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Association between dietary fiber and markers of systemic inflammation in the Women's Health Initiative Observational Study

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Abstract

Objective—Systemic inflammation may play an important role in the development of atherosclerosis, type 2 diabetes, and some cancers. Few studies have comprehensively assessed the direct relationships between dietary fiber and inflammatory cytokines, especially in minority populations. Using baseline data from 1,958 postmenopausal women enrolled in the Women's Health Initiative Observational Study, we examined cross-sectional associations between dietary fiber intake and markers of systemic inflammation (including serum C-reactive protein (hs-CRP), interleukin 6 (IL-6), and tumor necrosis factor α receptor 2 (TNF- α -R2)), as well as differences in these associations by ethnicity.

Method—Multiple linear regression models were used to assess the relationship between fiber intake and makers of systemic inflammation.

Results—After adjustment for covariates, intake of dietary fiber were inversely associated with both IL-6 (P values for trend were 0.01 for total fiber, 0.004 for soluble fiber, and 0.001 for insoluble fiber) and TNF- α -R2 (P values for trend were 0.002 for total, 0.02 for soluble, and <0.001 for insoluble fiber). Although the sample sizes were small in minority Americans, results were generally

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consistent with that found among European-Americans. We did not observe any significant association between intake of dietary fiber and hs-CRP.

Conclusions—These findings lend support to the hypothesis that a high-fiber diet is associated with lower plasma levels of IL-6 and TNF- α -R2. Contrary to previous reports, however, there was no association between fiber and hs-CRP among postmenopausal women. Future studies on the influence of diet on inflammation should include IL-6 and TNF- α -R2 and enroll participants from ethnic minorities.

Keywords

dietary fiber; C-reactive protein; interleukin-6; tumor necrosis factor-alpha receptor 2; inflammation; cytokines; epidemiology; cardiovascular disease; nutrition

INTRODUCTION

High sensitivity serum C-reactive protein (hs-CRP), plasma interleukin 6 (IL-6), and tumor necrosis factor α receptor 2 (TNF- α -R2) are markers of systemic inflammation in the body, and have been associated with many chronic diseases, including coronary heart disease (CHD) [1–6], metabolic syndrome [7–9], diabetes mellitus [10–13], and cancer [14,15].

Dietary fiber intake may reduce the risk of these diseases by mediating the pro-inflammatory process [16–18]. Two mechanistic hypotheses have emerged. First, dietary fiber may decrease oxidation of glucose and lipids, while maintaining a healthy intestinal environment. Second, dietary fiber may prevent inflammation by altering adipocytokines in adipose tissue and increasing enterohepatic circulation of lipids and lipophilic compounds [19]. The link between dietary fiber intake and reduced hs-CRP has been observed in several recent studies, including two analyses using cross-sectional data from NHANES 1999–2000 [20,21], an analysis using a longitudinal cohort of 524 healthy adults [22], and a small clinical trial [23]. However, one study has examined the association of dietary fiber with the pro-inflammatory cytokines IL-6 and TNF- α [24] and there is increasing clinical and experimental evidence for an important independent role of TNF- α -R2 signaling in chronic inflammatory conditions [25]. Detailed information regarding dietary fiber-inflammation relationships remains sparse, especially among diverse populations and by gender. For example, Hs-CRP levels are higher in women than men [26,27], and African Americans have higher hs-CRP than European Americans [26], whether there are differences by fiber intake is unclear.

We evaluated the relationship between dietary fiber intake and plasma levels of hs-CRP, IL-6 and TNF- α -R2 in 1,958 women for whom we had available baseline data on markers of systemic inflammation and dietary intake. These women were in the observational arm of the Women's Health Initiative (WHI) Study, a racially and ethnically diverse sample of postmenopausal women in the United States [28].

MATERIALS AND METHODS

Subjects

A detailed description of the WHI sample recruitment has been published elsewhere [29–31]. Briefly, WHI enrollment in the Observational Study was initiated in October 1993 and completed in December 1998 at 40 centers throughout the United States. Women learned of the WHI primarily from mailings sent by the Clinical Centers (CCs) and, if interested in participating, contacted their local CC for further information and to determine eligibility through a series of screening visits. Women eligible to enroll were: postmenopausal, aged 50–79 years, able and willing to provide written informed consent, and likely to be residing in the

study area for at least three years after being recruited. Exclusion criteria 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, and active participation in another intervention trial. Demographic information and dietary data were obtained by self-report using standardized questionnaires. Certified staff took physical measurements, including blood pressure, height and weight, and blood samples at the baseline clinic visit. The WHI protocol was approved by the institutional review boards at the Clinical Coordinating Center at the Fred Hutchinson Cancer Research Center (Seattle, WA) and at each of the 40 CCs.

