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Association between inflammatory potential of diet and mortality in the Iowa Women's Health study

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Abstract

Purpose—Chronic diseases such as cancer and cardiovascular disease (CVD) are well-established causes of disability and premature deaths. Dietary components that are known to affect chronic inflammation have been implicated in the etiology and prognosis of these chronic diseases. We examined the ability of the dietary inflammatory index (DII) to predict overall, cancer and CVD mortality in the Iowa Women's Health study.

Methods—The DII was computed from baseline dietary intake assessed in this cohort of 37,525 women, who were aged 55–69 years when enrolled starting in 1986. During the follow-up period, through December 31, 2010, in a total of 17,793 deaths, 5044 cancer- and 6528 CVD-related deaths were identified through mortality record linkage. Cox proportional hazards regression was used to estimate hazard ratios (HR) with DII expressed both as a continuous variable and as quartiles.

Results—Comparing subjects in DII Quartile 4 versus Quartile 1, modest positive associations were noted for all-cause mortality (HR_{Q4vsQ1} 1.07; 95 % CI 1.01–1.13; *p*-trend = 0.006), digestive cancer mortality (HR_{Q4vsQ1} 1.19; 95 % CI 1.00–1.43; *p*-trend = 0.05), CVD mortality (HR_{Q4vsQ1} 1.09; 95 % CI 1.01–1.18; *p*-trend = 0.08), non-cancer/non-CVD/non-acute mortality (HR_{Q4vsQ1}

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Compliance with Ethical Standards

Ethical disclosure: Dr. James R. Hébert owns controlling interest in Connecting Health Innovations LLC (CHI), a company planning to license the right to his invention of the dietary inflammatory index (DII) from the University of South Carolina in order to develop computer and smart phone applications for patient counseling and dietary intervention in clinical settings. Dr Nitin Shivappa is an employee of CHI.

Conflict of interest: None.

1.09; 95 % CI 1.00–1.19; *p*-trend = 0.19), coronary heart disease (CHD) mortality (HR_{Q4vsQ1} 1.17; 95 % CI 1.05–1.30; *p*-trend = 0.001) and chronic obstructive pulmonary disease (COPD) mortality (HR_{Q4vsQ1} 1.43; 95 % CI 1.18– 1.75; *p*-trend = 0.0006). No substantial associations were observed for mortality from stroke, Alzheimer's disease or unspecified dementia.

Conclusion—These results indicate that a pro-inflammatory diet, as evidenced by higher DII scores, may be associated with total mortality as well as mortality from digestive cancer, CVD, CHD and COPD.

Keywords

Diet; Inflammation; Mortality; Cohort; Women

Introduction

Inflammation is the body's appropriate response to tissue insult/injury or the presence of inflammatory stimulants [1, 2]. The acute inflammatory response represents an important step in the process of wound healing and tissue regeneration that, under normal circumstances, will lead to recovery within a few days [3, 4]. However, when this process of inflammation is not controlled properly via competent negative feedback, a chronic low-grade inflammatory state could result [4]. Chronic inflammation has been shown to be associated with many chronic conditions and outcomes, such as cancer and cardiovascular disease (CVD) incidence and death [1, 3, 5–10].

Research into the role of diet in inflammation and chronic disease mortality suggests that diet represents a complicated set of exposures that often interact, and whose cumulative effect influences both inflammatory responses and health outcomes [11, 12]. This has included effects on markers of systemic inflammation in carefully designed intervention trials [13, 14] and on incidence of colon cancer and precancerous lesions in large observational cohort studies [15, 16]. Several studies have evaluated the effect of a healthy diet as defined, a priori, by dietary patterns or scores and various health outcomes, including total mortality [17–21]. The three components (diet, inflammation and mortality) form a natural "triad"; however, a search combining all these three terms on MEDLINE® yielded very few results.

In an effort to fill a methodological gap, researchers at the University of South Carolina's Cancer Prevention and Control Program developed the dietary inflammatory index (DII), which can be used in diverse populations to predict levels of inflammatory markers and related health outcomes [22, 23]. The DII is based on reviewing and scoring the scientific literature on diet and inflammation, and obtaining nutritional surveillance data sets from around the world to which individuals' dietary intakes could be compared. A higher DII score indicates a pro-inflammatory dietary milieu, and a lower DII score indicates that diet is more anti-inflammatory [22]. Thus far, the DII has been found to be associated with C-reactive protein [23, 24], interleukin-6 [25–27] and homocysteine [25]. Additionally, DII has been shown to be associated with glucose intolerance and dyslipidemia components of the metabolic syndrome [28, 29], anthropometric measurements in Spain [30], asthma in Australia [27] respiratory conditions in Italy [31], bone mineral density among

postmenopausal women in Iran [32], colorectal cancer in two case–control studies in Spain and Italy [33, 34] and three cohort studies in the USA [15, 35, 36], and pancreatic and prostate cancers in Italian studies [37, 38].

The purpose of this study was to examine the association between the DII and total, cancer and CVD mortality in the IWHS, a large prospective cohort of post-menopausal women. We hypothesized that higher DII scores (indicating a pro-inflammatory diet) are associated with an increased risk of dying in general, as well as increased risk of mortality from specific chronic diseases.

Methods

Participants and study design

Full details regarding the IWHS design have been published elsewhere [39]. In brief, the IWHS was designed to examine the effect of host, dietary and lifestyle factors on the incidence of cancer among postmenopausal women. In total, 41,836 women, ages 55–69 years, were enrolled in 1986 and were asked to complete a 16-page self-administered questionnaire. The IWHS was approved by the University of Minnesota Institutional Review Board, and the return of the questionnaire was considered informed consent in concordance with prevailing practice in 1986. Women with extreme energy intake (<600 kcal or ≥5000 kcal per day) or incomplete dietary data (≥30 items blank) on the food frequency questionnaire (n = 3102) or with missing covariate data (n = 1209) were excluded from the present study, yielding a sample size for analysis of 37,525 study participants. The response rates by questionnaire were as follows: 1987 (91 % response rate), 1992 (83 %). Aspirin use was assessed in the 1992 questionnaire. At baseline, the total number of participants with any kind of cancer and heart disease was 3389 and 3214, respectively, and with prevalent diabetes, it was 1535. After excluding women with these preexisting conditions, the total sample size was 29,634; out of these, 957 women (3 % of the total sample size) were excluded because of missing information on the covariates selected for analyses to give a final analytic sample size of 28,677.

Dietary information

Dietary intake data were collected using a food frequency questionnaire (FFQ) at baseline (1986). This FFQ was adapted from the 126-item instrument developed by Willett et al. [40]. Dietary data were obtained from the Harvard University Food Composition Database, which was derived from US Department of Agriculture sources [40]. These FFQ-derived dietary data were used to calculate DII scores for all participants.

