may be the primary contribution, whereas lifestyle may also contribute substantially via other mechanisms.

Our findings that the DIS and LIS were positively associated with all-cause, all-cancer and all-CVD mortality (although the estimated positive DIS–all-CVD association among men and women combined was weaker and not statistically significant)

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Table 2. Baseline characteristics according to quintiles of DIS and LIS among participants in REGARDS (*n* 18 484), USA, 2003–2007 (Mean values and standard deviations; number and percentages)

			Dietary inflammation score quintiles*						Lifestyle inflammation score quintiles†					
	Total		1		3		5		1		3		5	
	(*n* 18 484)		(*n* 3696)		(*n* 3698)		(*n* 3696)		(*n* 4015)		(*n* 3105)		(*n* 4207)	
Characteristics‡	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Age (years)														
Mean	64·4		65·5		64·8		62·9		65·6		63·4		63·0	
SD	9·2		8·9		9·2		9·2		9·7		8·7		8·6	
Male	7936	42·9	1587	42·9	1588	42·9	1587	42·9	1978	49·3	1518	48·9	1219	29
Black American	6306	34·1	682	18·5	1195	32·3	1995	54·0	771	19·2	1075	34·6	2069	49·2
Stroke belt region§	10 497	56·8	1835	49·6	2130	57·6	2351	63·6	2196	54·7	1732	55·8	2519	59·9
College graduate	6927	37·5	1937	52·4	1383	37·4	756	20·5	2019	50·3	1215	39·2	1135	27·0
Income <$20 k	2856	17·4	322	10·0	511	15·6	983	29·9	359	10·2	403	14·3	985	26·5
Married	11 440	61·9	2442	66·1	2325	62·9	2044	55·3	2772	69·0	1993	64·2	2242	53·3
Has health insurance	17 293	93·6	3553	96·2	3487	94·3	3288	89·0	3857	96·1	2915	93·9	3823	91·0
Co-morbid conditions‖	7820	42·3	1415	38·3	1564	42·3	1727	46·7	1294	32·2	1273	41·0	2268	53·9
Take HRT (women only)	6265	59·4	1404	66·6	1297	61·5	1069	50·7	1351	66·3	991	62·4	1596	53·4
Regularly‖ take NSAID	2811	15·3	610	16·5	516	14·0	525	14·3	490	12·2	460	14·9	802	19·1
Regularly¶ take aspirin	8100	43·8	1762	47·7	1620	43·8	1409	38·1	1779	44·3	1421	45·8	1747	41·5
Current smoker	2509	13·6	214	5·8	447	12·1	914	24·7	198	4·9	463	14·9	857	20·4
BMI (kg/m^2)														
Mean	29·2		28·0		29·4		30·3		23·8		29·8		35·3	
SD	6·0		5·3		6·1		6·6		2·4		4·8		5·5	
Total energy intake (kcal/d)														
Mean	1705		1717		1684		1745		1689		1724		1709	
SD	710		658		714		765		650		715		761	
Heavy alcohol use**	811	4·4	178	4·8	154	4·2	155	4·2	0	0·0	171	5·5	249	5·9
Not physically active	5966	32·3	780	21·1	1191	32·2	1641	44·4	327	8·1	305	9·8	2294	54·5

DIS, dietary inflammation score; LIS, lifestyle inflammation score; HRT, hormone replacement therapy; NSAID, non-steroidal anti-inflammatory drug; REGARDS, REasons for Geographic and Racial Differences in Stroke.

* DIS quintile ranges were as follows: quintile 1, −10·4 to −2·1; quintile 3, −0·7 to 0·6; quintile 5, 2·1 to 10·0.

† LIS quintile ranges were as follows: quintile 1, −1·1 to −0·2; quintile 3, 0·5 to 0·8; quintile 5, 1·4 to 2·4.

‡ The following variables had missing values: income (11·5 %), insurance (<0·1 %), education (<0·1 %), regular NSAID use (0·3 %) and regular aspirin use (<0·1 %).

