Construct Validation of the Dietary Inflammatory Index among Postmenopausal Women

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Abstract

Purpose—Many dietary factors have either pro- or anti-inflammatory properties. We previously developed a dietary inflammatory index (DII) to assess the inflammatory potential of diet. In this study we conducted a construct validation of the DII based on data from a food frequency questionnaire and three inflammatory biomarkers in a subsample of 2,567 postmenopausal women in the Women's Health Initiative Observational Study.

Methods—We used multiple linear and logistic regression models, controlling for potential confounders, to test whether baseline DII predicted concentrations of interleukin-6 (IL-6), high-sensitivity C-reactive protein (hs-CRP), tumor necrosis factor alpha receptor 2 (TNFα-R2), or an overall biomarker score combining all three inflammatory biomarkers.

Results—The DII was associated with the four biomarkers with beta estimates (95%CI) comparing the highest with lowest DII quintiles as follows: IL-6: 1.26 (1.15, 1.38), P_{trend}<0.0001; TNFα-R2: 81.43 (19.15, 143.71), P_{trend}=0.004; dichotomized hs-CRP (odds ratio for higher versus lower hs-CRP): 1.30 (0.97, 1.67), P_{trend}=0.34); and the combined inflammatory biomarker score: 0.26 (0.12, 0.40), P_{trend}=0.0001.

Conclusion—The DII was significantly associated with inflammatory biomarkers. Construct validity of the DII indicates its utility for assessing the inflammatory potential of diet and for expanding its use to include associations with common chronic diseases in future studies.

INTRODUCTION

Many dietary factors are known to affect inflammation. A Western-style diet, rich in pro-inflammatory foods that are high in sugar (especially desserts and soft drinks), refined grains, red and processed meats, and fried foods, increases levels of inflammatory markers such as C-reactive protein (CRP) and interleukin-6 (IL-6) (1). By contrast, diets rich in fruits, vegetables, whole grains, legumes, nuts, olive oil and fish (e.g., Mediterranean-type diet) tend to be associated with reduced chronic inflammation (2–4). Specific components of such diets (e.g., fruits and vegetables, omega-3 polyunsaturated fatty acids, fiber, moderate alcohol intake, vitamin E, vitamin C, β-carotene, and magnesium) can reduce inflammatory biomarkers (5, 6).

Dietary indices and dietary pattern analysis have emerged as alternative and complementary approaches to examining relationships between diet and chronic diseases (7, 8). Conceptually, dietary indices or patterns represent a broader picture of food and nutrient consumption, and may thus be a better tool to predict disease risk than are individual foods or nutrients (9–11). Several dietary indices exist to assess the overall quality of diet (12–14).

The dietary inflammatory index (DII) (15) was developed in order to assess the quality of diet with regard to its inflammatory potential. The goal in creating the DII was to provide a tool that could assess an individual's diet on a continuum from maximally anti-inflammatory to maximally pro-inflammatory. Previously, the DII was construct validated using high-sensitivity CRP (hs-CRP) measurements in a longitudinal cohort of 494 individuals followed in Central Massachusetts with intensive dietary monitoring using 24-hour dietary recall interviews (24HR) and 7-day dietary recalls (7DDR) (16) for one year (17).

In the current study, our objective was to conduct a construct validation of the food frequency questionnaire (FFQ)-derived DII in a much larger population by evaluating its association with an extended number of inflammatory biomarkers [IL-6, hs-CRP, and tumor necrosis factor alpha receptor 2 (TNFα-R2)], and an overall inflammatory biomarker score derived from a combination of the three biomarkers.

METHODS

Participants

The design of the Women's Health Initiative (WHI), a large and complex investigation of strategies for the prevention and control of common causes of morbidity and mortality among postmenopausal women, has been described in detail elsewhere (18). Briefly, a total of 161,808 postmenopausal women 50 to 79 years old were enrolled at 40 sites in the United States between 1993 and 1998. The women were enrolled into either the Clinical Trials (CT) component that included 68,132 women or the Observational Study (OS) component that included 93,676 women (18). An emphasis was placed on the inclusion of women of racial/ethnic minority groups, who represented 17.1% of the overall sample.

Exclusion criteria for both the OS and CT included any medical condition associated with a predicted survival of less than three years, alcoholism, other drug dependency, mental illness (e.g., major depressive disorder), dementia, not likely to live in the area for at least three years, and active participation in another intervention trial. Demographic information and lifestyle data were obtained by self-report using standardized questionnaires. Certified staff performed physical measurements, including height and weight, and collected blood samples at the baseline clinic visit. The WHI protocol was approved by the institutional review boards (IRB) at the Clinical Coordinating Center (CCC) at the Fred Hutchinson Cancer Research Center (Seattle, WA) and at each of the 40 Clinical Centers (19). In addition, the University of South Carolina IRB approved the current analyses.

