Dietary Fiber and Reduced Cough with Phlegm

A Cohort Study in Singapore

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Smoking is the major risk factor for chronic respiratory symptoms, but dietary factors may also play a role. Most studies of diet and lung disease have been cross-sectional and conducted in populations with a Western-style diet. We analyzed the relation between dietary intake at baseline and new onset of cough with phlegm in a population-based cohort of 63,257 middle-aged Chinese men and women initiated in Singapore between 1993 and 1998. Beginning in 1999, we ascertained respiratory symptoms by telephone interview and have identified 571 incident cases of cough with phlegm among the 49,140 cohort members with completed follow-up. Nonstarch polysaccharides, a major component of dietary fiber, total fruit, and soy isoflavones had the strongest associations. Odds ratios comparing highest and lowest quartiles after adjustment for age, sex, dialect group, total energy intake, and smoking were 0.61 (95% confidence interval [CI]: 0.47, 0.78; p for trend < 0.001) for nonstarch polysaccharides, 0.67 (95% CI: 0.52, 0.87; p for trend = 0.006) for fruit, and 0.67 (95% CI: 0.53, 0.86; p for trend = 0.001) for soy isoflavones. These data suggest that a diet high in fiber from fruit and, possibly, soyfoods may reduce the incidence of chronic respiratory symptoms. Associated nutrients, such as flavonoids, may contribute to this association.

Keywords: chronic bronchitis; chronic obstructive pulmonary disease; dietary fiber; fruit; soy

Chronic respiratory symptoms are a major source of morbidity in adults (1). Cough and phlegm are frequently associated with chronic obstructive pulmonary disease, which may be caused by oxidative stress–mediated inflammation and tissue damage in the lung (2). Oxidants can cause direct damage by inactivating antiproteases or mediating other processes that promote the development of chronic lung damage (3). Cigarette smoke is a major source of exogenous oxidant exposure (4), and the major cause of chronic respiratory symptoms (5). However, susceptibility to respiratory morbidity varies among smokers and chronic cough and phlegm production and other respiratory-related morbidity occur in nonsmokers (6). This suggests that additional factors, including other environmental exposures, genetics, and diet, may play a role. There is evidence that dietary nutrients modulate oxidative stress–induced lung damage among both smokers and nonsmokers (7–10).

Fruits and vegetables are the major food sources of antioxidants that may protect the lung from oxidative stress (11). Fruit intake and, to a lesser extent, vegetable intake have been associated with higher lung function and reduced symptoms of cough with phlegm (12, 13). Cross-sectional studies support an association between vitamin C and lung function (14–18). However, the epidemiologic evidence is stronger for fruit intake than for individual fruit-related nutrients such as vitamin C and carotenoids (12, 13), suggesting that other nutrients associated with fruit may be more relevant in protecting the lung from oxidative stressors.

In addition to vitamin C and carotenoids, fruit and vegetables contain flavonoids (19, 20) and fiber. Flavonoids have free-radical scavenging properties that may influence lung disease (21, 22), but have rarely been evaluated in prospective studies (11). Some epidemiologic evidence suggests that flavonoid-containing fruits, such as apples and pears, are associated with improved lung function (23) and reduced nonspecific respiratory disease (24). Reduced chronic obstructive pulmonary disease symptoms were also reported among individuals with greater intake of the flavonoids known as catechins (25). In addition to fruit and vegetables, flavonoids are found in soyfoods (26, 27), tea (28), and wine (29). Soyfoods are a major source of flavonoids in the Asian diet. Although experimental evidence suggests that genistein, a flavonoid in soyfoods, acts as an antiinflammatory agent in the lung (30–32), the association between soyfoods and symptoms of chronic lung disease has not been investigated in an epidemiologic study. Dietary fiber is thought to contribute to the beneficial health effects of fruits and vegetables (33, 34), but has also not been studied in relation to lung disease.