§ North Carolina, South Carolina, Georgia, Arkansas, Tennessee, Alabama, Mississippi and Louisiana.

‖ Included diabetes, heart disease (surgery or procedure on arteries, angioplasty or stenting of coronary arteries, repair of an aortic aneurism, self-reported myocardial infarction, or evidence of a myocardial infarction via electrocardiogram) or kidney disease (based on glomerular filtration rate > 60 ml/min/1·73 square metres or a urinary albumin:creatinine ratio > 30 mg/g) at baseline (score 0–3).

¶ At least twice/week.

** >1 drink (>14 g ethanol)/d for women; >2 drinks (>14 g ethanol)/d for men.

are mostly supported by the only previous reported study of DIS–mortality and LIS–mortality associations, conducted by Li *et al.*[23], with some exceptions. For example, Li *et al.*, in a prospective study of White Iowa women, found a positive DIS–all-CVD mortality association that was similar to ours, but slightly stronger and statistically significant[23]. In our subgroup analyses, we found a positive DIS–all-CVD mortality association among women that was statistically significant and stronger than that among men. Moreover, in a recent meta-analysis, the DII, an alternative measure of the inflammatory potential of diet, was positively associated with CVD incidence or mortality risk among women but not men[31]. Other studies[15,16], though not all[21], also found stronger DII–all-CVD mortality associations among women than among men.

Other previous literature mostly supports our observation that a pro-inflammatory diet is associated with higher all-cause and all-cancer mortality risk, though most previous studies assessed inflammation from diet using the DII. According to recent meta-analyses, those in the highest relative to the lowest DII quantile had 21–23 % higher all-cause mortality risk[14,32] and 28 % higher all-cancer mortality risk[32] – results that are comparable to our estimates using the DII (22 % and 29 % for all-cause and all-cancer mortality, respectively). Studies published since the meta-analyses also support our positive associations with all-cause mortality[15,16,33] but were mixed with regard to all-cancer mortality, with some[15,19,21], but not all[16,18,33], studies supporting our findings. In our study, the DIS was more strongly directly associated with all-cause and all-cancer mortality than was the DII. These findings are consistent with those from our previous report, in which the DIS was more strongly associated with circulating inflammation biomarkers than was the DII[22]. This may be due to the food-based nature of the DIS (as opposed to the largely nutrient-based DII), which may more comprehensively account for known and unknown dietary constituents that may affect inflammation, and the complex interactions among them[34].

In contrast to recent meta-analyses[13,31,32,35], in our study, a pro-inflammatory diet assessed using the DIS or the DII was not statistically significantly associated with all-CVD mortality, although the estimated HR were >1·0. However, we did find evidence to suggest that the DIS may be more strongly associated with all-CVD mortality among women (as discussed above), younger participants and those without underlying baseline co-morbidities, though the CI for corresponding estimates across

