

Prospective study of dietary fiber and risk of chronic obstructive pulmonary disease among US women and men

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Abbreviations:

BMI: body mass index

CI: confidence interval

COPD: chronic obstructive pulmonary disease

FFQ: food frequency questionnaire

FEV₁: forced expiratory volume in one second

g/day: gram per day

HPFS: Health Professionals Follow-up Study

IU: international unit

kcal/day: kilocalories per day

kg/m²: kilogram by meter square

METs: metabolic equivalents

mg/day: milligram per day

NHS: Nurses' Health Study

RR: relative risk.

Abstract:

Little is known about the relation between dietary fiber intake and the incidence of respiratory diseases, especially chronic obstructive pulmonary disease (COPD). The authors investigated this issue among 111,580 US women and men (Nurses' Health Study and Health Professionals Follow-up Study). 832 cases of newly diagnosed COPD were reported between 1984 and 2000. The cumulative average intake of total fiber and of fiber from specific sources (cereal, fruit and vegetables) were calculated from food frequency questionnaires and food composition database, and divided into quintiles. After adjustment for 11 factors (age, sex, smoking, energy intake, body mass index, US region, physician visits, physical activity, diabetes, intakes of omega-3 and cured meat), total dietary fiber intake was negatively associated with risk of newly diagnosed COPD: RR for highest vs. lowest intake=0.67 (95% confidence interval, 0.50-0.90), *P for trend*=0.03. For specific fiber sources (cereal, fruit and vegetables), only cereal fiber was significantly associated with newly diagnosed COPD independently of other fiber sources: RR for highest vs. lowest intake=0.77 (95% confidence interval, 0.59-0.99), *P for trend*=0.04. These data suggest that a diet high in fiber, and possibly specifically cereal fiber, may reduce risk of developing COPD.

Keywords: diet, fiber, chronic obstructive pulmonary diseases, sex

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of mortality in the United States and in Europe (1). With the increase in cigarette smoking in developing countries, COPD is expected to become the third leading cause of death worldwide by 2020. Over the last decade, there has been growing interest in the identification of foods or nutrients with antioxidant or anti-inflammatory properties that affect level of lung function or COPD symptoms (2). Most of these epidemiological studies were cross-sectional, but the few longitudinal studies have reported a negative association between fruits, vegetables and vitamin C intakes with lung function decline. Using an overall approach to assess diet, we recently reported in large cohorts of US women (3) and men (4) that a “prudent” dietary pattern (i.e, with ample intake of fruits, vegetables, fish, whole grains) was associated with a decrease risk of newly diagnosed COPD, whereas a “Western” diet (i.e, with ample intake of cured and red meats, desserts, refined grains, French fries) was associated with an increase risk of newly diagnosed COPD. We also demonstrated that frequent consumption of cured meat (one item of the Western diet) was associated with an increased risk of COPD (5, 6). However, no others specific foods or nutrients were investigated in relation with respiratory diseases.

Despite the anti-inflammatory and antioxidant properties of fiber (7), little is known about its relation with lung function and COPD. The paucity of data is striking in comparison to the extensive scientific literature on the relation of dietary fiber with cardiovascular diseases (8), diabetes (9) and cancer (10). A recent study found that a high whole-grain food intake was associated with a

lower risk for respiratory disease mortality (11). Dietary fiber intake also was reported to be associated with a reduced incidence of cough with phlegm (12) and with a highest level of lung function and a lower prevalence of COPD (13).

We therefore investigated prospectively the association between dietary fiber intake and risk of newly diagnosed COPD in two large prospective US cohorts.

MATERIALS AND METHODS

Overview

The Nurses' Health Study (NHS) began in 1976, when 121,700 female nurses 30-55 years old living in 11 US states, responded to a mailed health questionnaire (14). The Health Professionals Follow-up Study (HPFS) began in 1986 when 51,529 US health professionals aged 40 to 75 years answered a detailed mailed questionnaire that included a diet survey and items on lifestyle practice and medical history. In both cohorts, follow-up questionnaires were sent every two years thereafter to update information on lifestyle factors and to ask about newly diagnosed medical conditions. Participants also completed a food frequency questionnaire (FFQ) in 1984 for NHS, and at baseline (1986) for HPFS. Similar FFQs were sent every 2-4 years thereafter. The institutional review board approved the NHS and the HPFS protocols and written consent was obtained from all subjects. The study is being conducted according to the ethical guidelines of Brigham and Women's Hospital (Boston, USA).

