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Association between dietary fiber and serum C-reactive protein-1,3

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Abstract

Background—High sensitivity C-reactive protein (CRP) is a marker of acute inflammation recently recognized as an independent predictor of future cardiovascular disease and diabetes. The identification of modifiable factors, such as diet, that influence serum CRP concentrations may provide the means for reducing the risk of these diseases. Data on longitudinal associations between dietary fiber intake and CRP are currently lacking.

Objective—The purpose of this study was to examine longitudinal associations between dietary fiber intake and CRP.

Design—Data collection took place at baseline and quarterly (every 13 wk) thereafter for a total of 5 visits, each including measurements of body composition, CRP, diet, and physical activity. Relations between serum CRP and dietary fiber were assessed by using linear mixed models and logistic regression, adjusted for covariates.

Results—A total of 524 subjects had multiple measurements of CRP and dietary factors. The average total dietary fiber intake was 16.11 g/d. Average serum CRP was 1.78 mg/L. We observed an inverse association between intake of total dietary fiber (separately for soluble and insoluble fiber) and CRP concentrations in both cross-sectional and longitudinal analyses. The likelihood of elevated CRP concentrations was 63% lower (OR: 0.37; 95% CI: 0.16, 0.87) in participants in the highest quartile of total fiber intake than in participants in the lowest quartile.

Conclusions—Our results suggest that dietary fiber is protective against high CRP, which supports current recommendations for a diet high in fiber.

Keywords

Dietary fiber; C-reactive protein; epidemiology; cardiovascular disease; nutrition

INTRODUCTION

C-reactive protein (CRP) is a marker of inflammation recently recognized as an independent predictor of future coronary heart disease (1-5). Furthermore, CRP is associated with the metabolic syndrome and diabetes mellitus (1,6). Based on data from the 1988 to 1994 third National Health and Nutrition Examination Survey (NHANES III), the prevalence of elevated CRP concentrations (>3.0 mg/L) was 13.7% for men and 27.3% for women (7). Lifestyle factors that influence CRP concentrations may provide an important intervention opportunity to reduce the risk of cardiovascular disease, diabetes, and their complications. One of the many

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modifiable risk factors for both cardiovascular disease and diabetes is diet. Fiber is an important dietary factor that may modify the risk of both diseases (8-12). Dietary fiber intake is associated with decreased oxidation of lipids, which in turn is associated with decreased inflammation (13). It has been postulated that a low-fiber diet with highly refined carbohydrates can contribute to hyperglycemia, which increases the proinflammatory cytokines plasma interleukin (IL) 6 (IL-6), tumor necrosis factor α , and IL-18 (14). IL-6 is a primary determinant of CRP production; thus, consistently elevated concentrations of IL-6 might result in elevated CRP concentrations.

To date, 2 epidemiologic studies, both using cross-sectional data from NHANES 1999–2000, have directly evaluated the relation between dietary fiber and CRP (13,15). Results from both studies indicated that dietary fiber intake was inversely associated with serum CRP concentrations. However, these cross-sectional studies faced several limitations. First, concentrations are known to be acutely influenced by infection and may not be stable; therefore, a single measurement of CRP may not be reliable as a biomarker (16). Second, because both CRP and diet were assessed at the same time, the temporal relation between these factors cannot be determined. Third, in both studies, diet was assessed with the use of a single 24-h diet recall. Using a one time measurement to represent an individual's diet may not accurately capture the true diet (17). Finally, different types of dietary fiber may vary in their physiologic effects; however, a comprehensive evaluation of the effects of fiber sub-types on CRP was not conducted in the 2 previous studies (13,15). The objective of the present study was to examine both cross-sectional and longitudinal relations of total dietary fiber, and soluble and insoluble fiber separately, with CRP.

SUBJECTS AND METHODS

Study design and population

The Seasonal Variation of Blood Cholesterol Levels Study (SEASONS) is a prospective observational study in which comprehensive data on serum CRP concentrations, diet, and many other factors were collected quarterly over a 1-y period in a cohort of healthy adults (18). The study design allows for both cross-sectional and longitudinal analyses, with the potential to examine both within- and between-person associations between fiber and CRP.

Participants between 20 and 70 y of age were recruited from the Fallon Healthcare System, a health maintenance organization in central Massachusetts. Persons using or planning to use lipid-lowering drugs; or being on or planning to go on a weight control diet were excluded (18). Six hundred and forty-one eligible participants were enrolled and followed for 1 y. Data collection took place at baseline and quarterly (every 13 wk) thereafter for a total of 5 visits, each of which included measurements of body composition, blood, diet, physical activity, and psychosocial variables. Data were collected between 1994 and 1998. Methods used in this project were approved by the ethics committee on Human Subject Research at the University of Massachusetts Medical School. Every participant read and signed an informed consent document.