Dietary inflammatory index (DII)

The DII is based on literature published through 2010 linking diet to inflammation. Individual intakes of food parameters on which the DII is based are then compared with a world standard database. A complete description of the DII is available elsewhere [22]. A description of validation work, including both dietary recalls and a structured questionnaire similar to an FFQ, also is available [23]. Briefly, to calculate DII for the participants of this study, the dietary data were first linked to the regionally representative world database that

we created that provided a robust estimate of a mean and standard deviation for each parameter. These then become the multipliers to express an individual's exposure, relative to the "standard global mean," as a *z*-score. This is achieved by subtracting the "standard global mean" from the amount reported and dividing this value by the standard deviation. To minimize the effect of "right skewing," this value is then converted to a centered percentile score. The centered percentile score for each food parameter for each individual was then multiplied by the respective food parameter effect score, which is derived from the literature review, in order to obtain a food parameter-specific DII score for an individual. All of the food parameter-specific DII scores are then summed to create the overall DII score for every participant in the study [22]. A higher DII indicates a more inflammatory diet. The range of DII scores in the IWHS was −5.75 to +4.66.

Ascertainment and classification of mortality

Deaths through December 31, 2010, were identified through the State Health Registry of Iowa or the National Death Index for women who did not respond to the last follow-up questionnaire (2004) or who emigrated from Iowa. International Classification of Diseases (ICD), 9th and 10th Edition codes (ICD-9, ICD-10), were used to determine the underlying cause of death. Deaths due to cancer were ascertained with ICD-9 codes 140–239 or ICD-10 codes C00-D48; death due to digestive cancers (esophagus, stomach, small intestine, colon, rectum and anus, liver and intrahepatic bile ducts, gallbladder, pancreas, and other and ill-defined sites of the digestive organs) was defined as ICD-9 150–159 or ICD-10 C15-C26. CVD deaths were ascertained through ICD-9 codes 390–459 or ICD-10 codes I00-I99. Deaths due to non-CVD/non-cancer/non-acute illnesses, including infection, benign tumor, endocrine, nutritional and metabolic disorders (except diabetes, hyperlipidemia or obesity), nervous system, respiratory, digestive, genitourinary, skin and subcutaneous tissue, and selected connective tissue disorders and arthropathies, were defined as ICD-9 codes 1–139, 240–249, 251–271, 273–277, 279–359, 460–629, 680–714, or 720 or ICD-10 codes A, B, E00–E09, E15–E64, E67–E77, E79–E90, F, G, H, J, K, L, M00–M14, M30–M36, M45–M46 or N. Out of these, most deaths were due to chronic obstructive pulmonary disease (COPD) defined as ICD-9 491–492 or ICD-10 J449, Alzheimer's disease defined as ICD-9 331 or ICD-10 J449, and unspecified dementia defined as ICD-9 294.8 or ICD-10 F03. Person-years of follow-up were accumulated from baseline until death or administrative censoring on December 31, 2010.

Other measurements

The baseline questionnaire included questions concerning potential confounders, including demographic factors (age, education), lifestyle factors (physical activity, smoking, alcohol use), medical history (high blood pressure, diabetes, heart disease, cancer), anthropometrics (height, weight, waist and hip circumference) and medication (hormone replacement therapy). Aspirin and nonsteroidal anti-inflammatory drug (NSAID) use was assessed in the 1992 survey. Physical activity was characterized according to the frequency (times per week) of self-reported moderate (mod) and vigorous (vig) activities: high = mod ≥ 5 or vig ≥ 2; moderate = mod ≥ 2 or mod ≥ 1 and vig ≥ 1; or otherwise low. Body mass index (BMI) was categorized as underweight (<18.5 kg/m^2), normal weight (18.5- <25 kg/m^2), overweight (25- <30 kg/m^2) and obese (≥30 kg/m^2). Participants received instructions for

measuring waist and hip circumference with a paper tape measure [41]. The study has been approved by the appropriate ethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Statistical analyses

DII was analyzed both as a continuous variable and as quartiles. Baseline characteristics were examined across quartiles of DII. The participants' characteristics including demographics, lifestyle factors, medical history, anthropometric characteristics and medications were examined using general linear model or Chi-square test for continuous and categorical variables, respectively. Hazards ratio and 95 % confidence intervals (HR; 95 % CI) were estimated using Cox proportional hazards regression models, adjusting only for age and total energy intake in the crude model and additionally adjusting for BMI, smoking status, pack-years of smoking, education, hormone replacement therapy (HRT) use, and history of diabetes, hypertension, cardiovascular disease and cancer. The covariates were chosen a priori as they previously had been shown to be strong risk factors for mortality in this cohort. Further adjustment for alcohol intake and physical activity did not substantially change the results; therefore, these variables were not included in the final model. The p value for the regression coefficient in the continuous model was used as the p value for trend. The assumption of proportional hazards was tested by adding to the model an interaction term between follow-up time and DII; there was no evidence that these assumptions were violated. Additionally, analyses were carried out and stratified by types of CVD deaths specifically coronary heart disease (CHD) and stroke, and major causes of death among the non-CVD/non-cancer category which are COPD and Alzheimer's and unspecified dementia. Finally, to examine effect modification due to BMI, physical activity, smoking status and aspirin use, interaction terms were introduced and if significant stratified analysis was carried out. A sensitivity analysis was performed whereby women with prevalent cancer, diabetes, or heart disease at baseline were excluded (n = 8138). Another sensitivity analysis was performed excluding the deaths in the first 3 years of follow-up. Statistical tests were performed using SAS® 9.3, (SAS Institute Inc., Cary, NC); all p values were derived from two-sided tests.

Results

Total person-years of observation for this study were 778,521, and mean length of follow-up was 20.7 ± 7.0 years. The mean DII at baseline was −0.87 (SD ± 2.02). Baseline characteristics by quartiles of DII are provided in Table 1. Decreasing trends for total energy intake and increasing trends for total fat intake were observed across DII quartiles (Table 1). Increasing frequencies for women with BMI ≥ 30 kg/m^2, waist-to-hip ratio (WHR) >0.869, current smokers, less than high school education and those reporting low levels of physical activity were observed across quartiles of DII. During the follow-up period, a total of 17,793 deaths from all causes, 5044 cancer-related deaths, 1240 digestive cancer deaths, 6528 CVD-related deaths and 4909 non-cancer/non-CVD/non-acute deaths were identified.

For all-cause mortality analysis, when DII was used as a continuous variable, significant positive associations were observed for all-cause mortality after age and total energy intake adjustment (HR 1.09; 95 % CI 1.07–1.10 per 1 unit of the DII). After additional adjustment for BMI, smoking status, pack-years of smoking, education, HRT use, and history of diabetes, CVD, hypertension and cancer, the HR was attenuated (HR 1.03; 95 % CI 1.01–1.05). When DII was fit as quartiles, significant associations were observed for women in quartile 4 versus quartile 1 (HR_{Q4vsQ1} 1.08; 95 % CI 1.03–1.13; *p*-trend = 0.0005) after multivariable adjustment.

For analysis of cancer-specific mortality, significant positive associations were observed with DII as continuous (HR 1.04; 95 % CI 1.01–1.07) after multivariable adjustment. When DII was fit as quartiles, women in the fourth quartile were at higher risk of dying from cancer compared with women in the first quartile in multivariable analysis (HR_{Q4vsQ1} 1.08; 95 % CI 0.99–1.18; *p*-trend = 0.01). For digestive cancer-specific mortality, increased DII score was associated with deaths both when presented as a continuous variable (HR 1.07; 95 % CI 1.01–1.14) and as quartiles (HR_{Q4vsq1} 1.19; 95 % CI 1.00–1.43; *p*-trend = 0.04.

