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Authors

Tabung, FK
Steck, SE
Zhang, J
et al.

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Construct Validation of the Dietary Inflammatory Index among Postmenopausal Women

Fred K. Tabung[a,b], **Susan E. Steck**[a,b,c], **Jiajia Zhang**[b], **Yunsheng Ma**[d], **Angela D. Liese**[b,c], **Ilir Agalliu**[e], **Melanie Hingle**[f], **Lifang Hou**[g], **Thomas G. Hurley**[a], **Li Jiao**[h], **Lisa W. Martin**[i], **Amy E. Millen**[j], **Hannah L. Park**[k], **Milagros C. Rosal**[d], **James M. Shikany**[l], **Nitin Shivappa**[a,b], **Judith K. Ockene**[d], and **James R. Hebert**[a,b,c]

[a]South Carolina Statewide Cancer Prevention and Control Program, University of South Carolina, Columbia, SC

[b]Department of Epidemiology and Biostatistics, Arnold School of Public Health, University of South Carolina, Columbia, SC

[c]Center for Research in Nutrition and Health Disparities, University of South Carolina, Columbia, SC

[d]Division of Preventive and Behavioral Medicine, University of Massachusetts Medical School; Boston, MA

[e]Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY

[f]Department of Nutritional Sciences, College of Agriculture & Life Sciences, The University of Arizona, AZ

[g]Department of Preventive Medicine and the Robert H. Lurie Comprehensive Cancer Center, Feinberg School of Medicine, Northwestern University, Chicago, IL

[h]Department of Medicine, Baylor College of Medicine, Houston, TX

[i]Cardiology Division, School of Medicine and Health Sciences, George Washington University, Washington, DC

[j]Department of Epidemiology and Environmental Health, University at Buffalo, The State University of New York, Buffalo, NY

[k]Department of Epidemiology, School of Medicine, University of California at Irvine, Irvine, CA

AUTHOR DISCLOSURES: All authors declare no conflict of interest. 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 also is an employee of CHI. This affiliation does not have any direct impact on the current study.

[I]Division of Preventive Medicine, School of Medicine, University of Alabama at Birmingham, Birmingham, AL

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.

Keywords

dietary inflammatory index; inflammatory biomarkers; construct validation; Women's Health Initiative

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:

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

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 ($P_{interaction}$<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

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.

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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