Participants without a completed FFQ at baseline were excluded from the analysis. Likewise, we excluded participants with unreasonably high (>3,500 kcal/day for women and >4,200 kcal/day for men) or low (<500 kcal/day for women and <800 kcal/day for men) intakes and those who had left more than 70 items blank. Women and men who reported a diagnosed asthma or COPD at baseline also were excluded from the present analysis. The final baseline population included 71,365 women and 40,215 men.

Assessment of dietary intake

Dietary intake information was collected by an FFQ designed to assess average food intake over the previous 12 months. Standard portion sizes were listed with each food. For each food item, participants indicated their average frequency of consumption over the past year in terms of the specified serving size by checking 1 of 9 frequency categories ranging from “almost never” to “≥6 times/d.”

Nutrient intakes were computed by multiplying the frequency response by the nutrient content of the specified portion sizes. Food composition values were obtained from the Harvard University Food Composition Database, which was derived from US Department of Agriculture sources and supplemented with information from the manufacturer. In the US Department of Agriculture database, dietary fiber was determined by enzymatic-gravimetric methods 985.29 and 991.43 of the Association of Official Analytical Chemists (15). We considered total fiber, cereal fiber, fruit fiber and vegetable fiber intakes. All the dietary factors were adjusted for total energy by using the residual method (16).

Fiber intakes were identified from each FFQs administered in 1984, 1986, 1990, 1994 and 1998 in the NHS, and in 1986, 1990 and 1994 in the HPFS. To reduce measurement errors and to represent long-term dietary intake, the cumulative average of dietary fiber was calculated, and then divided into quintiles. The cumulative average incorporated repeated measures of diet. For example, by using this method in the NHS, the 1984 total fiber intake was used

to predict newly-diagnosed COPD in 1984-1986; an average of the 1984 and 1986 total fiber intake, to predict COPD in 1986-1990; and so forth.

Assessment of respiratory phenotypes

In 1998 and 2000, a supplemental questionnaire on COPD was sent to every participant who reported a physician diagnosis of emphysema or chronic bronchitis prior to 1996 (on the biennial questionnaire). The specific questionnaire included, among others, information confirming a physician diagnosis of emphysema, chronic bronchitis, or COPD, as well as dates of symptom onset and diagnosis, tests performed to confirm the diagnosis or symptoms consistent with a diagnosis of chronic bronchitis.

Self-reported COPD was defined by the affirmative response to physician-diagnosed chronic bronchitis or emphysema and by the report of a diagnostic test at diagnosis (i.e., pulmonary function testing, chest radiograph, or chest computed tomography). Among women, 749 cases of newly diagnosed COPD were reported between 1984 and 2000, and among men, 83 cases of newly diagnosed COPD were reported between 1986 and 1998.

This epidemiologic definition was validated in a random sample of the Nurses' Health Study (17). We obtained participants' medical records and a physician reviewed them in a blinded fashion. The diagnosis of COPD was confirmed in 80% of 218 cases who meet this case definition and 88% of cases who met this definition and denied a physician diagnosis of asthma. Results of pulmonary function testing were available in the medical records of 71% of confirmed cases; the mean FEV₁ in this group was 50% of predicted.

Assessment of other variables

Information on smoking status, assessed every two years by self-reported questionnaires, included categories of never, ex and current smokers. Among ever smokers, the amount of tobacco smoke was available by pack-years of smoking. We used updated variables for smoking and pack-years, i.e. that smoking status in 1984 was used to predict newly-diagnosed COPD in 1984-1986; smoking status in 1986, to predict COPD in 1986-1998; and so forth. Total calorie intake was estimated through the FFQ and expressed in kilocalorie per day (kcal/d). Home residence was categorized into six US regions (New England, Mid-Atlantic, East North Central, South Atlantic, West South Central, Pacific) and physician exam in previous two years was categorized in three responses (no visit, screening visit, symptom-related visit). Body mass index (BMI) and physical activity (18) were assessed every two years by self-reported questionnaires.