Prospective data are optimal to evaluate dietary relations with chronic lung disease and symptoms. The few prospective data that are available have limited detail about fruit and fiber intake. In addition, the available prospective data come exclusively from populations with Western-style diets (24, 35–38). Studies in Asian populations may help to identify relations between lung disease and dietary factors, such as soy, which are uncommon elements of Western diets.

In a population-based cohort of Singaporeans of Chinese ethnicity, we assessed whether intake of fruit, vegetables, their associated nutrients, and other sources of flavonoids was associated with decreased risk of developing cough with phlegm. We used a dietary questionnaire, validated in our population, with extensive detail on the relevant foods (39). Some of the results of these analyses have been previously reported in the form of a poster presentation at the American Thoracic Society 2003 Conference (40).

METHODS

Study Population

The design of the Singapore Chinese Health Study has been described (41). Briefly, the cohort was drawn from men and women, aged 45–74 years, who were permanent residents or citizens of Singapore and resided in government-built housing estates (86% of the Singapore

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population reside in such facilities). We restricted the study to individuals belonging to the two major dialect groups of Chinese in Singapore: the Hokkiens and the Cantonese. Between April 1993 and December 1998, 63,257 individuals (~85% of those eligible) were enrolled. Enrollment in the cohort entailed completing a baseline in-person interview in the participant's home. The questionnaire elicited information on diet, demographics, current physical activity, reproductive history (women only), occupational exposure, and medical history. Beginning in 1999 and ongoing, study participants responded to a single telephone interview including standardized questions on history of asthma and cough with phlegm production (42) (*see* the online supplement for questionnaire items). The Institutional Review Boards at the University of Southern California (Los Angeles, CA), the National University of Singapore, and the National Institute of Environmental Health Sciences (Research Triangle Park, NC) have approved this study.

As of December 31, 2002, there were 5,846 deaths in the overall cohort, with 4,871 of these deaths occurring before we were able to collect follow-up questionnaire data on respiratory outcomes. We analyzed data from the 49,140 individuals with completed telephone interviews as of August 3, 2003, with an average of 5.4 years of follow-up among cases (range, 2.4–8.4; interquartile range, 4.4–6.4), and 5.2 years of follow-up among noncases (range, 1.2–9.2; interquartile range, 3.2–6.2). These 49,140 individuals represent 84.2% of the cohort available for respiratory outcome follow-up (*see* Table E1 in the online supplement for demographic, smoking, and dietary differences between those with and without respiratory outcome data). Incident cases were subjects who reported that they have cough with phlegm on arising or during the rest of the day, initiated after the baseline interview (n = 571). In a subset analysis, cases were further defined by having incident cough with phlegm for 3 months or more of the year (n = 359). We classified cough with phlegm production as incident with respect to baseline, if the difference in years between age at the follow-up interview, and the duration of concurrent cough with phlegm, was greater than age at the baseline interview. Noncases (n = 44,068) were cohort members without cough or phlegm. The remaining 4,498 individuals had either incident cough only (n = 512), incident phlegm only (n = 1,271), prevalent cough with phlegm (n = 668), or discordant incident/prevalent combinations of cough and/or phlegm (n = 2,047). *See* Tables E2–E6 in the online supplement for analyses of the 4,498 subjects with these secondary outcomes.

Dietary Assessment

At baseline, a 165-item quantitative food frequency questionnaire, developed for and validated in this population, along with color photographs to represent portion sizes, was used to assess usual diet over the past year (39). The questionnaire included 16 items on individual fruits and fruit juices, 24 items covering 34 specific vegetables, and 7 soyfood items (39). Total soyfood intake was measured as the summation of all soyfoods expressed in units of plain tofu equivalent, to account for the different percentage of water in each soyfood, as previously described (43). In a validation substudy, frequency of overall soy intake had a statistically significant dose-dependent association with urinary total isoflavones (daidzein, genistein, and glycitein) (44). The questionnaire also included items about black tea (Chinese red and Ceylon tea) and green tea (jasmine and woolong).