Dietary Assessment

We used dietary data from the self-administered WHI FFQ completed by a subsample of 2,567 WHI participants at baseline (1993–1998), reflecting average dietary intake over the previous three months. The nutrient database was derived from the University of Minnesota's Nutrition Coordinating Center nutrient database (20), which is based on the US Department of Agriculture Standard Reference Releases and manufacturer information. In a previous study, the WHI FFQ produced nutrient estimates which were similar to those obtained from short-term dietary recalls and records (21). The FFQ included questions on

nutritional supplement use for 15 nutrient components of the DII; namely, iron, magnesium, niacin, riboflavin, selenium, thiamine, beta-carotene, zinc, folic acid, and vitamins A, C, D, E, B6, and B12.

Description of the dietary inflammatory index (DII)

Details of the development (15) and construct validation (17) of the DII have been described elsewhere. Briefly, investigators performed an extensive literature search to identify studies published in peer-reviewed journals that examined the association between six inflammatory biomarkers (IL-1β, IL-4, IL-6, IL-10, TNFα, and CRP) and 45 specific foods and nutrients (see Table 1 for components of the DII). A total of 1,943 eligible articles published through 2010 were indexed and scored. One of three possible values was assigned to each article for each of up to 6 of the inflammatory markers based on the effect of the food or nutrient: '+1' was assigned if the effects were pro-inflammatory, '-1' if the effects were anti-inflammatory and '0' if the food or nutrient produced no significant change in the marker. Articles were weighted by study design; with human experimental studies assigned the highest weight and cell culture studies assigned the lowest. An inflammatory effect score for each DII component was calculated by subtracting the weighted anti-inflammatory fraction from the pro-inflammatory fraction. If the weighted article score was based on <236 articles (the median number of total weighted articles) then it was divided by 236 and the resulting fraction was used to adjust the inflammatory effect scores to adjust for the size of the literature base.

Actual dietary intake data were standardized to a representative global dietary database based on 11 dietary datasets from diverse populations in different parts of the world. The standardized dietary intake data were then multiplied by the adjusted inflammatory effect scores, as briefly described above, and summed to obtain the overall DII (15). The overall DII score characterizes an individual's diet on a continuum from maximally anti-inflammatory (the low end of the scale) to maximally pro-inflammatory (the high end of the scale). In the WHI FFQ, 32 of the 45 original DII components were available for inclusion in the overall DII score. Components not available in the WHI FFQ included: ginger, turmeric, garlic, oregano, pepper, rosemary, eugenol, saffron, flavan-3-ol, flavones, flavonols, flavonones, and anthocyanidins, and therefore were not included here (Table 1).

Inflammatory biomarkers

Inflammatory biomarkers were previously measured in a WHI ancillary study conducted in a sample of women in the WHI-OS at baseline from 1993 to 1998 (n=3,245) (22). The construct validation of the DII was conducted in this sample of women who had data on plasma IL-6, hs-CRP and TNFα-R2. We also derived an overall inflammatory biomarker score by standardizing each of the three inflammatory biomarkers as described under statistical analysis.

Methods for the collection and processing of blood samples have been described (22). Briefly, IL-6 and TNFα-R2 concentrations were measured by an ultrasensitive enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, Minnesota), and hs-CRP concentrations were measured on a chemistry analyzer (Hitachi 911; Roche Diagnostics,

Indianapolis, Indiana) using an immunoturbidimetric assay with reagents and calibrators (Denka Seiken Co. Ltd., Niigata, Japan). The coefficients of variation were: 7.6% for IL-6,1.6% for hs-CRP, and 3.5% for TNFα-R2 (22).

Statistical analysis

Among the 3,245 participants with inflammatory biomarker data, we excluded 311 whose hs-CRP values were 10 mg/L, because such high values are unlikely to be related to diet and are more likely caused by infection or medication use (23). From the remaining 2,934 participants, we excluded 198 for implausible reported energy intake values on the FFQ (<600 kcal/d or >5000 kcal/d) and 23 for extreme body mass index (BMI) (<15 kg/m^2 or >50 kg/m^2). Participants with missing values for inflammatory biomarkers and important covariates (n=146) also were excluded from the models, leaving a total of 2,567 participants for inclusion in the current analyses.

Participants' characteristics were summarized using frequencies for categorical variables and means and standard deviations (SD) for continuous variables or geometric means for log-transformed variables. TNFα-R2 was approximately normally distributed; however, the distributions of IL-6 and hs-CRP were heavily skewed, and the data were log-transformed (base 10) in order to normalize the distributions. Geometric means were calculated by back-transforming the arithmetic means of the log-transformed values. An overall inflammatory biomarker score was derived by computing a z-score for each of the three inflammatory biomarkers and then summing the z-scores to create a standardized overall inflammatory biomarker score for each participant as follows:

$$\text{Overall inflammatory biomarker score} = z-\text{score}(\log \text{ hs}-\text{CRP}) + z-\text{score}(\log \text{ IL}-6) + z-\text{score}(\text{TNF}\alpha-\text{R2})$$

The association between the DII and each biomarker of systemic inflammation (IL-6, hs-CRP, TNFα-R2 and the overall inflammatory biomarker score) was evaluated in four separate multivariable linear regression models. One model was fit for each inflammatory biomarker as the dependent variable and quintiles (Q) of DII as the independent variable of interest, adjusting for multiple covariates listed below. Parameter estimates for the association between IL-6 and hs-CRP were back transformed to the original units of measurement because IL-6 and hs-CRP were log transformed prior to analyses. A clinically relevant cutpoint (3 mg/L) was also used to dichotomize hs-CRP (23). The dichotomous variable was entered into logistic regression models to estimate odds ratios (ORs) of having higher hs-CRP levels (>3 mg/L) compared to lower levels (3 mg/L), with increasing DII. Tests of linear trend were conducted for each model by assigning the median DII for each quintile to all participants in the quintile as an ordinal variable. The *p*-value of this variable was interpreted as the *p*-value for trend.