Statistical analysis

All analyses were conducted using SAS software, version 9 (Cary, NC, USA) and included Chi-squared test, analysis of variance and Cox proportional hazard regression models. Data from the NHS and the HPFS were merged together. Models were adjusted for age, sex, smoking status, pack-years, pack-years² and energy intake, and then for four variables (US region, physician visits, body mass index and physical activity). We intensively adjusted for smoking (smoking status, pack-years, pack-years²) because it is the main risk factor for

COPD and because smokers tend to have a different diet than non smokers (19). We also adjusted for energy intake to better focus on the specific food, as opposed to the overall energy intake (16). To take into account geographical disparities in COPD and diet across the US, we also adjusted for US region, and physician visits was used in the model as a marker of healthy lifestyle. The adjustment for BMI and physical activity was motivated by the strong interrelationships between diet, BMI and physical activity. Furthermore, low BMI is highly related to COPD (20) and it has been reported that physical activity is associated with lower risk of COPD (21). As in the paper by Kan et al. (13), we further examined 8 others potentials confounders (diabetes, glycemic index, micronutrients from foods and supplements (carotenoids; vitamins C, D, E; and omega-3 PUFA), cured meat intake) and found that results did not differ in models with all of these factors (data not shown). Accordingly, to create a more parsimonious model, we further adjusted our model only for diabetes, and intakes of omega-3 PUFA (foods and supplements) and cured meat. Models for specific fiber types (i.e., cereal, fruit and vegetables) were adjusted for other sources of fiber intakes.

Residual confounding by smoking remains an important issue in all studies of diet and respiratory diseases. Accordingly, major analyses were repeated among ex-smokers and current smokers (there were too few cases to permit a meaningful analysis among never smokers only). We formally tested the interaction between fiber intake and smoking status. We also stratified the analyses according to sex and tested for the interaction. Finally, for total fiber intake only, an additional model was performed: log relative risks from the 2

cohorts (female, male) were pooled in a fixed-effects model and we tested for heterogeneity.

RESULTS

Participants with the highest intake of fiber were less often smokers, more physically active and reported a higher total energy intake, as compared to those with the lowest intake of fiber (Table 1). The intake of specific fiber types (cereal, fruit and vegetable) was correlated both in women and in men: cereal and fruit fibers ($r=0.30$ in women, 0.25 in men); cereal and vegetable fibers ($r=0.25$ in women, 0.24 in men); and fruit and vegetable fibers ($r=0.42$ in women, 0.38 in men).

Total fiber intake and newly-diagnosed COPD

Total fiber intake was inversely associated with newly diagnosed COPD, both in the age- and sex-adjusted model and in the multivariate model (Table 2). Further adjustments for diabetes, omega-3 and cured meat intakes led to similar results. The pooled relative risk of newly diagnosed COPD supported this result: relative risk (RR) for the highest vs. the lowest intake was 0.69 , 95% confidence interval (95%CI): $0.35-1.20$, P for trend= 0.14 . The test for heterogeneity of relative risk of newly diagnosed COPD in men vs. women was not significant ($P=0.72$).

In the multivariable model, cured meat remained significantly associated with COPD (RR for the highest vs. the lowest intake was 1.34 , 95%CI: $1.05, 1.72$, P for trend= 0.004), and a borderline significant association was reported with

omega-3 intake (RR for the highest vs. the lowest intake was 0.82, 95%CI: 0.64,1.05, *P for trend*=0.10).

Due to the potential overlap between the diagnosis of COPD and asthma, we also restricted analyses to ever smokers. The risk of newly diagnosed COPD decreased with increased intake of total fiber but the trend was borderline significant (Table 3).

We also examined whether sex modified the association between fiber intake and the risk of COPD. In women, after adjustment for confounders, the total fiber intake was negatively associated with newly diagnosed COPD (RR for the highest vs. the lowest intake was 0.62, 95%CI: 0.46, 0.85, *P for trend*=0.01). Further adjustments for diabetes, omega-3 and cured meat intakes led to similar results (*P for trend*=0.04). In this multivariate model, only cured meat remained positively associated with COPD (RR for the highest vs. the lowest intake was 1.21, 95%CI: 0.95, 1.55, *P for trend*=0.04).

In men, after adjustment for confounders, the risk of newly diagnosed COPD decreased with the intake of total fiber (RR for the highest vs. the lowest intake was 0.46, 95%CI: 0.19,1.09, *P for trend*=0.05). Further adjustments for diabetes, omega-3 and cured meat intakes led to a non-significant association (RR for the highest vs. the lowest intake was 0.64, 95%CI: 0.26, 1.59, *P for trend*=0.26). The loss of statistical significance appeared to be due to adjustment for cured meat intake; cured meat was strongly associated with newly diagnosed COPD: RR for the highest vs. the lowest intake was 3.00, 95%CI: 1.27, 7.09, *P for trend*=0.001). The formal test of interaction between fiber intake and sex was not statistically significant (*P*=0.29).