Outcome assessment

CRP was measured from blood samples taken at baseline and the 4 quarterly visits. Blood was collected after a 12-h fast between the hours of 0700 and 1000 and was stored in a freezer at -80°C . CRP concentrations were measured with the use of latex-enhanced immunonephelometric assays on a BN II analyzer (Dade Behring, Wilmington, DE). The measurement of CRP was performed in batches. The latex-enhanced method has been compared with the validated enzyme-linked immunosorbent assay and the sandwich enzyme immunoassay (16,19). CRP values obtained by the latex method have been observed to be

slightly lower than those obtained by enzyme-linked immunosorbent assay; however, they were highly correlated ($r = 0.95$) (16). When compared with the sandwich enzyme immunoassay, the correlation coefficient was also 0.95 for concentrations of CRP ranging from 0.2 to 3.6 mg/L (19). For the first batch, the detection limit of the assay was 0.15 mg/L, and the day-to-day imprecision (or CV%) was $\approx 5\%$ at concentrations of 0.035 to 0.5 mg/L (20). A previous study found a CV% of 6.4% at concentrations of 0.47 mg/L and 3.7% at concentrations of 10.5 mg/L with the latex-enhanced method (16). Blood analysis of 2207 CRP values obtained were carried out in the laboratory of Dr Nader Rifai at Children's Hospital, Boston, MA. We excluded 66 (3%) CRP values >10 mg/L from this analysis because such elevated concentrations are likely to be caused by an infection or underlying medical problem and are not related to diet (21,22).

Exposure assessment

Diet was assessed at baseline and at the 4 additional data collection periods by trained registered dietitians via telephone-based 24-h dietary recalls. The interviewers used the Minnesota Nutrition Data System (NDS DOS; versions 2.6, 2.7, and 2.8) developed by the Nutrition Coordinating Center at the University of Minnesota (23). The NDS provides a standardized method for entry of dietary information and includes prompts for complete food descriptions, detailed food preparation methods, and description of diverse portions. The telephone interviews occurred between 2 wk before and 3 wk after the subject's quarterly clinic visit. During each 5-wk period, 3 randomly selected 24-h dietary recalls were conducted, including 2 weekdays and 1 weekend day, for a total of fifteen 24-h dietary recalls per participant. The data collected from the 24-h dietary recalls (eg, total calories, total fiber, and soluble and insoluble fiber) were analyzed by using the University of Minnesota's Nutrition Coordinating Center's NDS for Research software. Glycemic index (GI; the quality of carbohydrate) was determined from the 24-h dietary recalls by using published tables (24,25) and was previously reported (26).

Covariate assessment

Many variables are associated with CRP, including body mass index (BMI), smoking, physical activity, infection status, and total energy, alcohol, and fat intakes (13,15). Age and sex also have the potential to be confounding factors. Height and weight were measured at baseline, and weight was measured every 3 mo thereafter. BMI was then calculated for each time point [$\text{BMI} = \text{weight (kg)} / \text{height}^2 \text{ (m)}$] and categorized into underweight or normal weight (<25), overweight (≥ 25.0 to ≤ 30), and obese (≥ 30). Smoking was assessed at baseline and the following 4 visits through self report and categorized as current and noncurrent smoking status. Subjects were asked at each clinic visit whether they had a recent or current cold or flu or other infection or allergies in the past 3 mo.

Physical activity was assessed through 15 telephone-administered 24-h dietary recalls administered at the same time as the dietary recalls. The questionnaire was adapted from methods developed for a 7-d recall of physical activity (20). We used methods described by Ainsworth et al (27) to estimate total daily energy expenditure in metabolic equivalent task hours (MET-h) based on the reported time spent at each activity and activity intensity level (28-30). This method was validated against the Actillum activity monitor (28).

Statistical analysis

The dependent variable for this analysis was CRP. CRP was analyzed as a continuous and dichotomous variable; measurements >3 mg/L were considered elevated (21). For the continuous variable, the distribution of CRP concentrations was examined and found to be highly positively skewed; therefore, the natural log transformation of CRP was used. Dietary fiber intake, including total dietary fiber and soluble and insoluble fiber, was used as the

independent variable and was included as both a continuous and a categorical (quartiles) variable.