Variables assessed for confounding included age (years); BMI [normal weight (<25 kg/m^2), overweight (25 to <30 kg/m^2), and obese (30 kg/m^2)]; race/ethnicity [European American, African American, Hispanic, and Asian or Pacific Islander]; education (less than high school, high school diploma/GED, some college/graduate education); smoking status (current, past, and never); physical activity (PA) categorized based on current public health

recommendations (24), as currently meeting or not meeting PA recommendations (150 minutes/week of moderate intensity PA or 75 minutes/week of vigorous intensity PA versus <150 minutes/week of moderate intensity PA or <75 minutes/week of vigorous intensity PA, respectively); regular [at least twice a week for the previous 2 weeks (25)] use of non-steroidal anti-inflammatory drugs (NSAIDs) (yes/no), anti-depressants (yes/no) or statins (yes/no) and co-morbidity (yes/no). The following conditions were included in the combined co-morbidity variable: history of ulcerative colitis, diabetes, Alzheimer's disease, arthritis, hypertension, cancer, and high cholesterol. Models were not adjusted for total energy intake by including energy intake as a variable in the models because it is one of the DII components (Table 1). In sensitivity analyses, results did not substantially change between models with and without total energy intake as a covariate.

Potential effect modification of the association between the DII and inflammatory biomarkers by BMI, race/ethnicity, and NSAIDs use was assessed by including DII*covariate interaction terms in all models. A *p*-value of the interaction term <0.10 indicated significant effect modification, and subgroup models were constructed in levels of the effect modifier, adjusted for all covariates listed above except the potential effect modifier.

All tests were 2-sided, and 95% confidence intervals (95% CI) not including zero for TNFα-R2 and combined biomarker score; and not including one for hs-CRP and IL-6, were considered to be statistically significant. All statistical analyses were performed using Statistical Analysis Systems software, version 9.3 (SAS Institute, Inc., Cary, NC).

RESULTS

Table 2 presents characteristics of study participants. Approximately one third of participants had normal BMI while two thirds were overweight or obese. Most (55%) study participants were European Americans, while 27% were African Americans, and 10% Hispanics; approximately 65% had four or more years of college education while 54%, 40%, and 6% of the participants were never, former, or current smokers, respectively; and 50% were regular NSAIDs users. The DII ranged from −6.23 to +5.22 with a mean of −0.62 (Table 2).

Table 3 presents parameter estimates of the association of the DII with the inflammatory biomarkers and combined score. Higher DII scores significantly predicted higher IL-6 concentrations [β (95%CI) for Q5 vs. Q1: 1.26 pg/mL, (1.15, 1.38), P_{trend}<0.0001]; but not higher hs-CRP concentrations [β (95%CI) for Q5 vs. Q1: 1.07 mg/L 0.95, 1.20), P_{trend}=0.37]. When hs-CRP was dichotomized, there was a suggestion that higher DII scores were associated with elevated hs-CRP concentrations, [OR (95%CI) for Q5 vs. Q1: 1.34 (0.97, 1.67); P_{trend} =0.34]. Higher DII scores significantly predicted higher TNFα-R2 concentrations [β (95%CI) for Q5 vs. Q1: 81.43 pg/mL (19.15, 143.71), P_{trend}=0.004]. A higher DII score was associated with an increased overall inflammatory biomarker score in the 4th [0.17 (0.04, 0.30)] and 5th [0.26 (0.12, 0.40)] DII quintiles, with a significant linear trend (P_{trend}=0.0001).

Table 4 presents results from subgroup analyses stratified by BMI categories, race/ethnicity, and NSAIDs use. Effect modification was evident ($P_{\text{interaction}} < 0.10$) in the IL-6 models by BMI and race/ethnicity, while effect modification by NSAIDs use was found in the TNFα-R2 and overall inflammatory biomarker score models. For example, a higher DII score was associated with a higher IL-6 in African Americans [β (95%CI) for Q5 vs. Q1: 1.41 (1.15, 1.70)] and in European Americans [β (95%CI) for Q5 vs. Q1: 1.38 (1.23, 1.55)] than in Hispanics [β (95%CI) for Q5 vs. Q1: 0.66 (0.48, 0.91)] or Asian/Pacific Islanders [β (95%CI) for Q5 vs. Q1:0.95 (0.63, 1.45), while the association of the DII score with overall inflammatory marker score among non-NSAIDs users [β (95%CI) for Q5 vs. Q1: 0.37 (0.18, 0.56)] was more than twice that observed in NSAIDs users [β (95%CI) for Q5 vs. Q1: 0.11 (−0.09, 0.31]. Though the interaction term for DII and NSAIDs use was not statistically significant (P=0.57) in the hs-CRP model, DII significantly predicted higher hs-CRP levels among non-users of NSAIDs but not among users. Non-users had 67% higher odds of an elevated CRP [OR (95%CI) for Q5 vs. Q1: 1.67 (1.09, 2.55); P_{trend} =0.10], while there was no significant association among users [OR (95%CI) for Q5 vs. Q1: 0.99 (0.65, 1.52); P_{trend} =0.53] (Table 4).