Specific sources of fiber intake and newly-diagnosed COPD

Cereal fiber contributed 27% of the total fiber intake. The risk of newly diagnosed COPD decreased with the intake of cereal fiber, even after adjustment for confounders and after further adjustment for diabetes, omega-3, cured meat, fruit fiber and vegetable fiber intakes (Table 2). In this model, among all the foods and nutrients intake, only cured meat intake was significantly associated with the risk of COPD (RR for the highest vs. the lowest intake was 1.32, 95% CI: 1.05,1.68, *P for trend*=0.004), and, with a borderline significance, omega-3 intake (RR for the highest vs. the lowest intake was 0.81, 95% CI: 0.64,1.03, *P for trend*=0.09). When the analyses were stratified according to smoking status, the risk of newly diagnosed COPD decreased with increased intake of cereal fiber both among ex and current smokers, but the association was borderline significant only in current smokers (Table 3). When stratified according to sex, the association between cereal fiber intake and newly diagnosed COPD was significant only among women (RR for the highest vs. the lowest intake was 0.74, 95% CI: 0.55,1.00, *P for trend*=0.04; RR for the highest vs. the lowest intake was 0.53, 95% CI: 0.24, 1.20, *P for trend*=0.17, respectively in women and men).

Fruit fiber contributed 22% of the total fiber intake. After adjustment for confounders, the risk of newly diagnosed COPD decreased with an increased intake of fruit fiber (Table 2). Further adjustment for diabetes, omega-3, cured meat, cereal fiber and vegetable fiber intakes led to a non-significant association. The loss of statistical significance was mostly due to the adjustment for cured meat and cereal fiber intakes. In the final model we found a significant positive

association between the risk of COPD with cured meat intake (*P for trend*=0.004) and with cereal fiber intake (*P for trend*=0.02). Stratification according to smoking or according to sex showed no significant association between fruit fiber intake and newly diagnosed COPD.

Vegetable fiber contributed 35% of the total fiber intake. After multivariate adjustment, the intake of vegetable fiber was not associated with newly diagnosed COPD (Table 2). Further adjustments for diabetes, omega-3 PUFA, cured meat intake, cereal fiber and fruit fiber led to similar results. When the analyses were stratified according to smoking, no associations were observed among ex and current smokers. The stratification according to sex yielded similar results (data not shown).

DISCUSSION

In two large cohorts of US women and men, we found that participants with a higher total fiber intake had a lower risk of newly-diagnosed COPD, even after adjustment for many potential confounders. The potentially beneficial effect was independent of other dietary factors, such as omega-3 and cured meat. Only cereal fiber was significantly associated with newly diagnosed COPD.

Many studies have examined antioxidants (or foods rich in antioxidants such as fruits and vegetables) in relation with lung function or COPD (2). The main epidemiological evidence in support of an antioxidant-COPD association suggests that vitamin C and fruits and vegetables have beneficial associations with lung function, both in cross-sectional and in longitudinal analyses. Relatively little attention has been paid to other foods or nutrients, except for cured meats which appear to have a deleterious effect on COPD risk (5,6,22).

Two studies have investigated the relation of a novel antioxidant, dietary fiber, to COPD or COPD symptoms (12,13). Butler et al. reported that non-starch polysaccharides, a major component of dietary fiber, had an independent, inverse association with the incidence of cough with phlegm in 63,257 Chinese Singaporean women and men (12). In the ARIC study (Atherosclerosis Risk in Communities, 11,897 US women and men), Kan et al. investigated the association between dietary fiber and respiratory phenotypes, both using a cross-sectional design (i.e. level of lung function and COPD prevalence) and a longitudinal design (i.e. mean changes of lung function) (13). In the cross-sectional analysis, they reported a negative association between dietary fiber intake from all sources and from cereal and fruits with the level of lung function

and the prevalence of COPD; in the longitudinal analysis (only 3 years apart), they reported a significant inverse association of decline in lung function with cereal fiber, but not with total or fruit fiber.