For the continuous CRP variable, we used a linear mixed model with a random intercept for each subject, and within-subject correlation was prescribed as autoregressive of order one as the serial autocorrelation of CRP was estimated as 0.70. With this model, we examined both 1) the cross-sectional association (between-subject, ie, the subject-specific average) between dietary fiber and CRP and 2) the longitudinal association (within-subject, ie, quarterly differences from the subject-specific average) between dietary fiber and CRP. Specifically, the cross-sectional effects for a variable were assessed by including a variable representing the subject mean; the longitudinal effects were assessed by including a variable representing the deviation from the subject mean. Thus, the cross-sectional analysis examined the association between the average CRP and average dietary fiber. The longitudinal analysis compared individual changes in CRP and dietary fiber between the quarters. Both the cross-sectional and longitudinal effects were included in the same model. This method was used in our previous analyses of the association between dietary carbohydrates and body weight and blood lipids (26,31). We ran the model with and without each of the potentially confounding factors. If a covariate changed either exposure coefficient by $\geq 15\%$ and was significant at $P = 0.15$, it was included in the final model. We then examined the association of CRP and dietary fiber within sex strata. Seasonality was also accounted for in the analysis by using the following categorization: winter, December 21 to March 20; spring, March 21 to June 20; summer, June 21 to September 20; and fall, September 21 to December 20.

To compare our results with the published data and estimate the magnitude of the association between fiber and elevated CRP, we used logistic regression models to compute the odds ratios (ORs) and 95% CIs for the probability of having an elevated CRP (21). In this analysis, subject-specific average data were used and dietary fiber variables were categorized into quartiles. Tests for trend with the use of simple linear regression analysis were performed by modeling the median values of each fiber category as a continuous variable. All analyses were performed by using STATA version 8.0 (Stata Corp, College Station, TX).

RESULTS

Of the 641 participants in SEASONS, 524 (72%) had ≥ 2 visits yielding both CRP and dietary fiber intakes and were included in the analyses. On average, subjects had a mean (\pm SD) of 3.8 ± 1.1 measures for the analysis.

The participants were predominantly white and had an average age of 48 y, and the distribution of men and women was approximately equal (Table 1). Sixty-two percent of the subjects were overweight or obese and had an average BMI of 27.2. The median CRP value was 1.2 mg/L, and the prevalence of elevated CRP (>3 mg/L) was 18% for both men and women (Table 2). The mean total dietary fiber intake was 16.1 g/d and ranged from 2.6 to 51.0 g/d. The mean soluble fiber intake was 5.8 g/d, and the mean insoluble fiber intake was 10.3 g/d.

The regression coefficients of dietary total fiber and soluble and insoluble fiber for predicting log CRP from a linear mixed model are shown in Table 3. The results of analyses using both cross-sectional and longitudinal data, unadjusted and adjusted for covariates, are presented. After control for multiple factors, a significant inverse relation was observed between log CRP and total daily dietary fiber intake in both the cross-sectional and the longitudinal analyses. Factors adjusted for in the analysis include BMI, current tobacco use, age, self-reported infection (defined as cold or flu), and season of year at CRP assessment.

To examine potential differences between soluble and insoluble fiber in relation to CRP concentrations, we conducted separate analyses for each and found inverse associations with

log CRP in both cross-sectional and longitudinal effects. The coefficient for the cross-sectional effect of dietary soluble fiber was -0.03 ($P = 0.12$), and the cross-sectional effect of insoluble fiber was -0.02 ($P = 0.02$). The coefficient for the longitudinal effect of soluble fiber was -0.02 ($P = 0.07$) and for insoluble fiber was -0.01 ($P = 0.02$).

To examine dietary fiber intake for a dose-response relation with CRP concentrations, we looked at quartiles of fiber intake with the outcome of a CRP concentration >3.0 mg/L (Table 4). With the lowest quartile of dietary fiber intake as the referent group, there was an inverse relation between highest quartile of total dietary fiber intake and CRP > 3 mg/L in both the unadjusted (OR: 0.27; 95% CI: 0.12, 0.57; P for trend <0.01) and adjusted (OR: 0.37; 95% CI: 0.16, 0.87; P for trend = 0.01) models. The overall F chi-square test was significant for total fiber in the adjusted model ($P = 0.05$). A similar pattern was observed for both water-soluble dietary fiber intake and insoluble dietary fiber intake. With the lowest quartile of water-soluble fiber intake, the odds for CRP concentrations >3 mg/L were reduced by 61% for subjects in the highest quartile of soluble fiber intake (OR: 0.39; 95% CI: 0.19, 0.78; P for trend = 0.006). With the lowest quartile of insoluble fiber intake, the OR for CRP concentrations >3 mg/L was reduced by 75% for subjects in the highest quartile of insoluble fiber intake (OR: 0.25; 95% CI: 0.12, 0.52; P for trend <0.01). These associations were slightly attenuated after adjustment for age, BMI, smoking status, and infection, but remained significant.