In analyses restricted to non-users of NSAIDs (n=1290) and stratified by categories of BMI, we found even stronger associations between the DII and hs-CRP, TNFα-R2 and the overall inflammatory biomarker score, especially in obese individuals (BMI 30kg/m^2) (Table 5). Odds of an elevated hs-CRP were 2.34 times higher in participants with the most pro-inflammatory diets compared to those with the most anti-inflammatory diets [OR (95%CI) for Q5 vs. Q1: 2.34 (1.17, 4.64); P_{trend} =0.11]. Parameter estimates for TNFα-R2 [β (95%CI) for Q5 vs. Q1: 282.63 pg/mL (126.71, 438.56), P_{trend} <0.0001] and the overall inflammatory biomarker score [β (95%CI) for Q5 vs. Q1: 0.74 (0.39, 1.09), P_{trend}<0.0001] were almost two times higher than corresponding estimates in the subgroup analyses shown in Table 4 that did not restrict to non-users of NSAIDs.

DISCUSSION

We demonstrated that the FFQ-derived DII significantly predicted higher plasma concentrations of IL-6, TNFα-R2, and levels of the combined inflammatory biomarker score, and was associated with increased odds of having elevated hs-CRP among non-users of NSAIDs especially those who were obese. Our results suggest that pro-inflammatory diets are associated with significantly higher concentrations of two inflammatory biomarkers, and a combined inflammatory biomarker score.

The WHI recruited a diverse study population, and these results provide the first examination of the association between the DII and markers of inflammation in racially and ethnically diverse postmenopausal women. A previous validation study of the DII in a sample of 494 adult men and women in Central Massachusetts using dietary data from 24HR and hs-CRP as a marker of inflammation found a positive association between the DII and hs-CRP (17). Similar to our results, a previous WHI ancillary study demonstrated that dietary fiber (an anti-inflammatory constituent of the DII) is inversely associated with TNFα-R2 and IL-6, though no association was observed with hs-CRP among postmenopausal women (19). It is unclear why associations between the DII and some

markers were observed, but not between the DII and hs-CRP in our study. The DII was developed based on approximately 2000 peer-reviewed articles that examined the effect of diet on six different inflammatory markers. The literature for all inflammatory markers was given the same weight in the scoring. There may have been more literature on IL-6 or CRP, for example, than some of the other inflammatory markers, but this is not a likely explanation for the different associations observed in our study.

Our results also are in agreement with several other studies of diets/dietary patterns and inflammatory biomarker levels (26–30). Regardless of the statistical method (e.g., factor analysis, reduced rank regression, *a priori* index calculations such as the Health Eating Index or Mediterranean Diet Score) used to define dietary patterns, consistent results have been reported in these studies. No previous study has directly compared the inflammatory predictive abilities of these other indices with the DII using the same study population. Therefore, we can only speculate that the DII would have superior predictive ability with regard to dietary inflammatory potential, given that inflammation was the central theme in its development.

There was significant effect modification in models for IL-6 by BMI and race/ethnicity and for TNFα-R2 and the overall inflammatory biomarker score by NSAIDs use. Higher levels of the DII were associated with higher plasma concentrations of IL-6 in overweight and obese women but not in normal weight women. This is consistent with other studies that found that overweight or obese participants had a greater increase in IL-6 with increasing weight, BMI, and waist circumference compared to normal-weight participants (31). Higher values of the DII also predicted higher IL-6 levels in African Americans and European Americans but not in Hispanics or Asian/Pacific Islanders, with the strongest association evident among African Americans. This is consistent with the idea that African Americans are more sensitive to the effects of inflammatory stimuli (32). Higher scores of the DII towards more pro-inflammatory values were associated with higher levels of TNFα-R2 and the combined inflammatory biomarker score among non-users of NSAIDs, but not among regular users of NSAIDs. In two previous studies, (33, 34) Tabung and colleagues found similar trends in the association of a combined lifestyle index on colorectal adenomatous polyps, by NSAIDs use. In one study, higher scores (representing a healthier lifestyle pattern) were associated with lower odds of colorectal adenomas in non-users of NSAIDs, but not in users (33). In the other study examining the association between the DII and risk of colorectal cancer significantly higher risk was observed in non-users of NSAIDs but not in users (34). The adverse effects of a pro-inflammatory diet on inflammation may be masked by the stronger effects of NSAIDs use among regular users.