REFERENCES

1. King DE, Egan BM, Geesey ME. Relation of Dietary Fat and Fiber to Elevation of Creactive Protein.[erratum appears in Am J Cardiol. 2004 Mar 15;93(6):812]. American Journal of Cardiology. 2003 Dec 1.92:1335–1339. [PubMed: 14636916]
2. Esposito K, Marfella R, Ciotola M, Di Palo C, Giugliano F, Giugliano G, D'Armiento M, D'Andrea F, Giugliano D. Effect of a Mediterranean-style Diet on Endothelial Dysfunction and Markers of Vascular Inflammation in the Metabolic Syndrome: A Randomized Trial. Journal of the American Medical Association. 2004 Sep 22.292:1440–1446. [PubMed: 15383514]
3. Serrano-Martinez M, Palacios M, Martinez-Losa E, Lezaun R, Maravi C, Prado M, Martínez JA, Martinez-Gonzalez MA. A Mediterranean Dietary Style Influences TNF-alpha and VCAM-1 Coronary Blood Levels in Unstable Angina Patients. European Journal of Nutrition. 2005 Sep. 44:348–354. [PubMed: 16151968]
4. Chrysohoou C, Panagiotakos DB, Pitsavos C, Das UN, Stefanadis C. Adherence to the Mediterranean Diet Attenuates Inflammation and Coagulation Process in Healthy Adults: The Attica Study. Journal of the American College of Cardiology. 2004 Jul 7.44:152–158. 2004. [PubMed: 15234425]
5. Nanri A, Moore MA, Kono S. Impact of C-Reactive Protein on Disease Risk and its Relation to Dietary Factors: Literature Review. Asian Pacific Journal of Cancer Prevention. 2007; 8:167–177. [PubMed: 17696726]
6. Giugliano D, Ceriello A, Esposito K. The Effects of Diet on Inflammation: Emphasis on the Metabolic Syndrome. Journal of the American College of Cardiology. 2006; 48:677–685. 8/15/. [PubMed: 16904534]
7. Hu F. Dietary Pattern Analysis: A New Direction in Nutritional Epidemiology. Current Opinion in Lipidology. 2002; 13:3–9. [PubMed: 11790957]
8. Moeller SM, Reedy J, Millen AE, Dixon LB, Newby PK, Tucker KL, Krebs-Smith SM, Guenther PM. Dietary Patterns: Challenges and Opportunities in Dietary Patterns Research: An Experimental Biology Workshop, April 1, 2006. Journal of the American Dietetic Association. 2007; 107:1233–1239. [PubMed: 17604756]
9. Jacques PF, Tucker KL. Are Dietary Patterns Useful for Understanding the Role of Diet in Chronic Disease? The American Journal of Clinical Nutrition. 2001 Jan 1.73:1–2. 2001. [PubMed: 11124739]
10. Miller P, Cross AJ, Subar AF, Krebs-Smith SM, Park Y, Powell-Wiley T, Hollenbeck A, Reedy J. Comparison of 4 Established DASH Diet Indexes: Examining Associations of Index Scores and Colorectal Cancer. The American Journal of Clinical Nutrition. 2013 Sep 1.98:794–803. 2013. [PubMed: 23864539]
11. Miller PE, Lazarus P, Lesko SM, Muscat JE, Harper G, Cross AJ, Sinha R, Ryczak K, Escobar G, Mauger DT, Hartman TJ. Diet Index-Based and Empirically Derived Dietary Patterns are

Associated with Colorectal Cancer Risk. The Journal of Nutrition. 2010 Jul.140:1267–1273. 2010. [PubMed: 20444952]