Statistical Analysis

We examined diet at baseline, in relation to the outcome of incident cough with phlegm reported on the follow-up questionnaire. Adjusted odds ratios and 95% confidence intervals were calculated from unconditional logistic regression models (version 8.1; SAS Institute, Cary, NC). All nutrient data were adjusted for total energy intake, using the residual method (45). We present intake of nonstarch polysaccharides, a major component of dietary fiber, instead of total dietary fiber to facilitate comparison across study populations (46, 47). We adjusted for age, sex, and dialect group because these were associated with the outcome although they did not necessarily appreciably alter the dietary associations. As expected, smoking was a strong risk factor for cough with phlegm in our study, and therefore we sought to carefully control for potential confounding by smoking by including terms for smoking status (never, current, past), age at starting to smoke, and amount smoked in adjusted models with dietary factors. Individuals were categorized as never smokers if they had never smoked at least one cigarette per day for 1 year or longer. Length of follow-up, defined as the interval from baseline to follow-up interview (48), was not included in the adjusted models, because it was not associated with the outcome and did not appreciably alter the dietary associations.

RESULTS

Cohort members with incident cough with phlegm were more likely to be male, older, and members of the Hokkien dialect group, compared with noncases (Table 1). Cases, regardless of symptom duration, were more likely to be current smokers, to have started smoking before age 20 years, and were heavier smokers (Table 1). The mean total energy intake was slightly higher among all cases, compared with noncases (1,621.9 kcal, standard deviation [SD] = 572.2 among cases, and 1,554.9, SD = 556.1 among noncases), although it was not associated with the outcome after adjustment for smoking. Characteristics that did not differ substantially by case status included body mass index (mean = 22.9 kg/m^2, SD = 3.5 among cases, and mean = 23.2 kg/m^2, SD = 3.3 among noncases), education level (22.6% cases and 26.2% noncases had no formal education), and physical activity (7.8% of cases and 8.4% of noncases with 4 hours or more per week of moderate activity).

Table 2 shows the associations between individual food and nutrient items and incident cough with phlegm adjusted, as were all subsequent models, for age, sex, dialect group, and smoking (never, past, or current smoking status, age at starting to smoke, and amount smoked). We did not include a separate term for years since quitting smoking or change in smoking status from baseline to follow-up in the adjusted models, because neither factor was an important predictor of the outcome. For years since quitting, this was consistent with the approximately equal proportion of past smokers among the cases and noncases. The associations did not substantially differ for any of the foods and nutrients when cases were restricted to those with cough plus phlegm lasting for 3 months or more of the year (Table 2), and therefore individual results reported in text refer to all 571 incident cases. The associations that we observed for the incident cough with phlegm category were generally not seen for those with incident cough only, incident phlegm only, or for the miscellaneous category (*see* Tables E3–E5 in the online supplement). The prevalent cough with phlegm category generally had findings similar to the incident category (*see* Tables E3–E5 in the online supplement).

Daily intake of nonstarch polysaccharides was inversely associated with incident cough plus phlegm (odds ratio [OR] = 0.61, 95% confidence interval [CI]: 0.47, 0.78 comparing highest with lowest quartiles; p for trend < 0.001) (Table 2). Total fruit, all grain products, and total vegetables were the greatest food sources of nonstarch polysaccharides, with each contributing 34.3, 24.6, and 22.2% of intake, respectively. Total fruit was also inversely associated with cough plus phlegm, but all grain products and total vegetable consumption were not (Table 2).

When we looked at specific antioxidant nutrients related to fruit intake, such as vitamin C, we found trends similar to those observed for fruit (Table 2). However, we found no association for carotenoids, including total carotenoids, β-carotene (Table 2), or other individual carotenoids, such as α-carotene, β-cryptoxanthin, lycopene, or lutein (data not shown). We also found no association for vitamin E (Table 2), magnesium, or vitamin B_6 (data not shown). Given the low frequency of vitamin or mineral supplement use (8.4% in cases and 8.2% in noncases), odds ratios for individual nutrients did not change when supplement users were removed from the models (data not shown).