Our study has several strengths and limitations to be considered. The WHI is a well-characterized study, and our large sample size provided ample power to detect significant associations, especially in subgroup analyses. In addition, we controlled for several covariates to examine the independent effects of the DII on the three inflammatory biomarkers. The study population was limited to postmenopausal women enrolled in the WHI; thus, the generalizability of the results is limited to this group. We used baseline FFQs because these were assessed around the same time blood was collected for testing inflammatory biomarkers; however, the cross-sectional design does not allow an evaluation

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of temporal relationships. Components missing from the FFQ including ginger, turmeric, garlic, oregano, pepper, rosemary, eugenol, saffron, flavan-3-ol, flavones, flavonols, flavonones, and anthocyanidins are anti-inflammatory. So, even though we showed previously that reasonable predictive ability was retained when replacing 24-hour recall-derived DII scores with those derived from a structured questionnaire (7-day dietary recalls) (17), the DII may have a lower predictive ability in a population that was actively trying to change to a more healthful diet and therefore might be more likely to begin consuming these food items that are not on the FFQ list. The DII score calculated from the 32 available components ranged from −6.23 to +5.22, which is similar to the range of −5.4 to +5.8 obtained in the first DII construct validation study using data from fifteen 24-hour dietary recalls with 44 of the 45 DII components (17). The DII obtained in the current study is also similar to the range of −5.36 to +6.25 in a Spanish study with 33 components of the DII available in the FFQ (35).

CONCLUSIONS

The DII was significantly associated with inflammatory biomarkers. Good construct validity of the DII indicates its utility for assessing the inflammatory potential of diet and for expanding its use to include examining associations with common chronic diseases in the WHI and other populations. Our results have important public health implications and may provide guidance for nutrition intervention and education to reduce the inflammatory potential of the diet as a means of reducing chronic inflammation.

Acknowledgments

ABBREVIATIONS

CCC	Clinical Coordinating Center
CVD	Cardiovascular disease
CT	Clinical trial
DII	Dietary inflammatory index
DM	Dietary Modification
FFQ	Food frequency questionnaire
hs-CRP	High sensitivity C-reactive protein
IL-6	Interleukin-6
IRB	Institutional review board
NDSR	Nutrition Data System for Research

NSAID	Non-steroidal anti-inflammatory drug
OS	Observational Study
PA	Physical activity
PUFA	Polyunsaturated fatty acid
TNFα-R2	Tumor necrosis factor alpha receptor 2
WH	Women's Health Initiative
7DDR	7-day dietary recalls
24HR	24-hour dietary recall

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APPENDIX – SHORT LIST OF WHI INVESTIGATORS

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For a list of all the investigators who have contributed to WHI science, please visit: https://www.whi.org/researchers/Documents%20%20Write%20a%20Paper/WHI%20Investigator%20Long%20List.pdf

Table 1

Components of the dietary inflammatory index with their inclusion status in the WHI FFQ

	DII component	Included in WHI FFQ?		DII component	Included in WHI FFQ?
1	Alcohol, g	Yes	24	Riboflavin, mg	Yes
2	Vitamin B12, ug	Yes	25	Saffron, g	No
3	Vitamin B6, mg	Yes	26	Saturated Fat, g	Yes
4	Beta Carotene, ug	Yes	27	Selenium, mg	Yes
5	Caffeine, g	Yes	28	Thiamin, mg	Yes
6	Carbohydrate, g	Yes	29	Trans Fat, g	Yes
7	Cholesterol, mg	Yes	30	Turmeric, mg	No
8	Energy, kcal	Yes	31	Vitamin A, ug	Yes
9	Eugenol, mg	No	32	Vitamin C, mg	Yes
10	Total Fat, g	Yes	33	Vitamin D, ug	Yes
11	Fiber, g	Yes	34	Vitamin E, mg	Yes
12	Folic Acid, mg	Yes	35	Zinc, mg	Yes
13	Garlic, g	No	36	Green tea/Black tea, g	Yes
14	Ginger, g	No	37	Flavan-3-ol	No
15	Iron, mg	Yes	38	Flavones, mg	No
16	Magnesium, mg	Yes	39	Flavonols, mg	No
17	MUFA, g	Yes	40	Flavonones, mg	No
18	Niacin, mg	Yes	41	Anthocyanidins, mg	No
19	Omega 3, g	Yes	42	Isoflavones, mg	Yes
20	Omega 6, g	Yes	43	Pepper, g	No
21	Onion, g	Yes	44	Thyme/Oregano, mg	No
22	Protein, g	Yes	45	Rosemary, mg	No
23	PUFA, g	Yes			

Table 2

Baseline characteristics of a subsample of 2,567 women participating in the Women's Health Initiative Observational Study, 1993–1998