The original study sample included the 3,245 women enrolled in the observational cohort of WHI at baseline for whom hs-CRP levels were available as part of an ancillary study to examine genetic and biochemical Predictors of type 2 diabetes. Detailed information was described elsewhere [12,13]. To clearly examine any associations between fiber and inflammatory markers, we excluded 917 participants with a prior history of cardiovascular disease, diabetes, cancers, or stroke at baseline. In addition, we excluded 163 women who reported an implausible daily total energy intake <600 kcal or > 5000 kcal based on self-report on a food frequency questionnaire (FFQ) [32], and two subjects without dietary data. We also excluded 205 subjects with hs-CRP values greater than 10 mg/L from this analysis because such elevated values are likely to be caused by infection or underlying medication problems and are unlikely to be related to diet [33]. The final study sample consisted of 1,958 women. Of these, 1,953 (99%) women had available measures of IL-6 and 1,948 (99%) had measures of TNF- α -R2.

Anthropometric and Diet Measures

WHI-trained staff measured height using a calibrated stadiometer and weight by balance-beam scale. Body mass index (BMI) was calculated as weight (kg)/height (m)². During screening, participants completed a standardized FFQ developed for the WHI to estimate average daily nutrient intake over the previous three-month period [32], which served as a baseline measure. The FFQ was based on instruments used in the WHI feasibility studies [34,35] and the original NCI/Block FFQ [36]. The WHI FFQ was self-administered and captured usual dietary intake for the previous three months. The three sections of WHI FFQ included 19 adjustment questions related to type of fat intake, 122 composite and single food line items asking about frequency of consumption and portion size, and four summary questions that asked about the usual intake of fruits and vegetables and added fats for comparison to information gathered from the line items. The nutrient database, linked to the University of Minnesota Nutrition Coordinating Center Nutrition Data System for Research (Nutrition Coordinating Center, Minneapolis, MN), is based on the USDA Standard Reference Releases and manufacturer information [37]. The construction of FFQs used at the Fred Hutchinson Cancer Research Center has been detailed [38]. Nutrient intake, including total calories, total fiber, soluble and insoluble fiber, alcohol, percentage of calories from fat, saturated fat, carbohydrates, and protein, were included in the analyses. This FFQ has demonstrated reasonably good validity as a measure of dietary intake compared to 24-hour dietary recall interviews (24HR) and food records [32]. The Pearson correlation coefficient between total dietary fiber assessed by FFQ and eight days of dietary intake (four 24HR and a 4-day food record) was 0.65 when energy intake was adjusted [32].

Measures of makers of systemic inflammation

Blood samples were collected from all Observational Study participants at baseline. They were obtained in a fasting state (at least 12 hours) and samples were maintained at 4°C for up to one hour until plasma or serum was separated from cells. Processed aliquots were placed in -70°C freezers within two hours of collection. Blood samples were sent on dry ice to the central repository, where they were kept in storage at -70°C until samples were sent to labs for analysis. All blood analyses for hs-CRP, IL6, and TNF- α -R2 were carried out in the laboratory of Dr. Nader Rifai at Children's Hospital, Boston, MA. Hs-CRP levels 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). IL-6 was measured by an ultrasensitive enzyme-linked immunosorbent assay (R&D Systems) and TNF- α -R2 levels by an enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, Minnesota). The coefficients of variation were: 1.61% for hs-CRP, 7.6% for IL-6, and 3.5% for TNF- α -R2 [13].

Statistical Methods

Participants' characteristics were summarized using mean (standard deviation) for continuous variables and frequency (%) for categorical variables. The distributions of hs-CRP, IL6 and TNF- α -R2 were heavily skewed, and thus natural logarithms of their values were used for subsequent analyses. Geometric means were calculated by exponentiating the means of the log-transformed values. Differences in concentration of hs-CRP, IL6, and TNF- α -R2 were compared using analysis of variance (ANOVA) between racial and ethnic groups.