We now report a significant, independent association between total fiber intake and the risk of COPD, particularly in women. Gender influences the epidemiology, diagnosis, and presentation of COPD, in addition to physiologic and psychologic impairments (23). In the study of Butler et al., results were adjusted for sex by statistical modeling; stratified results were not reported. Kan et al. formally tested the interaction between sex and total fiber intake on the level of lung function and they did not find a statistically significant interaction. As our formal test for interaction between fiber intake and sex was not statistically significant, it supports the likelihood that the difference we observed between men and women might be due to chance. We faced a statistical power issue in men since the number of cases was much lower in men as compared to women; the confidence interval for men actually included a strong inverse association. In men, we initially found a borderline significant negative association between the risk of newly diagnosed COPD with total fiber and cereal fiber intakes, associations that became non-significant after adjustment for cured meat. In women, we found independent effects of cured meat intake and fiber intake on COPD risk. In earlier work by our group, a very strong association was reported between cured meat intake and the risk of newly diagnosed COPD in men, with a RR for daily consumers of similar magnitude to ever smoking (6); in women, the magnitude of the association was smaller but also highly significant (5).

COPD is an oxidant- and nitrosant-related disease (24) with characteristic airway inflammation. Along those lines, a recent study found that the mortality risk of individuals with inflammatory respiratory diseases was significantly lower for those who reported the highest intake of whole-grain foods (11). The biological explanation for a potential benefit of fiber intake is related to both its antioxidant and anti-inflammatory properties. Even if the exact mechanism between dietary fiber and inflammation is unclear (7), it has been reported in epidemiological data that fiber intake is associated both with a lower level of CRP and of various proinflammatory cytokines such as IL-6, IL-18 and TNF- α (25, 26, 27) and with a highest level of the anti-inflammatory cytokine adiponectin (27, 28). Moreover, we cannot exclude that our findings are not an effect of fiber *per se*, but that they are due to other constituents of whole grains, including lignans.

Our primary findings for cereal fiber are consistent with the longitudinal finding of Kan et al. (13). Together, these data support the hypothesis that fiber from cereal, or another constituent of whole grains, may have physiologic effects that are more beneficial to the respiratory system than fiber from fruits or vegetables. Identification of the predominant mechanism for the beneficial effects of dietary fiber on COPD risk will require further study (7).

The study has few potential limitations. First, newly diagnosed COPD was defined by a self-reported physician-diagnosis of COPD and no lung function results were available. Nevertheless the questionnaire-based definition of newly diagnosed COPD was validated in a subset of the Nurses' Health Study (17). Secondly, we acknowledge that the association between fiber intake and newly diagnosed COPD may be due, in part, to residual confounding by cigarette

smoking. To minimize this possibility, multivariate models were adjusted with multiple time-varying measures of tobacco exposure (smoking habits, pack-years and pack-years²) which were assessed biennially since 1976, and analyses were stratified according to smoking status. Finally, we note the difficulty of studying the health effects of any specific nutrient given the complex inter-relations among intakes of different components of diet. Our fiber-COPD findings merit replication in other populations, preferably from cohorts with higher intake of fiber and different patterns of dietary intake.

In summary, the intake of fiber, and particularly cereal fiber, was negatively associated with the risk of newly diagnosed COPD in women. Similar, but weaker, associations were seen among men. Our results support the current dietary guidelines which recommend that Americans increase their daily consumption of whole grains (29). Besides potential prevention benefits for cardiovascular diseases, diabetes and cancer, fiber or another constituent of whole grains might also be involved through anti-inflammatory effects, in the pathogenesis of COPD. For COPD prevention, the most important public health message remains smoking cessation but our data suggest that diet, another modifiable risk factor, might influence COPD risk.

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Table 1 Age-standardized Baseline Characteristics of the Women from the Nurses' Health Study (1984-2000, n=71,365), and of the Men from the Health Professional Follow-up Study (1986-1998, n=40,215), According to Quintiles of Total Fiber Intake

	Women (n=71,365)						Men (n=40,215)					
	Quintile	Quintile	Quintile	Quintile	Quintile	p-value	Quintile	Quintile	Quintile	Quintile	Quintile	p-value
	1	2	3	4	5		1	2	3	4	5	
N	13,987	14,291	14,537	14,383	14,167		8,210	7,899	8,127	8,051	7,928	
Age (years), m (sd)	49.2 (7.0)	49.6 (7.1)	50.2 (7.1)	50.8 (7.1)	51.8 (7.1)	<0.001	51.4 (9.1)	52.1 (9.2)	52.7 (9.3)	53.0 (9.4)	53.7 (9.5)	<0.001
Smoking habits (%)												
Never smokers	37	42	45	48	52		43	46	48	51	54	
Ex smokers	37	39	40	40	39	<0.001	42	43	43	43	41	<0.001
Current smokers	26	19	15	12	9		15	11	9	6	5	