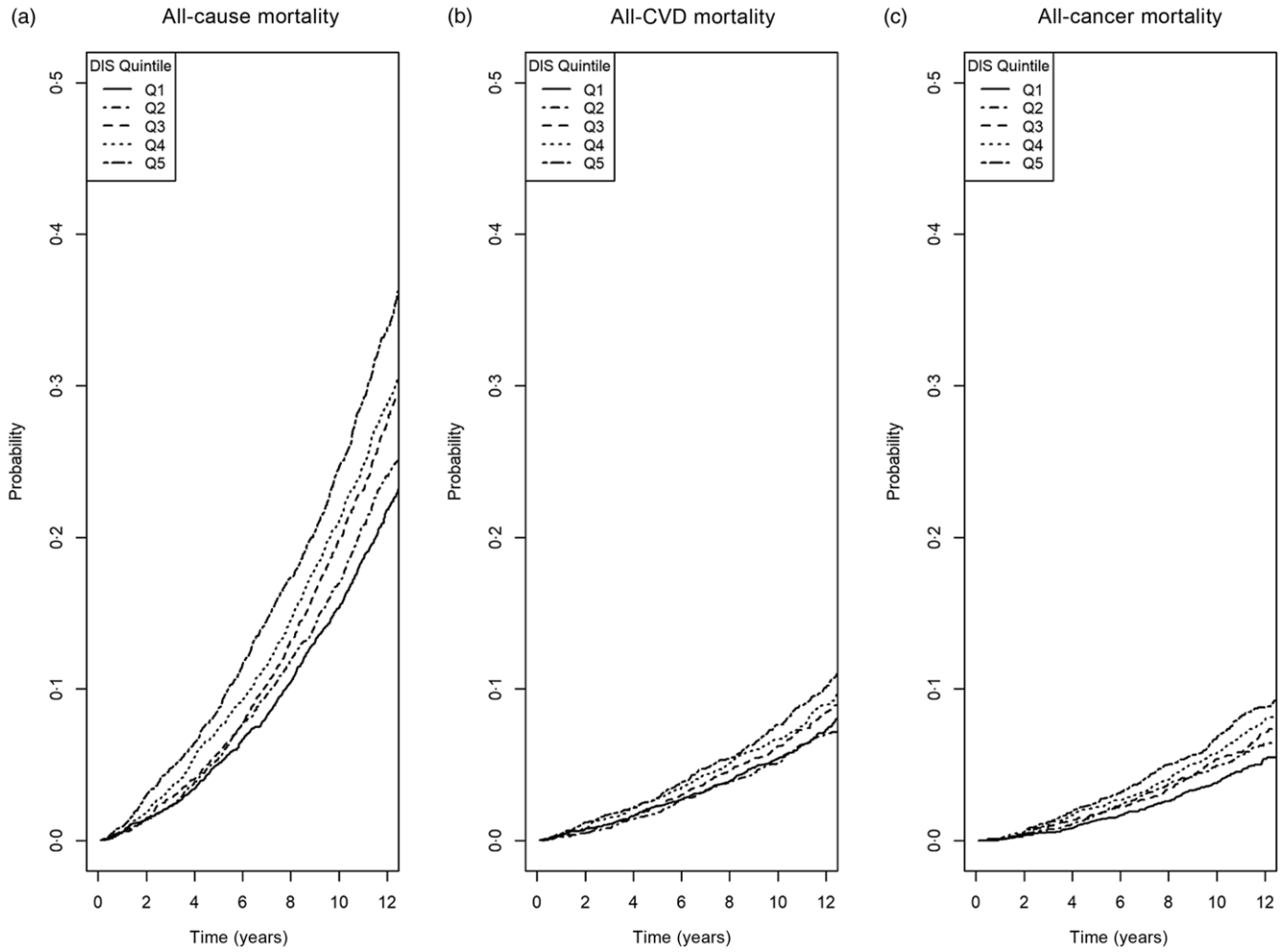

Fig. 2. Cumulative incidence of all-cause, all-CVD and all-cancer mortality according to quintiles of the baseline distribution of the DIS in REGARDS (*n* 18 484), USA, 2003–2016. DIS, diet inflammation score; REGARDS, REasons for Geographic and Racial Differences in Stroke. Results are unadjusted.

strata were wide and overlapped. Our observation of a possible stronger association among younger participants is in contrast to most[16,21,33], but not all[17], studies, and could be due to chance. Our observation of a possible stronger DIS–CVD mortality association among those without co-morbid conditions at baseline could suggest that participants with a baseline co-morbidity may have changed their diets from their long-term unhealthy diets to healthier diets, but that the disease process was sufficiently advanced such that diet could no longer have a substantial effect.

One other study, a prospective cohort study in Sweden[36], reported associations of a diet inflammation score (the anti-inflammatory dietary index) with mortality risk[37]. The food-based anti-inflammatory dietary index, derived using a data-driven approach and scored in the opposite direction of the DIS and DII, was inversely associated with all-cause, all-CVD and all-cancer mortality risk[36]. Discrepancies in findings for all-CVD mortality could be due to the aforementioned reasons.