For CVD-specific analysis, significant positive associations were observed with DII as continuous after multivariable adjustment (HR 1.04; 95 % CI 1.01–1.07). When DII was fit as quartiles, women in the fourth quartile were at higher risk of dying from CVD compared with women in the first quartile (HR_{Q4vsQ1} 1.09; 95 % CI 1.01–1.18; *p*-trend = 0.006) after multivariable analysis.

We found a positive association between DII and non-cancer/non-CVD/non-acute deaths in the adjusted model when DII was presented as quartiles (HR_{Q4vsQ1} 1.09; 95 % CI 1.00–1.19; *p*-trend = 0.16) (Table 2). Table 3 shows results for additional causes of deaths, and DII was associated with deaths from CHD (HR_{Q4vsQ1} 1.17; 95 % CI 1.05– 1.30; *p*-trend = 0.001) and COPD (HR_{Q4vsQ1} 1.43; 95 % CI 1.18–1.73; *p*-trend = <0.001).

Test for interaction was significant for smoking status for all-cause mortality, deaths due to cancer and marginally significant for deaths due to CVDs (data not shown). When stratified by smoking status, a stronger association was observed between DII and all-cause mortality among ever-smokers ($HR_{continuous}$ HR 1.13, 95 % CI 1.10–1.15) than among never-smokers ($HR_{continuous}$ HR 1.03, 95 % CI 1.00–1.05); similarly, a stronger association was observed between DII and cancer mortality, CVD mortality and non-CVD/non-cancer/non-acute mortality among ever-smokers compared with never-smokers (data not shown). Tests for interaction with BMI were marginally significant for all-cause mortality and deaths due to non-CVD/non-cancer/non-acute death. When stratified by BMI, DII was associated with all-cause mortality among overweight/obese ($HR_{continuous}$ HR 1.05, 95 % CI 1.03–1.08) and normal BMI category ($HR_{continuous}$ HR 1.13, 95 % CI 1.10–1.16), and non-CVD/non-cancer/non-acute death among overweight/obese ($HR_{continuous}$ HR 1.04, 95 % CI 1.00–1.09) and normal BMI category ($HR_{continuous}$ HR 1.16, 95 % CI 1.10–1.21).

There were no substantial changes in the magnitude of the association between DII as a continuous variable and as quartiles with all-cause, cancer and CVD mortality after excluding women with prevalent cancer, diabetes and heart disease at baseline (online only;

supplemental Table 1). However, associations with digestive-tract cancer mortality were attenuated and no longer statistically significant. Also, in the analyses performed after excluding deaths during the first 3 years of follow-up, the results were similar to those displayed in Table 2. We have looked at the attributable risk due to higher DII. The total number of expected deaths when keeping the rate of deaths in quartiles 2, 3 and 4 same as that in quartile 1 is 13,079, the total number of observed deaths for quartile 2–4 is 13,434, and the difference between expected and observed number of deaths is 355. Therefore, in the Iowa Women's Health study with a sample size of 37,525, 355 of the total 17,793 deaths can be attributed to increased inflammatory potential of diet *i*, *e* higher DII scores, and in the general population, 1261 deaths can be attributed to higher DII scores per 100,000 women.

In the analyses in which we examined results by duration of follow-up (Table 4), there was a slight pattern of stronger associations with shorter follow-up, with the maximum observed at 5–10 years out for all causes, all CVD, CHD and stroke. The maximal effect was at slightly longer durations for all cancers, digestive-tract cancers and for COPD (i.e., peaking at 10–15 years).

Discussion

In this population-based prospective cohort study of older women, we observed an association between consuming a more pro-inflammatory diet, as reflected in higher DII scores, with increased risk of all-cause, cancer-related, digestive cancer-related, CVD-related, CHD-related and COPD-related mortality. Consuming a more pro-inflammatory diet (about 5 point increase from quartile 1 to quartile 4 in DII) was associated with an approximate 7–9 % increased risk of mortality. The attributable risk of dying due to having a higher DII score (i.e., DII scores above first quartile) was 1261 deaths per 100,000 women. Studying individual food items such as red or processed meat or specific nutrients such as omega 3 fatty acids and dietary fiber in isolation can be problematic because these whole foods or nutrients are usually eaten with other food items and nutrients that may attenuate or accentuate the specific effects of the individual food or nutrient under study. Furthermore, the high correlation among nutrients and across foods may result in instability in risk estimation due to multicollinearity and possible loss of statistical power. As a consequence, previous studies have explored the association between dietary patterns and indices and mortality (both all cause and disease specific) [42–46] as a means of capturing the effect of the whole diet rather than individual dietary constituents.

The results of the current study are in accordance with the general findings that healthy diet pattern scores are inversely associated with mortality. In a previous study conducted among IWHS participants, both the Alternate Healthy Eating Index (AHEI) and the A Priori Diet Quality Score predicted total, CVD-, cancer-related, and non-CVD, non-CA, non-acute deaths [21]. In another study, adherence to the Dietary Approaches to Stop Hypertension (DASH) diet was not associated with CVD mortality in the IWHS [47]. In the Adventist Health Study-2, researchers observed a significant inverse association between a vegetarian dietary pattern and all-cause mortality and CVD mortality [46]. An inverse association was observed between Healthy Eating Index (HEI) and all-cause mortality in the National Health Nutrition and Examination Survey (NHANES) III; however, the association was restricted to

men [44]. Authors also have observed significant inverse associations between the AHEI, and all-cause and CVD mortality in the Whitehall cohort study, and a nonsignificant inverse association was observed with cancer mortality [43]. In the Netherlands component of the EPIC study, increasing Mediterranean score was found to have significant inverse association with CVD deaths [42]. It is important to note here that higher scores for these indices represent healthier diet, whereas for DII, higher scores indicate a more pro-inflammatory (i.e., unhealthy) diet.

Previous dietary patterns or indices focus on a limited number of food groups or nutrients specific to dietary guidelines or cultural ways of eating. In formulating the DII, an entirely different approach was taken by focusing on the functional effects of up to 45 foods and nutrients. As such, it relies on the very careful review and scoring of around 2000 publications in the medical literature specifically in relation to diet and inflammation. Also, it standardizes individual dietary intakes of pro- and anti-inflammatory food constituents to world referent values. In a previous study conducted in IWHS looking at DII and incident colorectal cancer as outcome, servings of food groups such as vegetables, fruits and fish were shown to decrease with increasing DII, while food groups such as fries and beer were shown to increase with DII [48]. Test for interaction was significant for smoking status for all-cause mortality and deaths due to cancer, but was marginally significant for deaths due to CVDs and for BMI for all-cause mortality and deaths due to non-CVD/non-cancer/non-acute death. These findings could have implications for public health messaging in the sense that synergistic and antagonistic effects call attention to focus on factors that may be especially effective or ineffective under certain circumstances. Results showing different effect results by duration of follow-up (i.e., stronger associations with shorter follow-up for all causes, all CVD, CHD and stroke and for longer durations for all cancers, digestive-tract cancers and for COPD) present interesting implications for timing of exposure relative to specific outcomes. However, more research will be needed to verify these findings.