Pack-years among ever smokers*†	27	24	22	20	18	<0.001	23	21	20	19	17	<0.001
Body mass index (kg/m ²)	24.9	25.0	25.0	25.0	24.8	<0.001	25.7	25.6	25.4	25.3	25.1	<0.001
US region (%)												
New England	15	15	15	14	13		22	22	21	20	21	
Mid-Atlantic	44	43	43	43	44		16	16	17	17	16	
East North Central	19	20	19	18	18	<0.001	20	20	19	21	21	<0.001
South Atlantic	6	6	6	6	6		35	35	36	35	35	
West South Central	5	5	5	5	5		1	1	1	1	1	
Pacific	11	11	12	14	14		5	5	6	6	6	
Physician exam (%)												
No physician visits	15	12	11	11	10		24	22	21	20	19	
Screening visits	17	17	17	18	18	<0.001	15	16	16	17	17	<0.001
Symptom-related	68	70	71	71	72		61	62	63	64	64	

visits												
Physical activity (METs hour/week)‡	11.0	12.6	13.7	15.2	18.9	<0.001	23.0	23.9	24.3	26.1	31.3	<0.001
Total energy (kcal/d)	1,311	1,564	1,731	1,914	2,185	<0.001	1,493	1,775	1,968	2,180	2,533	<0.001
Diabetes (%)	3.0	3.1	3.6	3.6	3.9	<0.001	2.6	3.0	3.3	3.4	3.7	<0.001
Dietary intake												
Total fiber (g/day)	10.2	13.9	16.8	20.1	26.6	<0.001	11.3	15.9	19.5	23.8	33.3	<0.001
Cereal fiber (g/day)	2.5	3.6	4.4	5.3	7.0	<0.001	3.0	4.4	5.5	6.8	9.5	<0.001
Fruit fiber (g/day)	1.8	2.7	3.5	4.4	6.3	<0.001	2.0	3.0	3.9	5.0	7.5	<0.001
Vegetable fiber (g/day)	4.0	5.3	6.2	7.4	9.9	<0.001	3.9	5.3	6.4	7.8	10.9	<0.001
Omega-3 (g/day)	0.10	0.10	0.10	0.11	0.11	<0.001	0.14	0.14	0.14	0.14	0.15	<0.001
Cured meat (servings/day)	0.28	0.31	0.32	0.33	0.31	<0.001	0.34	0.37	0.37	0.37	0.34	<0.001

* Age-adjusted mean (all such values).

† No. of packs smoked per day * no. of years smoked, among past and current smokers.

‡ METs, metabolic equivalent. MET-hour/week, sum of the average time per week spent in each activity * MET value of each activity.

Table 2 Association between Quintiles of the Cumulative Average of Fiber Intake and Newly Diagnosed Chronic Obstructive Pulmonary Disease in Women and Men, Nurses' Health Study (1984-2000) and Health Professional Follow-up Study (1986-1998), n=111,580

	Quintile of intake					<i>P</i> for trend
	Q ₁	Q ₂	Q ₃	Q ₄	Q ₅	
Total fiber						
Median in grams/day	11.2	15.0	18.2	22.0	28.4	
No. of cases / Person-years	234/154,421	182/157,000	153/158,251	156/157,270	107/155,614	
Multivariate RR (95% CI)*	1.00	0.72 (0.59-0.87)	0.57 (0.47-0.70)	0.56 (0.46-0.68)	0.36 (0.29-0.45)	<0.001
Multivariate RR (95% CI)†	1.00	0.80 (0.65-0.98)	0.70 (0.56-0.88)	0.75 (0.59-0.95)	0.55 (0.42-0.74)	<0.001
Multivariate RR (95% CI)‡	1.00	0.80 (0.65-0.99)	0.72 (0.57-0.90)	0.79 (0.62-1.01)	0.60 (0.45-0.80)	0.002
Multivariate RR (95% CI)§	1.00	0.82 (0.67-1.01)	0.76 (0.60-0.95)	0.85 (0.66-1.09)	0.67 (0.50-0.90)	0.03
Cereal fiber						
Median in grams/day	2.2	3.5	4.7	6.2	9.0	