Our study findings, except for our weak estimated DIS–CVD mortality risk association, generally align with those from previous studies that investigated various healthy diet pattern scores, albeit our findings were marginally weaker. In REGARDS, both Paleolithic and Mediterranean diet scores (with higher scores indicating 'healthier' diets) were inversely associated with all-cause, all-CVD and all-cancer mortality[38]. We expected that other non-mechanism-oriented, 'diet quality' dietary pattern scores and our equal-weight DIS would be more strongly associated with mortality than was our weighted DIS, because the DIS was designed to assess the effects of diet through *inflammation*, not through the collective effects of all mechanisms. However, the similarity of the findings using our equal-weight and weighted diet scores suggest that inflammation may be the primary mechanism through which diet affects mortality risk.

Our study is among the first to report that a LIS comprising components weighted according to their contributions to inflammation is associated with higher all-cause, all-CVD and all-cancer mortality risk. Our findings using the equal-weight LIS were substantially stronger than those using the weighted LIS, suggesting that lifestyle may affect mortality risk through inflammation as well as other mechanisms. For example, mortality risk may be increased by tobacco smoke mutagens[39], obesity

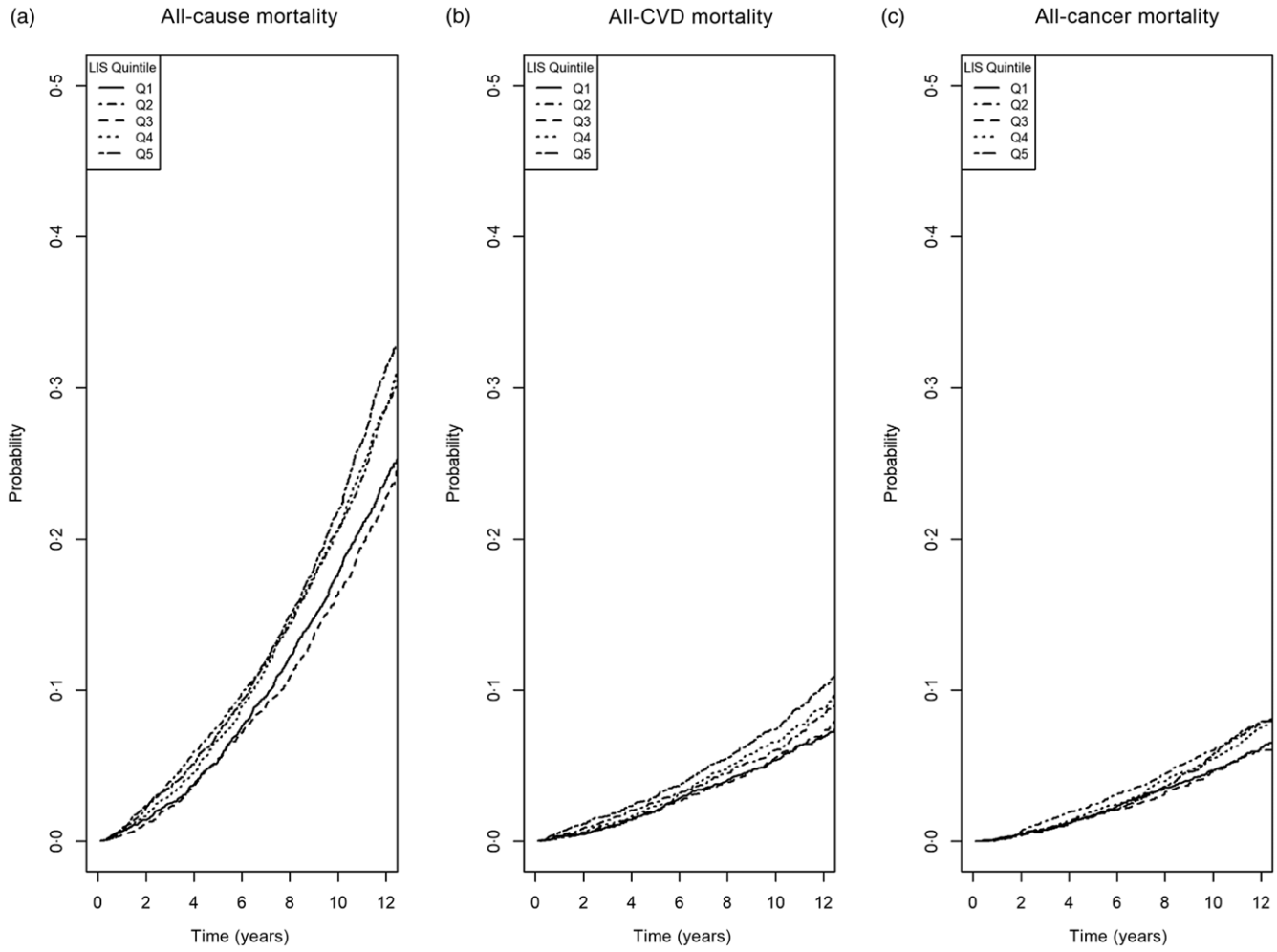

Fig. 3. Cumulative incidence of all-cause, all-CVD and all-cancer mortality according to quintiles of the baseline distribution of the LIS in REGARDS (*n* 18 484), USA, 2003–2016. LIS, lifestyle inflammation score; REGARDS, REasons for Geographic and Racial Differences in Stroke. Results are unadjusted.

through alterations in hormones and adipocytes[40,41], and physical inactivity through its effects on neuroendocrine and physiological responses to stressors[42]. Heavy alcohol intake may affect mortality risk through a variety of mechanisms, including damage to DNA and organs (e.g. liver), weakening the immune system, and increasing injury risk[43–45]. Findings from previous studies that reported non-mechanistic lifestyle scores (i.e. the components were not weighted according to their strengths of associations with inflammation biomarkers) generally align with ours[11,20,46–56], though there is substantial heterogeneity in how lifestyle scores were constructed and modelled.