The positive association of the DII with total, cancer and CVD mortality in the IWHS adds more evidence to the important role diet plays in disease through the process of inflammation. One of the possible mechanisms for this association would be through the effect of a pro-inflammatory diet on insulin resistance by increasing systemic inflammation [49, 50]. Insulin resistance can act as a common pathway for both cancer [51] and CVD [52].

For mechanisms specific to cancer, consumption of food items such as meat and butter has been shown to be associated with markers of inflammation such as high-sensitivity C-reactive protein, E-selectin and soluble vascular cell adhesion molecule-1 [49], which then is responsible for increasing insulin resistance [50]. Increased insulin resistance is associated with cancer, presumably by increasing circulating levels of insulin, triglycerides and non-esterified fatty acids [53, 54]. These circulating factors that promote excessive proliferation of epithelial cells, long-term exposure to reactive oxygen species, can result in the promotion of cancer, with the strongest evidence pertaining to colorectal cancer [53, 54]. Another theory suggests the role of diet on local inflammation and oxidation in the colon; local inflammation and oxidative stress as a result of activation of the COX-2 enzyme in the epithelial cells result in focal proliferation and mutagenesis [55].

There are several mechanisms through which diet increases or decreases the risk of CVD. Atherosclerosis is the most important pathologic process for underlying CVD, and this process is importantly influenced by inflammatory cytokines [56]. Calorie-restricted diets are known to reduce circulating levels of C-reactive protein, which is a marker of systemic inflammation that also may play a role itself in the inflammatory process, thus explaining why it has been shown to predict cardiovascular events in many studies [56]. Diets rich in omega-3 fatty acids appear to reduce atherosclerosis by the process of down-regulation of the intracellular mechanisms that lead to the expression of proatherogenic genes [56].

Strengths of the present study include prospective data collection with extended follow-up, large sample size, near-complete case ascertainment, adjustment for multiple potential confounding factors, and consideration of risk of overall mortality and cancer and CVD mortality with adequate statistical power to detect relevant differences across quartiles of DII. Carrying out analyses using broad cause of death categories was both a strength and a limitation. It was a strength because it takes into account the broad pathologic commonalities as explained earlier for cancer and CVD. However, the limitation is that broad categories of death could have missed important pathologic distinctions in which diet may have been related specifically to some more specific causes [56]. One recognized limitation is that dietary data were collected at baseline, so DII was calculated just once. However, adult dietary patterns appear to remain relatively stable over time [57–61]. Moreover, sensitivity analyses carried out by excluding participants with cancer, CVDs and diabetes at baseline did not yield any substantial change in the results and there was no specific dietary intervention applied to participants during the course of the study. We note the limitation of only two measurement point(s) and wanted to use only the first on in order to eliminate biases resulting from possible effects of preclinical disease. Another limitation is that the study is restricted to mostly older, non-Hispanic White women (99 % were White), and hence, the study results cannot be generalized to other populations that include men and individuals from different age and racial-ethnic groups.

In conclusion, a pro-inflammatory diet, as evidenced by higher DII scores, was associated with a modest increase in risk of all-cause, cancer-related, CVD-related and digestive cancer-related mortality. Future studies of DII and mortality should examine biomarkers of inflammation (e.g., CRP, IL-6, IL-8) as possible mediators of the association. The logical next steps would include using DII in other studies with participants representing different age groups and races and include males; this would help to discern the generalizability of the study results. It also would be interesting to compare the results of DII with other dietary indices such as HEI, AHEI and Mediterranean diet scores.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Keibel A, Singh V, Sharma MC. Inflammation, microenvironment, and the immune system in cancer progression. Curr Pharm Des. 2009; 15(17):1949–1955. [PubMed: 19519435]
2. Pan MH, Lai CS, Dushenkov S, Ho CT. Modulation of inflammatory genes by natural dietary bioactive compounds. J Agric Food Chem. 2009; 57(11):4467–4477. [PubMed: 19489612]
3. Thun MJ, Henley SJ, Gansler T. Inflammation and cancer: an epidemiological perspective. Novartis Found Symp. 2004; 256:6–21. discussion 22–28, 49–52, 266–269. [PubMed: 15027481]
4. Warnberg J, Gomez-Martinez S, Romeo J, Diaz LE, Marcos A. Nutrition, inflammation, and cognitive function. Ann N Y Acad Sci. 2009; 1153:164–175. [PubMed: 19236339]
5. Erlinger TP, Muntner P, Helzlsouer KJ. WBC count and the risk of cancer mortality in a national sample of U.S. adults: results from the second national health and nutrition examination survey mortality study. Cancer Epidemiol Biomarkers Prev. 2004; 13(6):1052–1056. [PubMed: 15184263]
6. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow?[see comment]. Lancet. 2001; 357(9255):539–545. [PubMed: 11229684]
7. Coussens LM, Werb Z. Inflammation and cancer. Nature. 2002; 420(6917):860–867. [PubMed: 12490959]
8. Balkwill F. Tumour necrosis factor and cancer. Nat Rev Cancer. 2009; 9(5):361–371. [PubMed: 19343034]
9. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO 3rd, Criqui M, Fadl YY, Fortmann SP, Hong Y, Myers GL, Rifai N, Smith SC Jr, Taubert K, Tracy RP, Vinicor F. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the centers for disease control and prevention and the american heart association. Circulation. 2003; 107(3):499–511. [PubMed: 12551878]
10. Cooney RV, Chai W, Franke AA, Wilkens LR, Kolonel LN, Le Marchand L. C-reactive protein, lipid-soluble micronutrients, and survival in colorectal cancer patients. Cancer Epidemiol Biomarkers Prev. 2013; 15:15.
11. Jacobs DR, Gross MD, Tapsell LC. Food synergy: an operational concept for understanding nutrition. Am J Clin Nutr. 2009; 89(5):1543S–1548S. [PubMed: 19279083]
12. Jacobs DR, Steffen LM. Nutrients, foods, and dietary patterns as exposures in research: a framework for food synergy. Am J Clin Nutr. 2003; 78(3):508S–513S. [PubMed: 12936941]
13. Hebert JR, Wirth M, Davis L, Davis B, Harmon BE, Hurley TG, Drayton R, Angela Murphy E, Shivappa N, Wilcox S, Adams SA, Brandt HM, Blake CE, Armstead CA, Steck SE, Blair SN. C-reactive protein levels in African Americans: a diet and lifestyle randomized community trial. Am J Prev Med. 2013; 45(4):430–440. [PubMed: 24050419]
14. Imayama I, Ulrich CM, Alfano CM, Wang C, Xiao L, Wener MH, Campbell KL, Duggan C, Foster-Schubert KE, Kong A, Mason CE, Wang CY, Blackburn GL, Bain CE, Thompson HJ, McTiernan A. Effects of a caloric restriction weight loss diet and exercise on inflammatory biomarkers in overweight/obese postmenopausal women: a randomized controlled trial. Cancer Res. 2012; 72(9):2314–2326. [PubMed: 22549948]
15. Shivappa N, Prizment AE, Blair CK, Jacobs DR Jr, Steck SE, Hebert JR. Dietary inflammatory index and risk of colorectal cancer in the Iowa women's health study. Cancer Epidemiol Biomarkers Prev. 2014; 23(11):2383–2392. [PubMed: 25155761]
16. Bobe G, Sansbury LB, Albert PS, Cross AJ, Kahle L, Ashby J, Slattery ML, Caan B, Paskett E, Iber F, Kikendall JW, Lance P, Daston C, Marshall JR, Schatzkin A, Lanza E. Dietary flavonoids and colorectal adenoma recurrence in the polyp prevention trial. Cancer Epidemiol Biomarkers Prev. 2008; 17(6):1344–1353. [PubMed: 18559549]
17. Cai H, Shu XO, Gao YT, Li H, Yang G, Zheng W. A prospective study of dietary patterns and mortality in Chinese women. Epidemiology. 2007; 18(3):393–401. [PubMed: 17435450]