Characteristic	
Continuous variables:	**Mean (SD)**
Dietary inflammatory index (DII)	−0.62 (2.69)
Inflammation biomarkers	
IL-6 (pg/mL)[*]	1.34 (1.42)
hs-CRP (mg/L)[*]	1.36 (1.57)
TNF α receptor 2 (pg/mL)	2578.85 (835.58)
Overall inflammatory score	−1.41 (1.19)
Total energy intake (Kcal/d)	1585.44 (659.91)
Categorical variables:	**Frequency (%)**
Age groups (years)	
<50–59	872 (34.0)
60–69	1186 (46.2)
70–79	509 (19.8)
Body mass index (kg/m^2)	
Normal (<25)	765 (29.8)
Overweight (25.0 – <30)	863 (33.6)
Obese (30)	939 (36.6)
Race/ethnicity	
European American	1418 (55.2)
African American	697 (27.2)
Hispanic/Latino	263 (10.2)
Asian or Pacific Islander	189 (7.4)
Educational level	
Less than high school	80 (3.1)
High school/GED	827 (32.2)
four or more years of college	1660 (64.7)
Smoking status	
Never	1381 (53.8)
Former	1038 (40.4)
Current	148 (5.8)
Physical activity (PA), minutes/week	
Not meeting PA recommendations	1530 (59.6)
Meeting PA recommendations	1037 (40.4)
Inflammation-related comorbid conditions[**]	
No	723 (28.2)
Yes	1844 (71.8)
Antidepressant use	
No	2282 (88.9)

Characteristic	
Yes	285 (11.1)
Non-steroidal Anti-inflammatory Drug (NSAID) use	
No	1290 (50.2)
Yes	1277 (49.8)

[*] Geometric means (coefficient of variation) are presented for hs-CRP and IL-6 since they were normalized by log-transformation,

[**] included history of ulcerative colitis, diabetes, Alzheimer's disease, arthritis, hypertension, cancer, and high cholesterol

Table 3

Association between the FFQ-derived DII and biomarkers of inflammation among 2,567 postmenopausal women participating in the Women's Health Initiative Observational Study, 1993–1998

Inflammatory biomarker	Quintiles (Q) of the DII: Estimate[1] (95% confidence interval)					Ptrend[2]
	Q1 (−6.230, < −3.126)	Q2 (−3.126, < −1.833)	Q3 (−1.833, < −0.023)	Q4 (−0.023, <2.147)	Q5 (2.147, 5.224)	
IL-6 model[3]						
Age-adjusted	referent	1.15 (1.05, 1.26)*	1.05 (1.12, 1.38)*	1.32 (1.20, 1.45)*	1.48 (1.35, 1.62)*	<0.0001
Fully adjusted[4]	referent	1.07 (0.98, 1.17)	1.12 (1.02, 1.20)*	1.15 (1.05, 1.26)*	1.26 (1.15, 1.38)*	<0.0001
hs-CRP model (hs-CRP continuous)[3]						
Age-adjusted	referent	1.26 (1.12, 1.45)*	1.26 (1.12, 1.45)*	1.29 (1.15, 1.45)*	1.29 (1.15, 1.48)*	0.0007
Fully adjusted[4]	referent	1.12 (1.00, 1.26)*	1.07 (0.95, 1.20)	1.12 (1.01, 1.26)*	1.07 (0.95, 1.20)	0.37
hs-CRP model (hs-CRP dichotomous; odds ratios)[5]						
Age-adjusted	referent	1.63 (1.26, 2.10)*	1.55 (1.20, 2.00)*	1.53 (1.19, 1.98)*	1.65 (1.28, 2.13)*	0.003
Fully adjusted	referent	1.45 (1.09, 1.92)*	1.22 (0.92, 1.62)	1.25 (0.94, 1.67)	1.30 (0.97, 1.67)	0.34
TNFα-R2 model						
Age-adjusted	referent	68.58 (−31.43, 168.60)	89.05 (−10.91, 189.02)	84.58 (−15.49, 184.57)	132.65 (32.64, 232.66)*	0.02
Fully adjusted[4]	referent	−23.31 (−88.69, 32.06)	−9.59 (−69.52, 50.35)	16.93 (−43.34, 77.20)	81.43 (19.15, 143.71)*	0.004
Overall inflammatory score (IS)[6]						
Age-adjusted	referent	0.19 (0.05, 0.33)*	0.24 (0.10, 0.38)*	0.26 (0.11, 0.40)*	0.35 (0.21, 0.49)*	<0.0001
Fully adjusted[4]	referent	0.09 (−0.04, 0.22)	0.11 (−0.02, 0.24)	0.17 (0.04, 0.30)*	0.26 (0.12, 0.40)*	0.0001

*
Statistically significant association;

[1]
Beta parameter;

[2]
The median of each quintile was assigned to all participants in the quintile and the variable introduced into models as an ordinal variable and its p-value interpreted as the p-value for tend;

[3]
Backtransformed (10^x) estimates since the data were log transformed to the base 10, prior to analyses;

[4]
All fully adjusted models were adjusted for age, BMI, race, educational level, smoking status, physical activity, inflammation-related comorbidity, regular use of antidepressants, statins, and NSAIDs;

[5]
Dichotomous hs-CRP (>3 mg/L, n=1066; ≤3 mg/L, n=1501) modeled the probability that hs-CRP >3 mg/L;

[6] The overall inflammatory score was computed by summing z-scores of all three biomarkers for each participant.