Our findings should be considered in context with our study's limitations. First, information on diet and lifestyle were self-reported and may be subject to measurement error. However, such misclassification is likely non-differential due to the prospective nature of the study and is not expected to account for our positive findings. Second, we lacked detailed information on diet, lifestyle and other factors related to chronic disease risk and subsequent mortality over the life course. For example, if someone previously had a diet and lifestyle with a high inflammatory potential and was diagnosed with CVD prior to study enrolment, it is possible that they made lifestyle changes in hopes of reducing CVD mortality risk. As a result, this participant would appear to have a diet and lifestyle with a low inflammatory potential but would still be at high risk for CVD-related mortality, which would likely attenuate results. We tried to mitigate this potential by controlling for and considering possible heterogeneity by co-morbidities and certain CVD-related medications (e.g. aspirin and statins) at baseline, but bias due to residual or unmeasured confounding cannot be ruled out. Also, our FFQ did not allow separation of types of oils (e.g. olive oil) consumed. Last, our study results may not be generalisable to adults <45 years of age and non-Black and non-White Americans. Strengths of our study include the prospective study design, large and racially diverse study population, and use of validated DIS and LIS[22].

In summary, our findings, taken together with previous literature, suggest that diets and lifestyles (summarised through physical activity, obesity, and alcohol and tobacco use) with higher inflammatory potentials, both alone and especially in combination, may be associated with higher mortality risk. In addition, inflammation may be the primary mechanism through

Table 3. Associations of DIS* and LIS† with all-cause, all-CVD and all-cancer mortality risk among participants in REGARDS (*n* 17 757), USA, 2003–2016 (Hazard ration and 95 % confidence intervals)