18. Zazpe I, Sanchez-Tainta A, Toledo E, Sanchez-Villegas A, Martinez-Gonzalez MA. Dietary patterns and total mortality in a mediterranean cohort: the SUN project. J Acad Nutr Diet. 2013; 1(13):01180–01185.

19. Mitrou PN, Kipnis V, Thiébaut AM, et al. Mediterranean dietary pattern and prediction of all-cause mortality in a US population: results from the NIH-AARP diet and health study. Arch Intern Med. 2007; 167(22):2461–2468. [PubMed: 18071168]

20. Huijbregts P, Feskens E, Räsänen L, Fidanza F, Nissinen A, Menotti A, Kromhout D. Dietary pattern and 20 year mortality in elderly men in Finland, Italy, and the Netherlands: longitudinal cohort study. BMJ. 1997; 315(7099):13–17. [PubMed: 9233319]

21. Mursu J, Steffen LM, Meyer KA, Duprez D, Jacobs DR Jr. Diet quality indexes and mortality in postmenopausal women: the Iowa women's health study. Am J Clin Nutr. 2013; 98(2):444–453. [PubMed: 23783291]

22. Shivappa N, Bosetti C, Zucchetto A, Montella M, Serraino D, LaVecchia C, Hebert JR. Association between dietary inflammatory index and prostate cancer among Italian men. Br J Nutr. 2014; 17:1–6.

23. Shivappa N, Steck SE, Hurley TG, Hussey JR, Ma Y, Ockene IS, Tabung F, Hebert JR. A population-based dietary inflammatory index predicts levels of C-reactive protein in the seasonal variation of blood cholesterol study (SEASONS). Public Health Nutr. 2014; 17(8):1825–1833. [PubMed: 24107546]

24. Wirth MD, Burch J, Shivappa N, Violanti JM, Burchfiel CM, Fekedulegn D, Andrew ME, Hartley TA, Miller DB, Mnatsakanova A, Charles LE, Steck SE, Hurley TG, Vena JE, Hebert JR. Association of a dietary inflammatory index with inflammatory indices and metabolic syndrome among police officers. J Occup Environ Med. 2014; 56(9):986–989. [PubMed: 25046320]

25. Shivappa N, Hebert JR, Rietzschel ER, De Buyzere ML, Langlois M, Debruyne E, Marcos A, Huybrechts I. Associations between dietary inflammatory index and inflammatory markers in the Asklepios Study. Br J Nutr. 2015; 113(4):665–671. [PubMed: 25639781]

26. Tabung FK, Steck SE, Zhang J, Ma Y, Liese AD, Agalliu I, Hingle M, Hou L, Hurley TG, Jiao L, Martin LW, Millen AE, Park HL, Rosal MC, Shikany JM, Shivappa N, Ockene JK, Hebert JR. Construct validation of the dietary inflammatory index among postmenopausal women. Ann Epidemiol. 2015

27. Wood LG, Shivappa N, Berthon BS, Gibson PG, Hebert JR. Dietary inflammatory index is related to asthma risk, lung function and systemic inflammation in asthma. Clin Exp Allergy. 2015; 45(1): 177–183. [PubMed: 24708388]

28. Aa Alkerwi, Shivappa N, Crichton G, Hébert JR. No significant independent relationships with cardiometabolic biomarkers were detected in the observation of cardiovascular risk factors in luxembourg study population. Nutr Res. 2014

29. Wirth MD, Burch J, Shivappa N, Violanti JM, Burchfiel CM, Fekedulegn D, Andrew ME, Hartley TA, Miller DB, Mnatsakanova A, Charles LE, Steck SE, Hurley TG, Vena JE, Hebert JR. Association of a dietary inflammatory index with inflammatory indices and metabolic syndrome among police officers. J Occup Environ Med. 2014; 56(9):986–989. [PubMed: 25046320]

30. Ruiz-Canela M, Zazpe I, Shivappa N, Hebert JR, Sanchez-Tainta A, Corella D, Salas-Salvado J, Fito M, Lamuela-Raventos RM, Rekondo J, Fernandez-Crehuet J, Fiol M, Santos-Lozano JM, Serra-Majem L, Pinto X, Martinez JA, Ros E, Estruch R, Martinez-Gonzalez MA. Dietary inflammatory index and anthropometric measures of obesity in a population sample at high cardiovascular risk from the PREDIMED (PRE-vencion con DIeta MEDiterranea) trial. Br J Nutr. 2015

31. Maisonneuve P, Shivappa N, Hébert J, Bellomi M, Rampinelli C, Bertolotti R, Spaggiari L, Palli D, Veronesi G, Gnagnarella P. Dietary inflammatory index and risk of lung cancer and other respiratory conditions among heavy smokers in the COSMOS screening study. Eur J Nutr. 2015

32. Shivappa N, Hebert JR, Karamati M, Shariati-Bafghi SE, Rashidkhani B. Increased inflammatory potential of diet is associated with bone mineral density among postmenopausal women in Iran. Eur J Nutr. 2015

33. Zamora-Ros R, Shivappa N, Steck SE, Canzian F, Landi S, Alonso MH, Hebert JR, Moreno V. Dietary inflammatory index and inflammatory gene interactions in relation to colorectal cancer

risk in the Bellvitge colorectal cancer case-control study. Genes Nutr. 2015; 10(1):447. [PubMed: 25488145]