The associations of concentration levels of hs-CRP, IL6 and TNF- α -R2 with total, soluble, and insoluble dietary fiber intake were analyzed using linear regression analyses. The dependent variables were the three markers of systemic inflammation. We used ordinary linear regression models while controlling a set of covariates known to be associated with these inflammatory markers. These covariates included age, ethnicity, BMI, minutes of leisure time physical activity per week (by quintile), arthritis status, current smoking status, female hormone use in the last 3 months, alcohol (5 categories) and energy intake [20,21,23,24,39–41]. BMI is categorized according standard categorization using the WHO guideline (<17; 17–<18.5; 18.5–<20; 20–<25; 25–<30; $\geq$ 30) [42]. Physical activity can not be normalized by log transformation, therefore, we categorized physical activity for five categories ((by quintile, <20 minutes/week, 20–100 minutes/week, 100–180 minutes/week, 180–300 minutes/week, and >300 minutes/week) based on the distribution. This is also to better represent the relationship of each covariate with the outcome (i.e., some were truly linearly related but others were not, so categorization was most appropriate). Alcohol consumption was categorized into 0, 0.1–4.9, 5.0–14.9, 15.0–29.9 and $\geq$ 30 g/day. These categories were created to correspond approximately to 0, 0.5, 1, 2 and >2 drinks/day[41]. Intakes of total, soluble, or insoluble dietary fiber were each divided into quintiles and included as ordinal covariates in the models. We examined biologically plausible interactions such as fiber intake and age, race and age, BMI categories and age, physical activity and age, smoking status and age, arthritis status and age, energy intake and age, fiber and energy intake, race and energy intake, smoking status and age, and arthritis and energy intake. None of these variables showed significant interactions, we therefore did not include them in the final models. The normality assumption was tested using the Cook and Weisberg test for heteroskedasticity in regression analysis as well as graphical examination of the residual distribution. We evaluated model adequacy using add-variable plot, Ramsey regression specification error test for omitted variables, Szroeter's rank test for heteroscedasticity, and DFBETA influence statistics. The multivariable-adjusted geometric means were computed based on the models by centering the covariates into their means. Tests for trends were performed by modeling the median values of each fiber category as a continuous variable. We also conducted stratified analysis by ethnic group. All analyses were performed using Stata SE 9.2 (College Station, Texas).

RESULTS

Table 1 presents the baseline characteristics of this diverse group of participants. Overall, participants were well educated (39% with a college degree or more), with a median age of 62 years (ranged from 50–79 years old) at baseline between 1993–1998, and overweight with an average BMI of nearly 29 kg/m². Approximately 5.7% of participants reported current

smoking, daily total energy intake was 1568 Kcal, total dietary fat intake was 31% of total energy, total dietary fiber was 16 grams, alcohol was 3.8 grams, and average weekly minutes of recreational physical activity was 152 minutes. Descriptive statistics of hs-CRP, IL-6, TNF- α -R2 data are summarized in Table 2, overall and by ethnicity. In every race/ethnic group except Asian, hs-CRP was found to be elevated with a geometric mean of 2.01 mg/L for the overall. The overall geometric mean for IL-6 was 1.9 pg/mL and 2423 pg/mL for TNF- α -R2. European Americans had significantly higher TNF- α -R2, 2604.51 pg/mL, as compared to all other race/ethnic groups. Asians had the lowest average values for hs-CRP, IL-6, and TNF- α -R2, which were significantly lower compared to European-American.

We performed primary analyses in all samples and summarized the results in Table 3, which presents geometric means and 95% confidence interval of hs-CRP, IL-6, and TNF- α -R2 by quintile of dietary total fiber, soluble, or insoluble fiber from multivariable linear regression analyses while adjusting for covariates. Although subjects in the second and third quintiles of total, soluble, and insoluble dietary fiber intake had slightly lower hs-CRP levels compared to subjects in the first quintile of intake, no linear association was observed between hs-CRP and intake of total, soluble, and insoluble dietary fiber (P values for trend were 0.40, 0.14, and 0.35, respectively). IL-6 was inversely associated with intake of total, soluble, and insoluble dietary fiber (P values for trend were 0.01, 0.004, and 0.001, respectively). Similar inverse associations were observed between TNF- α -R2 and intake of total, soluble, and insoluble dietary fiber (P for trend was 0.002, 0.02, and <0.001, respectively).