	All-cause mortality					All-CVD mortality					All-cancer mortality				
Inflammation score (quintiles)	# Deaths‡	Model 1§ HR	95 % CI	Model 2‖ HR	95 % CI	# Deaths‡	Model 1§ HR	95 % CI	Model 2‖ HR	95 % CI	# Deaths‡	Model 1§ HR	95 % CI	Model 2‖ HR	95 % CI
DIS quintiles‖															
1	629	1·00	Ref.	1·00	Ref.	218	1·00	Ref.	1·00	Ref.	154	1·00	Ref.	1·00	Ref.
2	711	1·17	1·05, 1·29	1·05	0·95, 1·17	210	0·99	0·82, 1·19	0·88	0·73, 1·07	191	1·28	1·04, 1·57	1·16	0·94, 1·44
3	779	1·35	1·22, 1·50	1·13	1·01, 1·26	240	1·2	1·01, 1·44	0·97	0·80, 1·16	203	1·44	1·17, 1·76	1·22	0·99, 1·51
4	824	1·54	1·39, 1·70	1·18	1·06, 1·31	259	1·39	1·17, 1·66	1·03	0·86, 1·24	224	1·71	1·40, 2·09	1·32	1·06, 1·63
5	950	2·07	1·88, 2·29	1·32	1·18, 1·47	289	1·83	1·54, 2·17	1·09	0·90, 1·32	246	2·15	1·76, 2·62	1·39	1·11, 1·73
$P_{\text{for trend}}$¶				< 0·01					0·14					< 0·01	
LIS quintiles**															
1	764	1·00	Ref.	1·00	Ref.	229	1·00	Ref.	1·00	Ref.	197	1·00	Ref.	1·00	Ref.
2	892	1·25	1·14, 1·37	1·09	0·99, 1·21	265	1·21	1·02, 1·44	1·05	0·88, 1·26	244	1·34	1·12, 1·61	1·21	1·00, 1·46
3	562	1·18	1·06, 1·31	1·01	0·90, 1·13	179	1·28	1·06, 1·55	1·03	0·85, 1·26	146	1·1	0·89, 1·36	1	0·81, 1·25
4	702	1·4	1·27, 1·55	1·08	0·97, 1·20	219	1·46	1·22, 1·74	1·04	0·86, 1·26	187	1·37	1·13, 1·67	1·19	0·97, 1·47
5	973	1·74	1·59, 1·91	1·25	1·12, 1·38	324	1·97	1·67, 2·33	1·26	1·05, 1·52	244	1·55	1·29, 1·88	1·33	1·09, 1·63
$P_{\text{for trend}}$††				< 0·01					0·02					0·03	

DIS, dietary inflammation score; LIS, lifestyle inflammation score; REGARDS, REasons for Geographic and Racial Differences in Stroke; HR, hazards ratio; Ref, referent; HRT, hormone replacement therapy; NSAID, non-steroidal anti-inflammatory drug.

* The 19-component DIS was calculated as described in the text and Table 1; a higher DIS reflects a more pro-inflammatory diet.

† The 4-component LIS was calculated as described in the text and Table 1; a higher LIS reflects a more pro-inflammatory lifestyle.

‡ Death counts are from multivariable models that exclude participants with missing data for covariates. Death counts from models adjusting for age only may be higher than those shown.

§ From age-adjusted Cox proportional hazards models.

‖ From multivariable Cox proportional hazards models. Models for DIS adjusted for age, sex/HRT use, race, income, education, insurance, marital status, region, co-morbidities (score 0–3), aspirin/NSAID use, statin use, total energy intake, physical activity (none, 1–3 times/week and ≥ 4 times/week), BMI (healthy weight, overweight and obese), alcohol intake (none, moderate and heavy) and tobacco use (pack-years). Models for LIS adjusted for age, sex/HRT use, race, income, education, insurance, marital status, region, co-morbidities (score 0–3), aspirin/NSAID use, statin use, total energy intake, former smoking status (yes and no) and the DIS (equal weights); excludes *n* 727 participants with missing data for covariates.