34. Shivappa N, Zucchetto A, Montella M, Serraino D, Steck SE, La Vecchia C, Hebert JR. Inflammatory potential of diet and risk of colorectal cancer: a case–control study from Italy. Br J Nutr. 2015:1–7.
35. Tabung FK, Steck SE, Ma Y, Liese AD, Zhang J, Caan B, Hou L, Johnson KC, Mossavar-Rahmani Y, Shivappa N, Wactawski-Wende J, Ockene JK, Hebert JR. The association between dietary inflammatory index and risk of colorectal cancer among postmenopausal women: results from the women's health initiative. Cancer Causes Control: CCC. 2015; 26(3):399–408. [PubMed: 25549833]
36. Wirth MD, Shivappa N, Steck SE, Hurley TG, Hébert JR. The dietary inflammatory index is associated with colorectal cancer in the National Institutes of Health–American Association of Retired Persons Diet and Health Study. Br J Nutr. 2015
37. Shivappa N, Bosetti C, Zucchetto A, Serraino D, La Vecchia C, Hebert JR. Dietary inflammatory index and risk of pancreatic cancer in an Italian case–control study. Br J Nutr. 2014
38. Shivappa N, Bosetti C, Zucchetto A, Montella M, Serraino D, La Vecchia C, Hebert JR. Association between dietary inflammatory index and prostate cancer among Italian men. Br J Nutr. 2014
39. Folsom AR, Kaye SA, Prineas RJ, Potter JD, Gapstur SM, Wallace RB. Increased incidence of carcinoma of the breast associated with abdominal adiposity in postmenopausal women. Am J Epidemiol. 1990; 131(5):794–803. [PubMed: 2138863]
40. Willett WC, Sampson L, Browne ML, Stampfer MJ, Rosner B, Hennekens CH, Speizer FE. The use of a self-administered questionnaire to assess diet four years in the past. Am J Epidemiol. 1988; 127(1):188–199. [PubMed: 3337073]
41. Park K, Harnack L, Jacobs DR Jr. Trends in dietary supplement use in a cohort of postmenopausal women from Iowa. Am J Epidemiol. 2009; 169(7):887–892. [PubMed: 19208725]
42. Hoevenaar-Blom MP, Nooyens AC, Kromhout D, Spijkerman AM, Beulens JW, van der Schouw YT, Bueno-de-Mesquita B, Verschuren WM. Mediterranean style diet and 12-year incidence of cardiovascular diseases: the EPIC-NL cohort study. PLoS One. 2012; 7(9):e45458. [PubMed: 23029021]
43. Akbaraly TN, Ferrie JE, Berr C, Brunner EJ, Head J, Marmot MG, Singh-Manoux A, Ritchie K, Shipley MJ, Kivimaki M. Alternative healthy eating index and mortality over 18 y of follow-up: results from the Whitehall II cohort. Am J Clin Nutr. 2011; 94(1):247–253. [PubMed: 21613557]
44. Kappeler R, Eichholzer M, Rohrmann S. Meat consumption and diet quality and mortality in NHANES III. Eur J Clin Nutr. 2013; 67(6):598–606. [PubMed: 23486512]
45. McCullough ML, Gapstur SM, Shah R, Jacobs EJ, Campbell PT. Association between red and processed meat intake and mortality among colorectal cancer survivors. J Clin Oncol. 2013; 31(22):2773–2782. [PubMed: 23816965]
46. Orlich MJ, Singh PN, Sabate J, Jaceldo-Siegl K, Fan J, Knutsen S, Beeson WL, Fraser GE. Vegetarian dietary patterns and mortality in adventist health study 2. JAMA Intern Med. 2013; 173(13):1230–1238. [PubMed: 23836264]
47. Folsom AR, Parker ED, Harnack LJ. Degree of concordance with DASH diet guidelines and incidence of hypertension and fatal cardiovascular disease*. Am J Hypertens. 2007; 20(3):225–232. [PubMed: 17324731]
48. Shivappa N, Prizment AE, Blair CK, Jacobs DR, Steck SE, Hébert JR. Dietary inflammatory index and risk of colorectal cancer in the iowa women's health study. Cancer Epidemiol Biomarkers Prev. 2014; 23(11):2383–2392. [PubMed: 25155761]
49. Esmaillzadeh A, Kimiagar M, Mehrabi Y, Azadbakht L, Hu FB, Willett WC. Dietary patterns and markers of systemic inflammation among Iranian women. J Nutr. 2007; 137(4):992–998. [PubMed: 17374666]
50. Festa A, D'Agostino R, Howard G, Mykkänen L, Tracy RP, Haffner SM. Chronic subclinical inflammation as part of the insulin resistance syndrome: the Insulin Resistance Atherosclerosis Study (IRAS). Circulation. 2000; 102(1):42–47. [PubMed: 10880413]

51. Djiogue S, Nwabo Kamdje AH, Vecchio L, Kipanyula MJ, Farahna M, Aldebasi Y, Seke Etet PF. Insulin resistance and cancer: the role of insulin and IGFs. Endocr Relat Cancer. 2013; 20(1):R1–R17. [PubMed: 23207292]
52. Pihlajamäki J, Gylling H, Miettinen TA, Laakso M. Insulin resistance is associated with increased cholesterol synthesis and decreased cholesterol absorption in normoglycemic men. J Lipid Res. 2004; 45(3):507–512. [PubMed: 14657199]
53. Bruce WR, Wolever TM, Giacca A. Mechanisms linking diet and colorectal cancer: the possible role of insulin resistance. Nutr Cancer. 2000; 37(1):19–26. [PubMed: 10965515]
54. Bruce WR, Giacca A, Medline A. Possible mechanisms relating diet and risk of colon cancer. Cancer Epidemiol Biomarkers Prev. 2000; 9(12):1271–1279. [PubMed: 11142411]
55. Bruce WR, Giacca A, Medline A. Possible mechanisms relating diet and risk of colon cancer. Cancer Epidemiol Biomark Prev. 2000; 9(12):1271–1279.
56. De Caterina R, Zampolli A, Del Turco S, Madonna R, Massaro M. Nutritional mechanisms that influence cardiovascular disease. Am J Clin Nutr. 2006; 83(2):421S–426S. [PubMed: 16470006]
57. Thompson FE, Metzner HL, Lamphiear DE, Hawthorne VM. Characteristics of individuals and long term reproducibility of dietary reports: the Tecumseh Diet Methodology Study. J Clin Epidemiol. 1990; 43(11):1169–1178. [PubMed: 2243254]
58. Jensen OM, Wahrendorf J, Rosenqvist A, Geser A. The reliability of questionnaire-derived historical dietary information and temporal stability of food habits in individuals. Am J Epidemiol. 1984; 120(2):281–290. [PubMed: 6465126]
59. Lindsted KD, Kuzma JW. Long-term (24-year) recall reliability in cancer cases and controls using a 21-item food frequency questionnaire. Nutr Cancer. 1989; 12(2):135–149. [PubMed: 2710656]
60. Jain M, Howe GR, Harrison L, Miller AB. A study of repeatability of dietary data over a seven-year period. Am J Epidemiol. 1989; 129(2):422–429. [PubMed: 2912050]
61. Thompson FE, Metzner HL, Lamphiear DE, Hawthorne VM. Characteristics of individuals and long term reproducibility of dietary reports: the Tecumseh Diet Methodology Study. J Clin Epidemiol. 1990; 43:1169–1178. [PubMed: 2243254]

Table 1

Prevalence of characteristics at baseline across quartiles of dietary inflammatory index (DII), IWHS, 1986