12. Puchau B, Zulet MA, de Echávarri AG, Hermsdorff HH, Martínez JA. Dietary Total Antioxidant Capacity: A Novel Indicator of Diet Quality in Healthy Young Adults. Journal of the American College of Nutrition. 2009 Dec 1.28:648–656. 2009. [PubMed: 20516264]
13. Haines PS, Siega-Riz AM, Popkin BM. The Diet Quality Index Revised: A Measurement Instrument for Populations. Journal of the American Dietetic Association. 1999; 99:697–704. [PubMed: 10361532]
14. Guenther PM, Kirkpatrick SI, Reedy J, Krebs-Smith SM, Buckman DW, Dodd KWCK, Carroll RJ. The Healthy Eating Index-2010 Is a Valid and Reliable Measure of Diet Quality According to the 2010 Dietary Guidelines for Americans. The Journal of Nutrition. 2014 Jan 22. 2014.
15. Shivappa N, Steck SE, Hurley TG, Hussey JR, Hebert JR. Designing and Developing a Literature-derived, Population-based Dietary Inflammatory Index. Public Health Nutrition. 2013 Aug 14.17:1689–1696. [PubMed: 23941862]
16. Hebert JR, Ockene IS, Hurley TG, Luippold R, Well AD, Harmatz MG. Development and Testing of a Seven-day Dietary Recall. Journal of Clinical Epidemiology. 1997; 50:925–937. [PubMed: 9291878]
17. Shivappa N, Steck SE, Hurley TG, Hussey JR, Ma Y, Ockene IS, Tabung FK, 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 Nutrition. 2013 Oct 10.17:1825–1833. [PubMed: 24107546]
18. Women's Health Initiative Study Group. Design of the Women's Health Initiative Clinical Trial and Observational Study. Controlled Clinical Trials. 1998; 19:61–109. [PubMed: 9492970]
19. Ma Y, Hébert JR, Li W, Bertone-Johnson ER, Olendzki B, Pagoto SL, Tinker L, Rosal MC, Ockene IS, Ockene JK, Griffith JA, Liu S. Association Between Dietary Fiber and Markers of Systemic Inflammation in the Women's Health Initiative Observational Study. Nutrition. 2008; 24:941–949. [PubMed: 18562168]
20. Nutrition Coordinating Center at the University of Minnesota M. [cited December 18, 2013] MN Nutrition Data System for Research (NDSR). 2013 Apr 8. 2013. Available from: http://www.ncc.umn.edu/products/ndsr.html
21. Patterson RE, Kristal AR, Tinker LF, Carter RA, Bolton MP, Agurs-Collins T. Measurement Characteristics of the Women's Health Initiative Food Frequency Questionnaire. Annals of Epidemiology. 1999; 9:178–187. [PubMed: 10192650]
22. Liu S, Tinker L, Song Y, Rifai N, Bonds DE, Cook NR, Heiss G, Howard BV, Hotamisligil GS, Hu FB, Kuller LH, Manson JE. A Prospective Study of Inflammatory Cytokines and Diabetes Mellitus in a Multiethnic Cohort of Postmenopausal Women. Archives of Internal Medicine. 2007 Aug 13.167:1676–1685. 2007. [PubMed: 17698692]
23. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO3rd, Criqui M, Fadl YY, Fortmann SP, Hong Y, Myers GL, Rifai N, Smith SC Jr, Taubert K, Tracy RP, Vinicor F. Centers for Disease Control and Prevention; American Heart Association. 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 Jan 28.107:499–511. [PubMed: 12551878]
24. Department of Health and Human Services. [cited 4/8/2013] 2008 Physical Activity Guidelines for Americans. 2008. Available from: http://www.health.gov/paguidelines/
25. Coghill A, Phipps AI, Bavry AA, Wactawski-Wende J, Lane DS, LaCroix A, Newcomb PA. The Association between NSAID Use and Colorectal Cancer Mortality: Results from the Women's Health Initiative. Cancer Epidemiology Biomarkers & Prevention. 2012 Nov 1.21:1966–1973. 2012.
26. Hoffmann K, Zyriax BC, Boeing H, Windler E. A Dietary Pattern Derived to Explain Biomarker Variation is Strongly Associated with the Risk of Coronary Artery Disease. The American Journal of Clinical Nutrition. 2004 Sep 1.80:633–640. 2004. [PubMed: 15321803]

27. Schulze MB, Hoffmann K, Manson JE, Willett WC, Meigs JB, Weikert C, Heidemann C, Colditz GA, Hu FB. Dietary Pattern, Inflammation, and Incidence of Type 2 Diabetes in Women. The American Journal of Clinical Nutrition. 2005 Sep 1.82:675–684. 2005. [PubMed: 16155283]
28. Fung T, Rimm EB, Spiegelman D, Rifai N, Tofler GH, Willett WC, Hu FB. Association between Dietary Patterns and Plasma Biomarkers of Obesity and Cardiovascular Disease Risk. The American Journal of Clinical Nutrition. 2001 Jan 1.73:61–67. 2001. [PubMed: 11124751]
29. Lopez-Garcia E, Schulze MB, Fung TT, Meigs JB, Rifai N, Manson JE, Hu FB. Major Dietary Patterns are Related to Plasma Concentrations of Markers of Inflammation and Endothelial Dysfunction. The American Journal of Clinical Nutrition. 2004 Oct 1.80:1029–1035. 2004. [PubMed: 15447916]
30. Esmaillzadeh A, Kimiagar M, Mehrabi Y, Azadbakht L, Hu FB, Willett WC. Fruit and Vegetable Intakes, C-reactive Protein, and the Metabolic Syndrome. American Journal of Clinical Nutrition. 2006; 84:1489–1497. [PubMed: 17158434]
31. Fransson EI, Batty GD, Tabák AG, Brunner EJ, Kumari M, Shipley MJ, Singh-Manoux A, Kivimäki M. Association between Change in Body Composition and Change in Inflammatory Markers: An 11-Year Follow-Up in the Whitehall II Study. Journal of Clinical Endocrinology & Metabolism. 2010 Dec 1.95:5370–5374. 2010. [PubMed: 20719833]
32. Hébert 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. American Journal of Preventive Medicine. 2013; 45:430–440. [PubMed: 24050419]
33. Tabung FK, Steck SE, Burch JB, Chen CF, Zhang H, Hurley TG, Cavicchia P, Alexander M, Shivappa N, Creek KE, Lloyd SC, Hebert JR. A Healthy Lifestyle Index Is Associated With Reduced Risk of Colorectal Adenomatous Polyps Among Non-Users of Non-Steroidal Anti-Inflammatory Drugs. J Primary Prevent. 2015; 36:21–31. 10/21/2014.
34. 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. 2014 12/31/2014;Epub ahead of print:1–10.
35. Zamora-Ros R, Shivappa N, Steck SE, Canzian F, Landi S, Alonso MH, Hébert 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. 2014; 10:1–9. 2014/12/09.