¶ DIS quintile ranges were as follows: quintile 1, −10·4 to −2·1; quintile 2, −2·2 to −0·6; quintile 3, −0·7 to 0·6; quintile 4, 0·6 to 2·2; and quintile 5, 2·1 to 10·0.

** $P_{\text{for trend}}$ calculated by assigning the median of each DIS or LIS quintile to each quintile and treating this quintile exposure as a continuous variable.

†† LIS quintile ranges were as follows: quintile 1, −1·1 to −0·2; quintile 2, −0·2 to 0·5; quintile 3, 0·5 to 0·8; quintile 4, 0·9 to 1·3; and quintile 5, 1·4 to 2·4.

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Table 4. Joint/combined (cross-classification) associations* of the DIS and LIS with all-cause mortality risk in REGARDS (*n* 17 757), USA, 2003–2016 (Hazard ration and 95 % confidence intervals)

		LIS quintiles†											
		1			2		3		4		5		
		# deaths	HR	95 % CI	# deaths	HR	95 % CI	# deaths	HR	95 % CI	# deaths	HR	95 % CI
DIS quintiles‡	1	173	1·00	Ref.	157	1·12	0·90, 1·39	100	1·25	0·97, 1·60	82	0·98	0·76, 1·28	117	1·48	1·16, 1·87
	2	182	1·28	1·04, 1·58	167	1·13	0·91, 1·40	94	0·95	0·73, 1·22	108	1·15	0·91, 1·47	160	1·88	1·51, 2·34
	3	159	1·33	1·07, 1·65	193	1·54	1·25, 1·89	122	1·22	0·97, 1·55	151	1·43	1·14, 1·78	154	1·29	1·03, 1·61
	4	136	1·26	1·00, 1·58	174	1·48	1·19, 1·82	122	1·38	1·09, 1·74	166	1·62	1·30, 2·01	226	1·64	1·34, 2·01
	5	114	1·46	1·15, 1·85	201	1·82	1·48, 2·24	124	1·77	1·40, 2·25	195	1·72	1·39, 2·13	312	1·91	1·57, 2·33§

DIS, diet inflammation score; LIS, lifestyle inflammation score; REGARDS, REasons for Geographic and Racial Differences in Stroke; HR, hazards ratio; Ref, referent; HRT, hormone replacement therapy; NSAID, non-steroidal anti-inflammatory drug.

* From multivariable Cox proportional hazards model adjusting for age, sex/HRT use, race, income, education, insurance, marital status, region, co-morbidities (score 0–3), aspirin/NSAID use, statin use and total energy intake. The interaction between the DIS and the LIS was modelled by including dummy variables representing the 2nd through 5th quintiles of the DIS and the LIS (four dummy variables each, with quintile 1 as the referent group) as well as their product terms (sixteen total product terms). Excludes 727 participants with missing data for covariates.

† LIS quintile ranges were as follows: quintile 1, −1·1 to −0·2; quintile 2, −0·2 to 0·5; quintile 3, 0·5 to 0·8; quintile 4, 0·9 to 1·3; and quintile 5, 1·4 to 2·4.

‡ DIS quintile ranges were as follows: quintile 1, −10·4 to −2·1; quintile 2, −2·2 to −0·6; quintile 3, −0·7 to 0·6; quintile 4, 0·6 to 2·2; and quintile 5, 2·1 to 10·0.

§ From DIS x LIS interaction term in the Cox proportional hazards model; relative excess risk due to interaction = −0·02, 95 % CI: (−0·48, 0·44); likelihood ratio test for multiplicative interaction: $\chi^2 = 40·8$, $P < 0·01$.

which diet affects mortality risk, and although inflammation may be a major mechanism through which lifestyle affects mortality risk, other mechanisms also likely substantially contribute; further investigations in these regards are needed. Our findings also support the use of our DIS and LIS. Finally, if our findings were to be consistently replicated, studies to test the effects of more anti-inflammatory diets and lifestyle on inflammation biomarkers and chronic disease incidence would be indicated.

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Supplementary material

For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S0007114522001349

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