Characteristics[a,b] (mean ± SD or percentage)	**Dietary inflammatory index (higher means more inflammatory)**			
	Quartile 1 −5.7509 to −2.5041 Median = −3.14 *N* = 9380	**Quartile 2 −2.5040 to −1.2066 Median = −1.89 *N* = 9382**	**Quartile 3 −1.2065 to 0.6468 Median = −0.39 *N* = 9381**	**Quartile 4 0.6469–4.6598 Median = 1.85 *N* = 9382**
Age (years)	61.9 ± 4.3	61.6 ± 4.2	61.5 ± 4.2	61.2 ± 4.2
Total energy intake (kcal/day)	2115.4 ± 666.2	1927.6 ± 593.3	1740.3 ± 477.9	1411.7 ± 419.7
Total fat (% kcal/day)	31.8 ± 5.4	33.8 ± 5.3	34.5 ± 5.6	35.8 ± 6.0
BMI categories (%) (kg/m^2)				
Underweight (<18.5)	0.9	1.1	1.0	1.2
Normal weight (18.5–24.9)	41.0	39.1	37.7	37.8
Overweight (25.0–29.9)	37.2	36.9	37.0	35.9
Obese (≥30.0)	20.9	22.9	24.3	25.1
WHR tertiles (%)				
<0.795	37.0	34.3	32.2	30.4
0.795–0.869	32.9	33.3	33.4	33.4
>0.869	30.1	32.4	34.4	36.1
Education (%)				
Less than high school	14.9	16.6	18.4	21.1
High school	37.2	41.6	43.0	46.9
More than high school	47.9	41.8	38.7	32.0
Smoking (%)				
Never	69.8	66.9	65.4	59.5
Former	20.3	19.3	19.5	19.5
Current	9.9	13.8	15.1	21.0
Alcohol intake (grams/day)				
0	57.6	53.1	54.0	54.6
<15	35.4	40.6	40.0	38.5
≥15	7.1	6.4	6.0	7.0
Level of physical activity				
Low	34.9	45.0	51.0	59.4
Medium	30.0	29.1	27.1	24.0
High	35.1	25.9	22.0	16.6
Hormone replacement therapy (yes, %)	43.4	39.8	37.4	35.0
Prevalent diabetes	6.7	6.0	6.2	5.2
Prevalent high blood pres-Sure	35.3	36.2	37.6	36.9
Prevalent heart disease	10.4	9.3	9.4	9.5
Prevalent cancer	9.1	8.7	9.2	9.2
History of aspirin use (1992	72.4	72.6	70.4	70.7

Characteristics[a,b] (mean ± SD or percentage)	**Dietary inflammatory index (higher means more inflammatory)**			
	Quartile 1 −5.7509 to −2.5041 Median = −3.14 *N* = 9380	**Quartile 2 −2.5040 to −1.2066 Median = −1.89 *N* = 9382**	**Quartile 3 −1.2065 to 0.6468 Median = −0.39 *N* = 9381**	**Quartile 4 0.6469–4.6598 Median = 1.85 *N* = 9382**
survey, ever %)				
History of non-aspirin NSAIDs use (1992 survey, ever %)	41.0	40.6	39.2	37.7
History of any NSAIDs use (1992 survey, ever %)	83.3	83.9	81.5	81.6

[a] All variables are at baseline unless otherwise noted

[b] 957 or 3 % of women had missing data on the parameters

Table 2

Dietary inflammatory index (DII) and death; IWHS, 1986–2010

	DII	DII quartiles				
	Continuous	**1**	**2**	**3**	**4**	***p*-trend**
Participants	37,525	9380	9382	9381	9382	
Person-years of observation	778,521	195,996	195,505	194,823	192,198	
Total mortality						
Cases	17,793	4359	4419	4420	4595	
HR[a]	1.09	1.00	1.06	1.09	1.23	<0.0001
95 % CI	1.07–1.10	Reference	1.02–1.11	1.04–1.13	1.17–1.29	
Adjusted HR[b]	1.03	1.00	1.02	1.01	1.08	0.0005
95 % CI	1.01–1.05	Reference	0.97–1.06	0.96–1.05	1.03–1.13	
All cancer						
Cases	5044	1198	1204	1279	1363	
HR[a]	1.11	1.00	1.04	1.12	1.27	<0.0001
95 % CI	1.07–1.14	Reference	0.96–1.12	1.03–1.22	1.16–1.38	
Adjusted HR[b]	1.04	1.00	0.98	1.03	1.08	0.01
95 % CI	1.01–1.07	Reference	0.91–1.07	0.95–1.12	0.99–1.18	
Digestive cancers						
Cases	1240	285	302	314	339	
HR[a]	1.11	1.00	1.09	1.15	1.31	0.001
95 % CI	1.04–1.18	Reference	0.93–1.29	0.98–1.36	1.10–1.56	
Adjusted HR[b]	1.07	1.00	1.06	1.09	1.19	
95 % CI	1.01–1.14	Reference	0.90–1.24	0.92–1.28	1.00–1.43	0.04
All CVD						
Cases	6528	1615	1628	1620	1665	
HR[a]	1.08	1.00	1.07	1.08	1.22	<0.0001
95 % CI	1.05–1.11	Reference	0.99–1.14	1.01–1.16	1.13–1.32	
Adjusted HR[b]	1.04	1.00	1.03	1.00	1.09	0.006
95 % CI	1.01–1.07	Reference	0.96–1.10	0.93–1.08	1.01–1.18	

	DII	DII quartiles				
	Continuous	**1**	**2**	**3**	**4**	***p* -trend**
Non-cancer/Non-CVD/Non-acute deaths						
Cases	4909	1210	1253	1183	1263	
HR[a]	1.09	1.00	1.10	1.07	1.26	<0.0001
95 % CI	1.05–1.12	Reference	1.01–1.19	0.98–1.16	1.16–1.38	
Adjusted HR[b]	1.02	1.00	1.04	0.98	1.09	0.16
95 % CI	0.99–1.06	Reference	0.96–1.13	0.90–1.07	1.00–1.19	

[a]Adjusted for age (continuous) and total energy intake (continuous)

[b]Adjusted for age (continuous), BMI (continuous), smoking status (never, former, current), pack-years of smoking (continuous), HRT use (ever, never), education(<high school, high school graduate, more than high school), prevalent diabetes (yes/no), prevalent hypertension (yes/no), prevalent heart disease (yes/no), prevalent cancer (yes/no), total energy intake (continuous)

[c]Digestive cancers include cancer of the esophagus (*N* = 44), stomach (*N* = 78), small intestine (*N* = 16), colon (*N* = 536), rectum and anus (*N* = 70), liver and intrahepatic bile ducts (*N* = 88), gallbladder (*N* = 49), pancreas (*N* = 341), and other and ill-defined sites of the digestive organs (*N* = 18)

Table 3

Dietary inflammatory index and mortality due to CHD, stroke, COPD and Alzheimer's disease and unspecified dementia