No. of cases / Person-years	230/153,150	195/156,321	150/157,597	145/157,597	112/157,984	
Multivariate RR (95% CI)*	1.00	0.84 (0.69-1.01)	0.63 (0.51-0.77)	0.59 (0.48-0.72)	0.42 (0.33-0.52)	<0.001
Multivariate RR (95% CI)†	1.00	0.99 (0.81-1.20)	0.84 (0.68-1.05)	0.86 (0.69-1.09)	0.71 (0.55-0.92)	0.007
Multivariate RR (95% CI)‡	1.00	0.99 (0.81-1.21)	0.85 (0.68-1.06)	0.87 (0.69-1.09)	0.72 (0.56-0.93)	0.008
Multivariate RR (95% CI)§	1.00	0.99 (0.82-1.21)	0.86 (0.69-1.08)	0.90 (0.72-1.14)	0.77 (0.59-0.99)	0.04

Fruit fiber

Median in grams/day	1.4	2.6	3.7	5.1	7.6	
No. of cases / Person-years	264/154,559	170/157,843	152/158,025	147/157,378	99/154,751	
Multivariate RR (95% CI)*	1.00	0.55 (0.45-0.67)	0.45 (0.37-0.55)	0.40 (0.33-0.49)	0.25 (0.20-0.31)	<0.001
Multivariate RR (95% CI)†	1.00	0.82 (0.67-0.99)	0.82 (0.67-1.01)	0.88 (0.71-1.08)	0.63 (0.49-0.81)	0.003
Multivariate RR (95% CI)‡	1.00	0.83 (0.68-1.01)	0.86 (0.70-1.05)	0.93 (0.75-1.16)	0.68 (0.52-0.87)	0.02
Multivariate RR (95% CI)§	1.00	0.86 (0.70-1.05)	0.91 (0.74-1.13)	1.02 (0.82-1.28)	0.77 (0.59-1.01)	0.31

Vegetable fiber

Median in grams/day	3.5	5.0	6.2	7.8	10.7	
No. of cases / Person-years	206/154,603	154/157,742	176/158,033	157/157,186	139/154,992	

Multivariate RR (95% CI)*	1.00	0.71 (0.58-0.88)	0.79 (0.65-0.97)	0.70 (0.57-0.86)	0.60 (0.49-0.75)	<0.001
Multivariate RR (95% CI)†	1.00	0.76 (0.61-0.94)	0.88 (0.71-1.08)	0.81 (0.65-1.01)	0.74 (0.58-0.93)	0.04
Multivariate RR (95% CI)‡	1.00	0.77 (0.62-0.95)	0.89 (0.73-1.10)	0.85 (0.68-1.06)	0.81 (0.64-1.03)	0.22
Multivariate RR (95% CI)δ	1.00	0.79 (0.63-0.97)	0.94 (0.76-1.16)	0.92 (0.73-1.15)	0.92 (0.71-1.18)	0.89

RR denotes relative risk; CI, confidence interval.

* Multivariate RRs have been adjusted for age and sex.

† Multivariate RRs have been adjusted for age, sex, smoking status, pack years, pack years² and energy intake.

‡ Multivariate RRs have been adjusted for age, sex, smoking status, pack years, pack years², energy intake, US region, physician visits, body mass index and physical activity.

δ Multivariate RRs have been adjusted for age, sex, smoking status, pack years, pack years², energy intake, US region, physician visits, body mass index, physical activity, diabetes, omega-3 PUFA intake (from foods and supplements), cured meat intake and other sources of fiber (total fiber intake not adjusted for the specific fiber types).

Table 3 Association between Quintiles of the Cumulative Average of Fiber Intake and Newly Diagnosed Chronic Obstructive Pulmonary Disease in Women and Men Among Ex Smokers (n=51,652) and Current Smokers (n=32,353), Nurses' Health Study (1984-2000) and Health Professional Follow-up Study (1986-1998)

	Quintile of intake					<i>P for trend</i>
	Q ₁	Q ₂	Q ₃	Q ₄	Q ₅	
EX SMOKERS						
Total fiber						
Median in grams/day	11.3	15.1	18.3	22.0	28.4	
No. of cases / Person-years	49/57,235	45/61,659	48/62,775	40/62,015	44/60,314	
Multivariate RR (95% CI)*	1.00	0.74 (0.48-1.13)	0.74 (0.48-1.15)	0.56 (0.35-0.91)	0.60 (0.36-0.99)	0.03
Multivariate RR (95% CI)†	1.00	0.76 (0.50-1.16)	0.78 (0.50-1.21)	0.61 (0.37-1.00)	0.68 (0.40-1.16)	0.11
Cereal fiber						
Median in grams/day	2.2	3.5	4.7	6.2	9.0	
No. of cases / Person-years	50/58,278	53/60,803	37/62,282	42/61,553	44/61,082	