When stratified by ethnicity (results not shown), the only significant associations were observed among European-Americans. Significantly reduced levels of IL-6 and TNF- α -R2 were observed in groups with higher fiber intake among European Americans. For example, IL-6 values for subjects in each quintile of total dietary fiber from 1–5 were 1.70, 1.96, 1.19, 1.48, and 1.14 pg/mL for Asians (p value for trend=0.09); 2.35, 1.99, 2.41, 1.98, and 1.77 pg/mL for African-Americans (p value for trend=0.07); 2.11, 1.85, 1.88, 2.11 and 2.12 pg/mL for Hispanic (p value for trend=0.85), while the values for European-Americans were 2.17, 1.76, 1.98, 1.75 and 1.65 pg/mL (p value for trend=0.007).

DISCUSSION

In the present study of postmenopausal women, greater intake of total fiber, soluble fiber and insoluble fiber was related to lower plasma concentrations of IL-6 and TNF- α -R2, but not hs-CRP. Results suggest that IL-6 and TNF- α -R levels may be more sensitive to dietary fiber intake than hs-CRP levels in postmenopausal women. A growing body of evidence connects inflammation with increased risk for atherosclerosis [1–6], type 2 diabetes [11,13], and cancer [14,15], but much less is known about the role of diet in inflammation. Most studies to date have focused on the relationship between hs-CRP and diet as well as other lifestyle variables, however, two previous studies have found that IL-6 and TNF- α levels may be stronger predictors of incident cardiovascular events than hs-CRP level [43,44]. There is an emerging distinct role of TNF- α -R2 signaling in chronic inflammatory conditions [25], including diabetes [13]. The current study focuses on the effect of diet on the inflammation markers IL-6 and TNF- α -R2, which suggests that further interventional studies are needed.

It has been proposed [45] that dietary fiber may inhibit inflammation through its effects on lowering glycemia [24,46]. In a small clinical trial, Gonzalez and colleagues demonstrated that hyperglycemia increases TNF- α release from mononuclear cells in women with polycystic ovary syndrome [47]. In a laboratory study, monocytic cells were cultured in the presence of 5.5 mmol/l (normal) or 15 mmol/l (high) glucose and mannitol. Secreted IL-6, intracellular IL-6, and IL-6 mRNA were found to be significantly increased with hyperglycemia (P < 0.001) [48]. In addition, Qi and colleagues found that diets high in fiber may increase plasma

adiponectin concentrations in diabetic patients [49] and adiponectin has been found to have profound anti-inflammatory effects [50].

We did not find an association between dietary fiber intake and hs-CRP in the current study, which is in contrast to other studies that examined this association in mixed gender samples [20–22]. In an analysis of 1999–2000 NHANES data from both men and women, with 67% of the study population <56 years, King and colleagues [21] found that subjects in the highest quartile of total fiber consumption had a lower risk of elevated hs-CRP than did subjects in the lowest quartile (OR: 0.58; 95% CI: 0.38, 0.88). Our group previously reported an inverse association between hs-CRP and total fiber, soluble, and insoluble fiber intake in a healthy adult sample that was largely Caucasian, 48% female, and had a mean age of 48 years [22], with an average hs-CRP level of 1.8 mg/L. In a recent clinical trial of 28 women and 7 men (averages age 38 years old), increased fiber intake, either through a diet naturally high in fiber or through fiber supplementation, was associated with significant decreases in hs-CRP levels [23]. The study population in the present study was older (mean age = 62 years) and exclusively female, with an average hs-CRP of 2.0 mg/L which may account for discrepant findings. Additionally, Hs-CRP may differ by menopausal status, however, a recent study did not support this hypothesis [51]. Future studies should further examine gender, age, and ethnic differences in these associations.

Potential mechanisms for the found association between IL-6 and TNF- α -R2 with dietary fiber intake, in the absence of an association between dietary fiber and hs-CRP, could be that IL-6 and TNF- α are inflammatory cytokines that regulate inflammatory marker CRP [13], therefore, any dietary influence would first influence IL-6 and TNF- α and affect CRP indirectly. It also could be that IL-6 and TNF- α -R2 are more sensitive to dietary fiber increase than hs-CRP.