Table 4

Association between the FFQ-derived DII and biomarkers of inflammation in subgroups of BMI, race/ethnicity and NSAIDs use among post-menopausal women; Women's Health Initiative Observational Study, 1993–1998

Inflammatory biomarker	Quintiles (Q) of the DII: Estimate[1] (95% confidence interval)				
	Q1 (−6.230, <−3.126)	Q3 (−1.833, <−0.023)	Q5 (2.147, 5.224)	Ptrend[2]	P(interaction)[3]
Subgroup analyses for IL-6 model[4]					
Body mass index, kg/m^{2}					0.02
Normal weight (<25)	referent	1.00 (0.89, 1.12)	1.02 (0.89, 1.10)	0.85	
Overweight (25 – <30)	referent	1.01 (0.91, 1.12)	1.20 (1.10, 1.32)*	<0.0001	
Obese (≥30)	referent	1.01 (0.91, 1.10)	1.15 (1.05, 1.26)*	0.0002	
Race/ethnicity					0.0007
African American	referent	1.26 (1.02, 1.55)*	1.41 (1.15, 1.70)*	0.0007	
European American	referent	1.15 (1.02, 1.26)*	1.38 (1.23, 1.55)*	<0.0001	
Hispanic	referent	0.72 (0.51, 1.17)	0.66 (0.48, 0.91)*	0.29	
Asian/Pacific Islander	referent	0.79 (0.56, 1.12)	0.95 (0.63, 1.45)	0.99	
NSAID use					0.29
Non NSAIDs users	referent	1.12 (0.99, 1.29)	1.29 (1.15, 1.48)*	0.0003	
NSAIDs users	referent	1.10 (0.98, 1.23)	1.23 (1.07, 1.41)*	0.001	
Subgroup analyses for hs-CRP model (hs-CRP dichotomous; odds ratios)[5]					
Body mass index, kg/m^{2}					0.57
Normal weight (<25)	referent	0.76 (0.41, 1.40)	1.11 (0.60, 2.03)	0.71	
Overweight (25 – <30)	referent	1.11 (0.68, 1.81)	1.48 (0.90, 2.48)	0.31	
Obese (≥30)	referent	1.78 (1.12, 2.82)*	1.41 (0.88, 2.27)	0.58	
Race/ethnicity					0.58
African American	referent	1.42 (0.76, 2.66)	1.35 (0.75, 2.43)	0.94	
European American	referent	1.30 (0.91, 1.85)	1.45 (0.97, 2.17)	0.24	
Hispanic	referent	0.65 (0.23, 1.81)	1.01 (0.38, 2.65)	0.80	
Asian/Pacific Islander	referent	0.82 (0.18, 3.72)	0.61 (0.11, 3.25)	0.90	
NSAID use					0.28

Inflammatory biomarker	Quintiles (Q) of the DII: Estimate[1] (95% confidence interval)			Ptrend[2]	P(interaction)[3]
	Q1 (−6.230, < −3.126)	Q3 (−1.833, < −0.023)	Q5 (2.147, 5.224)		
Non NSAIDs users	referent	1.47 (0.96, 2.25)	1.67 (1.09, 2.55)*	0.10	
NSAIDs users	referent	1.05 (0.71, 1.54)	0.99 (0.65, 1.52)	0.53	
Subgroup analyses for TNFα-R2 model					
Body mass index, kg/m²					0.93
Normal weight (<25)	referent	19.61(−91.52, 130.74)	24.42(−95.62, 144.46)	0.62	
Overweight (25 – <30)	referent	13.95(−110.60, 82.70)	47.37(−50.56, 145.30)	0.18	
Obese (30)	referent	−29.35(−132.37, 73.67)	147.45(39.41, 255.50)*	0.003	
Race/ethnicity					0.22
African American	referent	192.22(−15.61, 400.05)	258.47(62.92, 454.03)*	0.006	
European American	referent	77.69(−49.22, 204.60)	180.45(35.57, 325.33)*	0.05	
Hispanic	referent	−175.10(−507.20, 157.01)	−74.71(−393.47, 244.05)	0.44	
Asian/Pacific Islander	referent	−199.14(−482.13, 83.85)	−239.28(−576.91, 98.35)	0.76	
NSAID use					0.06
Non NSAIDs users	referent	34.28(−105.17, 173.72)	213.63(74.38, 352.88)*	0.0006	
NSAIDs users	referent	51.53(−82.36, 185.42)	37.85(−109.70, 185.39)	0.76	
Subgroup analyses for overall inflammatory biomarker score[3],6					0.32
Body mass index, kg/m²					
Normal weight (<25)	referent	0.06 (−0.16, 0.28)	0.08 (−0.16, 0.32)	0.49	
Overweight (25 – <30)	referent	0.16 (−0.07, 0.39)	0.29 (0.06, 0.53)*	0.02	
Obese (30)	referent	0.15 (−0.88, 0.38)	0.41 (0.17, 0.65)*	0.0005	
Race/ethnicity					0.10
African American	referent	0.38 (0.10, 0.66)*	0.47 (0.20, 0.74)*	0.001	
European American	referent	0.15 (−0.02, 0.32)	0.40 (0.15, 0.53)*	0.003	
Hispanic	referent	−0.38 (−0.83, 0.07)	−0.24 (−0.68, 0.19)	0.77	
Asian/Pacific Islander	referent	−0.34 (−0.75, 0.08)	−0.33 (−0.82, 0.17)	0.90	
NSAID use					0.02
Non NSAIDs users	referent	0.11 (−0.08, 0.30)	0.37 (0.18, 0.56)*	<0.0001	