Because the GI could be a possible confounder or effect modifier, we stratified analyses by GI; the strength of the association (OR) by quartile was similar to our reported results. However, some of these ORs were not significant because of the small sample size in each strata. For example, for subjects in the highest quartile of GI, the OR of total fiber was 0.32 ($P = 0.30$) for subjects in the highest quartile compared with the lowest quartile of total fiber intake, whereas for subjects in the 2nd quartile of GI, the OR of total fiber was 0.27 ($P = 0.07$) for subjects in the highest quartile compared with the lowest quartile of total fiber intake.

DISCUSSION

In both the cross-sectional and longitudinal analyses we found inverse associations between total dietary fiber, soluble fiber, insoluble fiber and CRP. These results support our hypothesis that persons consuming higher amounts of dietary fiber would have lower concentrations of CRP. In addition, this study provides evidence that both soluble and insoluble dietary fiber are associated with CRP concentrations.

The mechanism between dietary fiber and inflammation is unclear. In a recent review article (8), King suggested that dietary fiber decreases lipid oxidation, which in turn is associated with decreased inflammation. Normal bowel flora also contribute to a healthy intestinal environment, which helps to prevent inflammation (8). The antiinflammatory effects of fiber are intriguing, because prior work had focused on the ability of fiber to reduce other substances that cause inflammation (eg, the inhibition of hyperglycemia and its effects on lipids, particularly LDL cholesterol).

Our findings are consistent with the 2 prior studies that directly evaluated the relation between dietary fiber and CRP (13,15). Using cross-sectional data from the 1999–2000 NHANES, Ajani et al (13) reported that the OR of the likelihood of elevated CRP concentration is 0.49 (95% CI: 0.37, 0.65) for the highest quintile of total fiber intake (32 g/d) compared with the lowest quintile (5.1 g/d). Using the same data, King et al (15) found that subjects in the highest quartile of total fiber consumption had a lower risk of elevated CRP than did subjects in the lowest quartile (OR: 0.58; 95% CI: 0.38, 0.88). Differences in findings may be due to different control variables. Our findings of a 63% reduction were somewhat stronger. This may be due to the fact that our study population is predominately white, whereas NHANES has a national representative sample. Differences in race or ethnicity may lead to differences in factors that

affect both fiber consumption and CRP concentrations. In addition, the quintiles and quartiles of dietary fiber intake differ between the studies. However, all 3 studies observed a significant inverse relation between dietary fiber intake and CRP concentrations.

The relation of dietary patterns and CRP have been explored in several other studies (14,32). In a cross-sectional study, Lopez-Garcia et al (32) compared a prudent dietary pattern (vegetables, legumes, and whole grains) with a Western diet (sweets, meat, and refined grain products). Those categorized as having the most prudent (high fiber) diet had average CRP concentrations of 0.13 compared with an average CRP concentration of 0.17 in those classified as having the most Western (low fiber) diet. The prudent diet was negatively related to CRP ($P = 0.02$), and the Western diet was positively related to CRP ($P = 0.001$).