The current study suggests that high fiber diet might be one way to reduce inflammation and therefore reduce diseases that are associated with increased inflammation. The identification of dietary factors that reduce inflammation could have significant public health implications for the prevention of diabetes mellitus, cardiovascular disease, and metabolic syndrome.

Our study had several strengths. First, the total sample size was large and from a national study recruited women across the United States. Second, few studies have examined the role of dietary fiber in relation to markers of inflammation, and especially data in postmenopausal women are lacking. Third, we analyzed the associations of dietary fiber with hs-CRP, IL-6 and TNF- α -R2 by ethnicity. Fourth, the FFQ used in this study was well validated and provides estimation of many nutrients including fiber. Finally, several covariates were controlled for in the analyses including energy and alcohol intake, BMI, arthritis status, smoking, and use of hormone therapy.

This study also had several limitations worth noting. First, the weaker associations observed between fiber and pro-inflammatory cytokines in ethnic minorities could be due to the smaller sample size available for Asian (n=153), African-American (n=570), and Hispanic (n=228) women. To confirm ethnic differences in the association, studies with larger samples of minority participants are needed. Second, presence of active infections would reduce the association of between dietary fiber and inflammatory markers, though we did exclude 205 women with hs-CRP values greater than 10 (indicating active infection). Although we controlled for arthritis status in analyses, other chronic infections could not be identified in this study, which could impact the levels of inflammatory markers. Third, direct TNF- α measurement was not possible using frozen WHI specimen, however, TNF- α signals through at least 2 known cell surface receptors, namely TNF- α -R1 and TNF- α -R2. One study demonstrated a strong positive correlation between TNF- α -R2 and TNF- α mRNA expression level in human adipose tissue and suggested that these two moieties may be regulated by the

same signal [52]. Thus, we used TNF- α -R2 as a measure of TNF- α . Fourth, role of other unmeasured factors not included in study and/or analyses such as the use of aspirin and lipid lowering medications, which are also associated with markers of inflammation, cannot be ruled out. However, women with prior history of cardiovascular disease and diabetes were excluded from study sample to minimize the impact of these factors on analysis. In addition, women with these chronic diseases are more likely to have changed their diet [53,54], and this could bias the results toward null. Fifth, prevalence of smoking was low (only 5.7% smoking) and average minutes of exercise was high (over 150 minutes a week) in the study population. These characteristics may affect generalizability of the study. As we also excluded women with prior history of cardiovascular disease and diabetes, our results can only be generalizeable to apparently healthy postmenopausal women. Sixth, there is limitation on FFQ to measure diet with possible of under-reporting [55,56]. We adjusted total energy intake in the analyses, Willett has demonstrated some of the underreporting bias could be corrected with energy adjusted model [57]. Seventh, only 20% of the sample population reported hormone use and 80% were unknown, which limited our ability to control effect of hormone use when examining fiber-inflammation relationship. Finally, hs-CRP measures have been shown to be variable [58,59], potentially underestimating the potential fiber-inflammation relationship. Longitudinal measures of hs-CRP, IL-6 and TNF- α -R2 may be needed to examine changes in these markers in relation to diet.

CONCLUSION

The overall result of the study is that total, soluble and insoluble fiber was inversely associated with IL-6 and TNF- α -R2, whereas no association with CRP was observed among postmenopausal women. That IL-6 and TNF- α -R2 were inversely associated with dietary fiber intake has implications for dietary approaches to disease prevention, considering their sensitivity as markers of host response to disease, particularly in predicting diabetes and cardiovascular diseases. Findings lend further support to the notion that the effects of high-fiber diet on risk of chronic diseases might be mediated through their effects on systemic inflammation markers including IL6 and TNF- α -R2. Given the strong evidence that systemic inflammation markers is associated with risk of diabetes within the same study population [13], this study suggests a diet high in fiber may play a role in reducing inflammation and thus risk of diabetes for postmenopausal women. In addition, daily total dietary fiber intake was only 16 grams in this study and others [20,21,60], while 20–35 g/day has been recommended by the current dietary guidelines [61]. Therefore, there is significant room for engaging patients in nutrition education programs focusing on behavior modification and dietary fiber; it is never too late for diabetes prevention even among postmenopausal women with average age over 60 years old.