Multivariate RR (95% CI)*	1.00	1.03 (0.69-1.54)	0.68 (0.44-1.07)	0.76 (0.48-1.18)	0.73 (0.46-1.14)	0.07
Multivariate RR (95% CI)†	1.00	1.04 (0.69-1.54)	0.71 (0.46-1.12)	0.81 (0.52-1.28)	0.80 (0.51-1.29)	0.20

Fruit fiber

Median in grams/day	1.4	2.6	3.7	5.1	7.6	
No. of cases / Person-years	47/56,217	47/61,520	44/62,604	51/62,612	37/61,045	
Multivariate RR (95% CI)*	1.00	0.95 (0.63-1.43)	0.84 (0.55-1.28)	0.94 (0.62-1.43)	0.64 (0.40-1.01)	0.09
Multivariate RR (95% CI)†	1.00	0.98 (0.65-1.48)	0.91 (0.59-1.39)	1.05 (0.68-1.61)	0.75 (0.46-1.23)	0.41

Vegetable fiber

Median in grams/day	3.5	5.0	6.2	7.8	10.6	
No. of cases / Person-years	49/56,095	42/61,292	49/62,338	38/62,683	48/61,590	
Multivariate RR (95% CI)*	1.00	0.76 (0.50-1.15)	0.87 (0.58-1.31)	0.65 (0.42-1.01)	0.82 (0.53-1.28)	0.31
Multivariate RR (95% CI)†	1.00	0.78 (0.51-1.19)	0.92 (0.59-1.40)	0.72 (0.45-1.14)	0.95 (0.59-1.54)	0.77

CURRENT SMOKERS

Total fiber

Median in grams/day	10.8	14.9	18.1	22.0	28.7	
No. of cases / Person-years	168/39,819	123/30,031	86/25,014	90/20,443	41/16,942	
Multivariate RR (95% CI)*	1.00	0.84 (0.66-1.08)	0.70 (0.52-0.93)	0.91 (0.67-1.23)	0.56 (0.38-0.85)	0.03
Multivariate RR (95% CI)†	1.00	0.85 (0.66-1.08)	0.70 (0.54-0.97)	0.96 (0.69-1.29)	0.60 (0.40-0.94)	0.09

Cereal fiber

Median in grams/day	2.1	3.4	4.6	6.1	9.0	
No. of cases / Person-years	162/40,488	126/30,423	94/24,541	84/20,469	42/16,328	
Multivariate RR (95% CI)*	1.00	1.02 (0.80-1.30)	0.94 (0.72-1.24)	0.98 (0.73-1.30)	0.63 (0.44-0.91)	0.05
Multivariate RR (95% CI)†	1.00	1.02 (0.79-1.30)	0.95 (0.73-1.26)	0.99 (0.76-1.36)	0.66 (0.46-0.94)	0.09

Fruit fiber

Median in grams/day	1.2	2.5	3.7	5.0	7.6	
No. of cases / Person-years	200/44,676	114/29,369	90/23,304	68/19,006	36/15,894	

Multivariate RR (95% CI)*	1.00	0.88 (0.69-1.11)	0.93 (0.72-1.21)	0.94 (0.70-1.25)	0.65 (0.45-0.95)	0.09
Multivariate RR (95% CI)†	1.00	0.90 (0.71-1.14)	0.98 (0.75-1.27)	1.00 (0.74-1.35)	0.72 (0.49-1.06)	0.33

Vegetable fiber

Median in grams/day	3.4	4.9	6.2	7.7	10.8	
No. of cases / Person-years	133/32,290	97/28,263	107/25,770	101/23,385	70/22,541	
Multivariate RR (95% CI)*	1.00	0.80 (0.61-1.04)	0.93 (0.72-1.21)	1.02 (0.78-1.34)	0.82 (0.60-1.13)	0.74
Multivariate RR (95% CI)†	1.00	0.81 (0.62-1.06)	0.97 (0.75-1.27)	1.09 (0.82-1.45)	0.92 (0.66-1.28)	0.68

RR denotes relative risk; CI, confidence interval.

* Multivariate RRs have been adjusted for age, sex, pack years, pack years², energy intake, US region, physician visits, body mass index and physical activity.

† Multivariate RRs have been adjusted for age, sex, pack years, pack years², energy intake, US region, physician visits, body mass index, physical activity, omega-3 PUFA intake (from foods and supplements), cured meat intake and other sources of fiber (total fiber intake not adjusted for the specific fiber types).