Our study had several strengths and limitations. First, multiple 24-h dietary recalls reduce measurement error, and 15 dietary recalls are considered more than adequate to capture a person's usual intake of carbohydrate, protein, fat, and fiber (33). To account for seasonal variation, measurements were taken 5 times over the year. This is a strength in comparison with NHANES (13,15). However, this is an observational study in which the change in total fiber is small [mean (\pm SD) change = 0.57 ± 6.37 g/d]. Therefore, in comparison with the cross-sectional results, we observed only a small magnitude of association between dietary fiber and CRP in the longitudinal analyses. Second, storage of serum samples for CRP may have resulted in degradation of the samples. However, this measurement error would be similar for all subjects and thus would have biased our results toward the null. In addition, the laboratory technicians were unaware of the participants' exposure status, and all samples were handled in the same way. A quality-control study of CRP samples suggests that CRP concentrations remain stable in serum stored at < -70 °C for >2 decades (34). Third, use of statins and female hormones could affect CRP concentrations (35,36). However, our data came from a study of seasonal variation in blood lipids (18,37), and patients planning to use or using lipid medications and hormone therapy were excluded. At baseline, only one patient was using hormonal contraceptives, and one other patient was using lipid medication. However, because we did not obtain medication refill data to verify statin and hormone use, a small number of subjects may have begun use of these medications during the study. We were unable to control for medication use in our analyses. Fourth, we observed a correlation coefficient between insoluble and soluble fiber of 0.87 ($P < 0.01$). We did not include soluble and insoluble fiber in the same model because of concerns about collinearity. We cannot therefore tease apart their effects because they are part of the same foods. Fifth, the prospective nature of the study provides an opportunity for loss to follow-up and the potential for it to be differential by exposure and outcome status. Loss to follow-up in this study was relatively low because we excluded 49 subjects with only one measurement. The study was designed to have 5 measurements of both CRP and dietary fiber. Sixth, our power to detect the association between soluble fiber and CRP concentrations may be limited because of the narrow range of soluble fiber intake in the population. However, we standardized soluble and insoluble fiber intakes using quartiles, so we were able to compare results between soluble and insoluble fiber and results from studies. In addition, the early version of the NDS database may have been lacking complete distinction between the different types of fiber. Despite this possible measurement error, we detected a statistically significant association between soluble fiber and CRP concentrations. In fact, associations may actually be stronger for soluble fiber than for insoluble fiber, for physiologic reasons, such as a cholesterol-lowering effect (38,39). Finally, generalizability may be limited to a predominately white population. In a previous study by Khera et al (40), CRP concentrations were found to vary by sex and race-ethnicity. However, the difference in CRP concentrations was not statistically significant between sexes in our study. Sex differences between our findings and those of prior studies may have been due to the overall healthy sample of our study population, but could also have been due to the race distribution and relatively small size of our sample. However, data on the association between

dietary fiber intake and CRP concentrations from the NHANES (13,15) suggest that this relation is relevant to other racial and ethnic groups.

In conclusion, this observational study—which involved multiple assessments—provides important information about the relation between dietary fiber and CRP. Increased consumption of dietary fiber appears to be strongly associated with lower CRP concentrations. Given the strong evidence that CRP is associated with risk of cardiovascular disease events and diabetes, this study suggests that a diet high in fiber may play a role in reducing inflammation and, thus, the risk of cardiovascular disease and diabetes. Our results support the current dietary guidelines, which recommend that Americans consume 20–35 g fiber/d, including both soluble and insoluble fiber (41,42). However, the average American currently consumes one-half this amount (13,15,43). Thus, there is an opportunity to position fruit, vegetables, and whole grains as the foundation of America's diet to combat heart disease and diabetes. Randomized controlled trials of high- and low-fiber diets are needed before definitive public health recommendations can be made.

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TABLE 1

Characteristics of participants ($n = 524$) in the Seasonal Variation of Blood Cholesterol Study, Worcester, MA (1994–1998)¹

	Value
Categorical variable [n (%)]	
Sex	
Male	268 (51.2)
Female	256 (48.8)
Race-ethnicity	
White	444 (87.1)
Nonwhite	66 (12.9)
Marital status	
Married	402 (77.01)
Not married	120 (22.99)
Education	
High school or less	128 (24.6)
Some college	190 (36.5)
Bachelor's degree or more	203 (38.9)
BMI (kg/m^2)	
Normal, 18.5–24.9	198 (37.8)
Overweight, 25–29.9	207 (39.5)
Obese, ≥ 30	119 (22.7)
Current smoking	
Yes	75 (15.40)
No	412 (84.60)
Infection status	
Reported infection at all 5 visits	56 (10.69)
Reported infection at ≥ 1 visit	345 (65.84)
No infection	123 (23.47)
Continuous variable ²	
Age (y)	48.3 \pm 12.4
BMI (kg/m^2)	27.2 \pm 5.4
Physical activity	
Energy expenditure (MET-h/d)	
Total	30.2 \pm 4.6
Leisure	1.9 \pm 2.0
Occupational	4.4 \pm 5.5
Household	4.7 \pm 3.3

¹ Because of missing values, the total numbers of subjects differ. MET-h/d, metabolic equivalent hours per day.

² All values are $\bar{x} \pm \text{SD}$.