APPENDIX – SHORT LIST OF WHI INVESTIGATORS

Program Office: (National Heart, Lung, and Blood Institute, Bethesda, Maryland) Jacques Rossouw, Shari Ludlam, Dale Burwen, Joan McGowan, Leslie Ford, and Nancy Geller

Clinical Coordinating Center: (Fred Hutchinson Cancer Research Center, Seattle, WA) Garnet Anderson, Ross Prentice, Andrea LaCroix, and Charles Kooperberg

Investigators and Academic Centers: (Brigham and Women's Hospital, Harvard Medical School, Boston, MA) JoAnn E. Manson; (MedStar Health Research Institute/Howard University, Washington, DC) Barbara V. Howard; (Stanford Prevention Research Center, Stanford, CA) Marcia L. Stefanick; (The Ohio State University, Columbus, OH) Rebecca Jackson; (University of Arizona, Tucson/Phoenix, AZ) Cynthia A. Thomson; (University at Buffalo, Buffalo, NY) Jean Wactawski-Wende; (University of Florida, Gainesville/Jacksonville, FL) Marian Limacher; (University of Iowa, Iowa City/Davenport, IA) Robert Wallace; (University of Pittsburgh, Pittsburgh, PA) Lewis Kuller; (Wake Forest University School of Medicine, Winston-Salem, NC) Sally Shumaker

Women's Health Initiative Memory Study: (Wake Forest University School of Medicine, Winston-Salem, NC) Sally Shumaker

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

	Quintiles (Q) of the DII: Estimate[1] (95% confidence interval)					
Inflammatory biomarker	**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 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

	Quintiles (Q) of the DII: Estimate[1] (95% confidence interval)				
Inflammatory biomarker	**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					
African American	referent	1.42 (0.76, 2.66)	1.35 (0.75, 2.43)	0.94	0.58
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)				
	Q1 (−6.230, < −3.126)	Q3 (−1.833, < −0.023)	Q5 (2.147, 5.224)	Ptrend[2]	P(interaction)[3]
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/m^2					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]					
Body mass index, kg/m^2					0.32
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)				
	Q1 (−6.230, < −3.126)	Q3 (−1.833, < −0.023)	Q5 (2.147, 5.224)	Ptrend[2]	P(interaction)[3]
NSAIDs users	referent	0.09 (−0.09, 0.27)	0.11 (−0.09, 0.31)	0.32	

*Statistically significant association;

1Beta parameters;

2The 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;

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

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

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

6The 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

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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)

	Quintiles (Q) of the DII: Estimate[1] (95% confidence interval)					
Inflammatory Biomarker	**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