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Table 1

Characteristics of study participants (N=1958), Women's Health Initiative(WHI)

	Mean (SD)
Continuous variable	
Age (years)	62.2 (7.0)
Body mass index (kg/m ²)	28.8 (6.4)
Dietary variable	
Energy intake (kcal/day)	1568.2 (646.1)
Carbohydrate (% of energy)	52.6 (9.5)
Protein (% of energy)	16.5 (3.5)
Alcohol (g/day)	3.82 (9.9)
Fat (% of energy)	31.2 (8.5)
Total fiber (g/day)	15.7 (7.0)
Water-soluble dietary fiber (g/day)	4.2 (1.9)
Insoluble dietary fiber (g/day)	11.4 (5.2)
Physical activity	
Minutes of recreational physical activity per week *	151.9 (145.1, 158.9)
Categorical variable Ethnicity/Race	Frequency (%)
Asian or Pacific Islander	153 (7.8)
African American	570 (29.1)
Hispanic/Latino	228 (11.6)
European American (not of Hispanic origin)	1007 (51.4)
Education	
<High school	154 (7.9)
High school/GED	295 (15.1)
>High school, <4 year college	729 (37.2)
≥4 year college	756 (38.6)
Smoking status	
Never	1037 (53.0)
Former	787 (40.2)
Current	111 (5.7)
Hormone therapy use last 3 months	
Yes	22 (1.1)
No	359 (18.3)
Ever had arthritis?	
Yes	906 (46.6)
No	1039 (53.4)

Note: numbers and % may not add up to 1958 and 100% due to missing data.

* Geometric mean and 95% confidence interval were presented.

Table 2

Geometric means and 95% confidence intervals of high sensitivity serum C-reactive protein (hs-CRP), interleukin 6 (IL-6), and tumor necrosis factor α receptor 2 (TNF- α -R2) for overall participants and by race/ethnicity (N=1958), Women's Health Initiative (WHI)

	hs-CRP (mg/L)	IL-6 (pg/mL)	TNF- α -R2 (pg/mL)
Overall (n=1958)	2.01 (1.91, 2.10)	1.90 (1.84, 1.97)	2422.89 (2389.89, 2456.35)
Asian (n=153)	0.87 (0.73, 1.04)*	1.50 (1.31, 1.72)*	2145.47 (2047.80, 2247.80)*
African-American (n=570)	2.02 (1.85, 2.21)	2.12 (1.98, 2.27)*	2240.36 (2183.99, 2298.20)*
Hispanic (n=228)	2.20 (1.94, 2.50)	2.01 (1.81, 2.23)	2322.50 (2236.02, 2412.32)*
European-American (not of Hispanic origin) (n=1007)	2.22 (2.10, 2.36)	1.83 (1.75, 1.92)	2604.51 (2556.99, 2652.91)
Normal range	Low risk: less than 1 mg/L, average risk: 1 to 3 mg/L, high risk >3 mg/L	1.5–9 pg/mL	1798–2052 pg/mL [§]

* indicate a significant different from value from European-American (P< 0.05).

[§] normal range for TNF- α -R2 was based on a publication by Richard C. Ho et al. Cytokine 2005; 30:14–21.

Table 3

Geometric means and 95% confidence intervals of high sensitivity serum C-reactive protein (hs-CRP), interleukin 6 (IL-6), and tumor necrosis factor α receptor 2 (TNF- α -R2) by quintile of dietary total fiber, soluble, or insoluble fiber from multivariable linear regression analyses* (N=1958), Women's Health Initiative (WHI)