	DII	DII quartiles				
	Continuous	**1**	**2**	**3**	**4**	***p* -trend**
CHD						
Cases	3381	803	821	862	895	
HR[a]	1.12	1.00	1.09	1.17	1.34	<0.0001
95 % CI	1.07–1.16	Reference	0.98–1.20	1.06–1.29	1.20–1.49	
Adjusted HRR[b]	1.07	1.00	1.04	1.07	1.17	0.001
95 % CI	1.03–1.11	Reference	0.94–1.15	0.97–1.19	1.05–1.30	
Stroke						
Cases	1439	376	375	341	347	
HR[a]	1.04	1.00	1.06	0.98	1.11	0.21
95 % CI	0.98–1.10	Reference	0.92–1.22	0.84–1.14	0.94–1.30	
Adjusted HR[b]	1.01	1.00	1.04	0.94	1.04	0.69
95 % CI	0.95–1.08	Reference	0.90–1.20	0.81–1.09	0.88–1.22	
COPD						
Cases	1039	201	251	270	317	
HR[a]	1.36	1.00	1.38	1.62	2.27	<0.0001
95 % CI	1.27–1.46	Reference	1.14–1.66	1.34–1.96	1.86–2.76	
Adjusted HR[b]	1.13	1.00	1.16	1.28	1.43	0.0006
95 % CI	1.05–1.21	Reference	0.96–1.40	1.06–1.55	1.18–1.75	
Alzheimer's disease and unspecified dementia						
Cases	1244	330	334	285	295	
HR[a]	1.00	1.00	1.07	0.92	1.05	0.98
95 % CI	0.94–1.07	Reference	0.92–1.24	0.78–1.08	0.88–1.25	
Adjusted HR[b]	0.99	1.00	1.06	0.91	1.03	0.73
95 % CI	0.93–1.05	Reference	0.91–1.24	0.77–1.07	0.86–1.23	

[a]Adjusted for age (continuous) and total energy intake (continuous)

[b] Adjusted for age (continuous), BMI (continuous), smoking status (never, former, current), pack-years of smoking (continuous), HRT use (ever, never), education(<high school, high school graduate, more than high school), prevalent diabetes (yes/no), prevalent hypertension (yes/no), prevalent heart disease (yes/no), prevalent cancer (yes/no), total energy intake (continuous)

Table 4

Association between DII and mortality by 5-year intervals

	DII	Years of follow-up				
	Continuous, all years of follow-up	**0–4.99**	**5.00–9.99**	**10.00–14.99**	**15.00–19.99**	**20.00–25.00**
Total mortality						
Cases	17,793	1345	2127	3254	4794	6273
HR[a]	1.09	1.11	1.13	1.11	1.09	1.05
95 % CI	1.07–1.10	1.04–1.18	1.08–1.19	1.06–1.15	1.06–1.13	1.02–1.08
Adjusted HRR[b]	1.03	1.04	1.07	1.04	1.04	1.01
95 % CI	1.01–1.05	0.98–1.11	1.01–1.12	1.00–1.09	1.01–1.08	0.98–1.04
All cancer						
Cases	5044	680	897	1119	1192	1156
HR[a]	1.11	1.05	1.08	1.18	1.10	1.10
95 % CI	1.07–1.14	0.97–1.14	1.00–1.16	1.10–1.26	1.04–1.18	1.03–1.18
Adjusted HR[b]	1.04	0.98	1.00	1.10	1.05	1.05
95 % CI	1.01–1.07	0.90–1.07	0.93–1.08	1.03–1.18	0.98–1.12	0.99–1.13
Digestive cancers						
Cases	1240	178	207	270	288	297
HR[a]	1.11	1.01	1.15	1.21	1.06	1.11
95 % CI	1.04–1.18	0.86–1.19	0.98–1.34	1.06–1.38	0.93–1.21	0.98–1.27
Adjusted HR[b]	1.07	0.98	1.08	1.17	1.03	1.10
95 % CI	1.01–1.14	0.83–1.15	0.93–1.27	1.02–1.34	0.90–1.18	0.97–1.25
All CVD						
Cases	6528	417	736	1177	1825	2373
HR[a]	1.08	1.13	1.18	1.06	1.10	1.04
95 % CI	1.05–1.11	1.01–1.26	1.09–1.28	1.00–1.13	1.05–1.16	0.99–1.09
Adjusted HR[b]	1.04	1.06	1.14	1.01	1.07	1.00
95 % CI	1.01–1.07	0.95–1.19	1.05–1.24	0.94–1.07	1.01–1.13	0.96–1.05
CHD						
Cases	3381	260	447	681	918	1075

	DII	Years of follow-up				
	Continuous, all years of follow-up	**0–4.99**	**5.00–9.99**	**10.00–14.99**	**15.00–19.99**	**20.00–25.00**
HR[a]	1.12	1.19	1.19	1.05	1.15	1.08
95 % CI	1.07–1.16	1.04–1.37	1.07–1.32	0.96–1.14	1.07–1.24	1.01–1.16
Adjusted HR[b]	1.07	1.13	1.15	0.98	1.12	1.03
95 % CI	1.03–1.11	0.98–1.31	1.03–1.28	0.90–1.07	1.04–1.20	0.96–1.11
Stroke						
Cases	1439	54	129	233	441	582
HR[a]	1.04	1.13	1.08	1.10	1.06	0.98
95 % CI	0.98–1.10	0.84–1.52	0.89–1.32	0.96–1.28	0.95–1.18	0.89–1.07
Adjusted HR[b]	1.01	1.05	1.07	1.06	1.04	0.96
95 % CI	0.95–1.08	0.77–1.42	0.87–1.31	0.92–1.23	0.93–1.16	0.87–1.06
Non-cancer/non-CVD/non-acute deaths						
Cases	4909	181	371	738	1414	2205
HR[a]	1.09	1.29	1.18	1.10	1.11	1.04
95 % CI	1.05–1.12	1.09–1.52	1.05–1.32	1.01–1.19	1.05–1.18	0.99–1.09
Adjusted HR[b]	1.02	1.18	1.07	1.03	1.04	0.99
95 % CI	0.99–1.06	1.00–1.40	0.95–1.21	0.95–1.12	0.98–1.10	0.95–1.04
COPD						
Cases	1039	64	126	181	307	361
HR[a]	1.36	1.64	1.27	1.49	1.37	1.27
95 % CI	1.27–1.46	1.23–2.18	1.04–1.55	1.27–1.77	1.20–1.55	1.13–1.43
Adjusted HR[b]	1.13	1.38	1.05	1.23	1.10	1.08
95 % CI	1.05–1.21	1.04–1.83	0.86–1.28	1.04–1.45	0.98–1.26	0.96–1.21
Alzheimer’s disease and unspecified dementia						
Cases	1244	0	0	52	332	860
HR[a]	1.00	–	–	0.83	1.09	0.98
95 % CI	0.94–1.07	–	–	0.60–1.13	0.96–1.23	0.91–1.06
Adjusted HR[b]	0.99	–	–	0.80	1.08	0.97
95 % CI	0.93–1.05	–	–	0.58–1.11	0.95–1.22	0.90–1.05

[a] Adjusted for age (continuous) and total energy intake (continuous)

[b] Adjusted for age (continuous), BMI (continuous), smoking status (never, former, current), pack-years of smoking (continuous), HRT use (ever, never), education(<high school, high school graduate, more than high school), prevalent diabetes (yes/no), prevalent hypertension (yes/no), prevalent heart disease (yes/no), prevalent cancer (yes/no), total energy intake (continuous)

[c] Digestive cancers include cancer of the esophagus (*N* = 44), stomach (*N* = 78), small intestine (*N* = 16), colon (*N* = 536), rectum and anus (*N* = 70), liver and intrahepatic bile ducts (*N* = 88), gallbladder (*N* = 49), pancreas (*N* = 341), and other and ill-**defined** sites of the digestive organs (*N* = 18)