Inflammatory biomarker	Quintiles (Q) of the DII: Estimate[1] (95% confidence interval)			Ptrend[2]	P(interaction)[3]
	Q1 (−6.230, < −3.126)	Q3 (−1.833, < −0.023)	Q5 (2.147, 5.224)		
NSAIDs users	referent	0.09 (−0.09, 0.27)	0.11 (−0.09, 0.31)	0.32	

*
Statistically significant association;

[1]
Beta parameters;

[2]
The median of each quintile was assigned to all participants in the quintile and the variable introduced into models as an ordinal variable and its p-value interpreted as the p-value for tend;

[3]
P-values for interaction were from the main models and considered significant if <0.1;

[4]
Backtransformed (10^x) estimates since the data were log transformed to the base 10, prior to analyses;

[5]
Dichotomous hs-CRP (>3 mg/L, 3 mg/L) modeled the probability that hs-CRP >3 mg/L;

[6]
The overall inflammatory score was computed by summing z-scores of all three biomarkers for each participant. All models were adjusted for age, BMI, race, educational level, smoking status, physical activity, inflammation-related co-morbidity, regular use of antidepressants, statins, and NSAIDs, but were not adjusted for the covariate on which the subgroup analyses were conducted, e.g. BMI was not adjusted for in the three BMI models for each inflammatory biomarker

Table 5

Associations between the FFQ-derived dietary inflammatory index and biomarkers of inflammation in subgroups of BMI (kg/m^2), in non-users of NSAIDs (n=1290)

Inflammatory Biomarker	Quintiles (Q) of the DII: Estimate[1] (95% confidence interval)					
	Q1 (−6.230, <−3.126)	Q2 (−3.126, <−1.833)	Q3 (−1.833, <−0.023)	Q4 (−0.023, <2.147)	Q5 (2.147, 5.224)	Ptrend[2]
IL-6[3]						
Normal weight (<25)	referent	0.93 (0.81, 1.10)	0.98 (0.87, 1.12)	1.05 (0.93, 1.20)	1.10 (0.93, 1.29)	0.10
Overweight (25 – <30)	referent	1.02 (0.87, 1.17)	0.98 (0.85, 1.15)	1.05 (0.91, 1.23)	1.15 (1.02, 1.32)*	0.01
Obese (≥30)	referent	1.10 (0.95, 1.26)	0.95 (0.93, 1.17)	1.05 (0.93, 1.17)	1.12 (0.99, 1.29)	0.02
hs-CRP model (hs-CRP dichotomous; odds ratios)[4]						
Normal weight (<25)	referent	0.94 (0.39, 2.23)	1.04 (0.45, 2.43)	1.30 (0.61, 2.79)	1.08 (0.46, 2.52)	0.60
Overweight (25 – <30)	referent	2.14 (1.01, 4.56)*	1.10 (0.51, 2.37)	1.51 (0.70, 3.23)	1.77 (0.86, 3.68)	0.33
Obese (≥30)	referent	2.63 (1.28, 5.42)*	2.38 (1.20, 4.71)*	2.50 (1.27, 4.93)*	2.34 (1.17, 4.64)*	0.11
TNFα-R2						
Normal weight (<25)	referent	2.38 (−148.28, 153.05)	−45.15(−192.48, 102.18)	93.12 (−40.84, 227.07)	11.59 (−136.84, 160.02)	0.30
Overweight (25 – <30)	referent	−26.13 (−170.83, 118.57)	−22.57 (−162.88, 117.83)	45.63(−98.32, 189.58)	35.44 (−91.46, 162.33)	0.42
Obese (≥30)	referent	−37.76 (−209.02, 133.51)	−132.84(−286.05, 20.37)	110.87(−38.02, 259.75)	282.63(126.71, 438.56)*	<0.0001
Overall inflammatory biomarker score[3],[5]						
Normal weight (<25)	referent	0.08 (−0.22, 0.39)	02 (−0.28, 0.32)	0.25 (−0.03, 0.53)	0.14 (−0.17, 0.44)	0.18
Overweight (25 – <30)	referent	0.29 (−0.12, 0.57)	0.17 (−0.17, 0.52)	0.29 (−0.06, 0.64)	0.30 (−0.40, 0.63)	0.12
Obese (≥30)	referent	0.39 (0.30, 0.75)*	0.18 (−0.16, 0.53)	0.54 (0.20, 0.88)*	0.74 (0.39, 1.09)*	<0.0001

* Statistically significant association;

[1] Beta parameters;

[2] The median of each quintile was assigned to all participants in the quintile and the variable introduced into models as an ordinal variable and its p-value interpreted as the p-value for tend;

[3] Backtransformed (10^X) estimates since the data were log transformed to the base 10, prior to analyses;

[4] Dichotomous hs-CRP (>3 mg/L, ≤ 3 mg/L) modeled the probability that hs-CRP >3 mg/L;

[5] The overall inflammatory score was computed by summing z-scores of all three biomarkers for each participant. All models were adjusted for age, race, educational level, smoking status, physical activity, inflammation-related co-morbidity, regular use of antidepressants, and statins use