Outcome	Predictor	Geometric mean	95% confidence interval
hs-CRP (mg/L)	Total fiber (g/day)		
	Quintile 1 (median, 7.7)	2.31	[2.08, 2.56]
	Quintile 2 (median, 11.4)	1.85	[1.69, 2.03]
	Quintile 3 (median, 14.7)	1.87	[1.71, 2.05]
	Quintile 4 (median, 18.3)	2.04	[1.86, 2.24]
	Quintile 5 (median, 24.7)	1.98	[1.79, 2.21]
	p-value for trend [†]	0.40	
	Water soluble dietary fiber (g/day)		
	Quintile 1 (median, 2.1)	2.20	[2.01, 2.41]
	Quintile 2 (median, 3.1)	2.00	[1.88, 2.13]
	Quintile 3 (median, 3.9)	1.95	[1.84, 2.06]
IL-6 (pg/mL)	Quintile 4 (median, 4.9)	1.97	[1.85, 2.10]
	Quintile 5 (median, 6.7)	1.91	[1.74, 2.10]
	p-value for trend [†]	0.14	
	Insoluble fiber (g/day)		
	Quintile 1 (median, 5.5)	2.25	[2.04, 2.48]
	Quintile 2 (median, 8.2)	1.92	[1.77, 2.09]
	Quintile 3 (median, 10.6)	1.87	[1.73, 2.02]
	Quintile 4 (median, 13.4)	2.04	[1.89, 2.21]
	Quintile 5 (median, 18.0)	1.97	[1.78, 2.17]
	p-value for trend [†]	0.35	
	Total fiber (g/day)		
TNF- α -R2 (pg/mL)	Quintile 1 (median, 7.7)	2.16	[1.99, 2.35]
	Quintile 2 (median, 11.4)	1.87	[1.74, 2.02]
	Quintile 3 (median, 14.7)	2.01	[1.87, 2.16]
	Quintile 4 (median, 18.3)	1.82	[1.69, 1.96]
	Quintile 5 (median, 24.7)	1.68	[1.55, 1.83]
	p-value for trend [†]	0.01	
	Water soluble dietary fiber (g/day)		
	Quintile 1 (median, 2.1)	2.06	[1.91, 2.22]
	Quintile 2 (median, 3.1)	1.96	[1.86, 2.07]
	Quintile 3 (median, 3.9)	1.93	[1.85, 2.02]
	Quintile 4 (median, 4.9)	1.84	[1.75, 1.93]
	Quintile 5 (median, 6.7)	1.73	[1.61, 1.87]
hs-CRP (mg/L)	p-value for trend [†]	0.004	
	Insoluble fiber (g/day)		
	Quintile 1 (median, 5.5)	2.12	[1.96, 2.29]
	Quintile 2 (median, 8.2)	1.95	[1.82, 2.08]
	Quintile 3 (median, 10.6)	1.94	[1.82, 2.06]
	Quintile 4 (median, 13.4)	1.81	[1.70, 1.93]
	Quintile 5 (median, 18.0)	1.72	[1.59, 1.86]
	p-value for trend [†]	0.001	
	Total fiber (g/day)		
	Quintile 1 (median, 7.7)	2540.68	[2460.36, 2623.62]
	Quintile 2 (median, 11.4)	2436.74	[2367.52, 2507.98]
	Quintile 3 (median, 14.7)	2405.62	[2338.50, 2474.67]
	Quintile 4 (median, 18.3)	2410.45	[2342.03, 2480.88]
	Quintile 5 (median, 24.7)	2325.28	[2250.20, 2402.87]
	p-value for trend [†]	0.002	
	Water soluble dietary fiber (g/day)		
	Quintile 1 (median, 2.1)	2497.73	[2427.40, 2570.10]
	Quintile 2 (median, 3.1)	2452.41	[2403.66, 2502.16]
	Quintile 3 (median, 3.9)	2413.34	[2371.78, 2455.63]
	Quintile 4 (median, 4.9)	2385.12	[2339.58, 2431.55]
	Quintile 5 (median, 6.7)	2367.45	[2299.16, 2437.76]
	p-value for trend [†]	0.02	
	Insoluble fiber (g/day)		
	Quintile 1 (median, 5.5)	2540.82	[2464.93, 2619.05]
	Quintile 2 (median, 8.2)	2447.82	[2386.52, 2510.70]
	Quintile 3 (median, 10.6)	2410.38	[2353.54, 2468.60]
	Quintile 4 (median, 13.4)	2405.55	[2346.95, 2465.60]
	Quintile 5 (median, 18.0)	2314.80	[2246.31, 2385.38]

Outcome	Predictor	Geometric mean	95% confidence interval
	p-value for trend [†]	<0.001	

* Adjusted for BMI (categories), age (continuous), race (categories), recreational physical activity (categories), arthritis (categories), smoking status (categories), hormones therapy use in last 3 months (categories), alcohol intake (categories), and energy intake (continuous).

[†] P-value for trend across categories calculated using the median value of each category as a continuous variable.