TABLE 2

Average C-reactive protein (CRP) concentrations and dietary factors in participants ($n = 524$) in the Seasonal Variation of Blood Cholesterol Study, Worcester, MA (1994–1998)

Variables	$\bar{x} \pm SD$	Median	Range
CRP (mg/L)	1.78 \pm 1.66	1.20	0.03–9.64
Log CRP	0.04 \pm 0.97	0.04	–3.73–2.27
Dietary factors			
Daily energy (kcal)	1956 \pm 574	1876	557–4417
Carbohydrate (% of energy)	51.36 \pm 7.47	50.83	28.92–75.68
Protein (% of energy)	16.06 \pm 2.62	15.85	10.01–26.81
Fat (% of energy)	31.44 \pm 6.06	31.77	13.02–49.83
Saturated fat (% of energy)	11.23 \pm 2.87	11.10	3.60–21.07
Alcohol (g/d)	7.68 \pm 13.40	2.08	0–115.21
Total fiber (g/d)	16.11 \pm 5.89	15.26	2.57–51.06
Soluble fiber (g/d)	5.79 \pm 2.06	5.44	0.98–17.36
Insoluble fiber (g/d)	10.33 \pm 4.02	9.72	1.59–33.07

TABLE 3

Regression coefficients (β) of dietary total fiber and soluble and insoluble fiber for predicting log C-reactive protein (CRP) according to a linear mixed model in the Seasonal Variation of Blood Cholesterol Study, Worcester, MA (1994–1998)

	Unadjusted				Adjusted ¹			
	Cross-sectional		Longitudinal		Cross-sectional		Longitudinal	
	β (SE)	P	β (SE)	P	β (SE)	P	β (SE)	P
Total fiber (g/d)	-0.03 (0.007)	< 0.001	-0.006 (0.004)	0.11	-0.01 (0.006)	0.03	-0.008 (0.004)	0.03
Water-soluble dietary fiber (g/d)	-0.05 (0.02)	0.005	-0.009 (0.01)	0.35	-0.03 (0.02)	0.12	-0.02 (0.01)	0.07
Insoluble dietary fiber (g/d)	-0.04 (0.01)	< 0.001	-0.01 (0.005)	0.07	-0.02 (0.008)	0.02	-0.01 (0.005)	0.02

¹ Adjusted for BMI, smoking status, age, current infection status, and season of year at the time of the CRP assessment.

TABLE 4

Odds ratios (ORs) and 95% CIs of the likelihood of elevated C-reactive protein concentrations (>3.0 mg/L) from logistic regression using cross-sectional analyses in the Seasonal Variation of Blood Cholesterol Study, Worcester, MA (1994–1998)

	Unadjusted		Adjusted ¹	
	OR (SE)	95% CI	OR (SE)	95% CI
Total fiber (g/d)				
Quartile 1 (median, 10.22)	1.00	Referent	1.00	Referent
Quartile 2 (median, 13.50)	1.09 (0.31)	0.61, 1.91	1.13 (0.38)	0.58, 2.19
Quartile 3 (median, 16.82)	0.62 (0.19)	0.33, 1.14	0.75 (0.27)	0.37, 1.52
Quartile 4 (median, 22.36)	0.27 (0.10)	0.12, 0.57	0.37 (0.16)	0.16, 0.87
<i>P</i> for trend ²	<0.01		0.01	
Water-soluble dietary fiber (g/d)				
Quartile 1 (median, 3.80)	1.00	Referent	1.00	Referent
Quartile 2 (median, 4.89)	1.00 (0.30)	0.56, 1.79	1.24 (0.43)	0.63, 2.44
Quartile 3 (median, 6.22)	0.79 (0.24)	0.43, 1.44	0.92 (0.33)	0.46, 1.85
Quartile 4 (median, 7.84)	0.39 (0.14)	0.19, 0.78	0.58 (0.23)	0.26, 1.28
<i>P</i> for trend ²	0.006		0.11	
Insoluble dietary fiber (g/d)				
Quartile 1 (median, 6.37)	1.00	Referent	1.00	Referent
Quartile 2 (median, 8.75)	0.75 (0.22)	0.42, 1.32	0.76 (0.26)	0.39, 1.47
Quartile 3 (median, 10.84)	0.52 (0.16)	0.29, 0.96	0.64 (0.22)	0.32, 1.27
Quartile 4 (median, 14.39)	0.25 (0.09)	0.12, 0.52	0.32 (0.13)	0.14, 0.72
<i>P</i> for trend ²	<0.01		0.005	

¹ Adjusted for age, BMI, smoking status, and infection status.

² Calculated across categories by using the median value of each category as a continuous variable.