Given the association with total fruit consumption, we examined associations with individual fruits. We categorized intake

TABLE 1. CHARACTERISTICS OF THE SINGAPORE CHINESE HEALTH STUDY FOR SUBJECTS WITH AND WITHOUT INCIDENT COUGH WITH PHLEGM*

	Noncases (*n* = *44,068*)	All Cases of Incident Cough with Phlegm (*n* = *571*)§	Cases with Symptoms for ⩾ 3 mo/yr (*n* = *359*)§
Sex, %			
Men	40.3	58.3	58.5
Women	59.7	41.7	41.5
Age, mean yr (SD)	55.7 (7.7)	58.0 (7.9)	58.0 (8.1)
Dialect group, %			
Hokkien	51.1	58.5	67.7
Cantonese	48.9	41.5	32.3
Smoking status, %			
Never†	74.3‡	49.9	49.3
Past	10.3	12.1	12.8
Current	15.5	38.0	37.9
Age at starting to smoke, % of ever smokers			
⩾ 30 yr	9.6	7.0	5.0‡
20–29 yr	36.0	28.7	31.9
15–19 yr	37.4	41.6	42.9
⩽ 14 yr	17.0	22.7	20.3
Years smoked, % of ever smokers			
⩽ 9 yr	6.7	4.6	3.3
10–19 yr	10.3	5.6	6.0
20–29 yr	21.6	14.3	17.0
30–39 yr	31.4	29.7	30.8
⩾ 40 yr	30.0	45.8	42.9
Cigarettes smoked per day, % of ever smokers			
⩽ 6	16.6	9.1	8.8
7–12	25.4	21.3	19.2
13–22	36.5	39.9	41.8
23–32	9.5	16.1	14.3
33–42	7.2	8.4	8.8
⩾ 43	4.8	5.2	7.1

* Individuals (n = 4,498) with other cough and phlegm symptom outcomes (incident cough or phlegm alone, prevalent cough and/or phlegm, and discordant incident/prevalent combinations) are not included, but are included in the online supplement (*see* Table E2 for characteristics).

† Individuals were categorized as never smokers if they had never smoked at least one cigarette a day for 1 year or longer.

‡ Percentages do not add up to 100, because of rounding.

§ χ^2 or Student's *t* test p values were less than 0.01 for all factors comparing the case group with the noncases, with one exception (age at starting to smoke) comparing cases with symptoms for 3 months or more with noncases (p = 0.056).

by tertiles rather than quartiles, because the frequency of consumption of any individual fruit was, as expected, lower than for total fruit. We observed the strongest inverse dose–response associations for apples, pears, and grapes (Table 3).

Soyfoods made the next greatest contribution to nonstarch polysaccharide intake after fruit, grain products, and vegetables. Total soyfood and soy isoflavone intake had modest inverse associations with cough plus phlegm (Table 4). Comparing the fourth with the first quartiles, odds ratios were virtually identical for the individual isoflavones genistein (OR = 0.68; 95% CI: 0.53, 0.87), daidzein (OR = 0.67; 95% CI: 0.53, 0.86), and glycitein (OR = 0.68; 95% CI: 0.54, 0.87).

We examined whether associations between cough with phlegm production and individual foods and nutrients were altered by adjustment for total nonstarch polysaccharides (Table 5). Odds ratios for all dietary factors were attenuated after adjustment for nonstarch polysaccharides; odds ratios for all grain products remained near the null. The inverse association between apples (OR = 0.79; 95% CI: 0.64, 0.98, comparing third with first tertile) and grapes (OR = 0.79; 95% CI: 0.62, 0.99, comparing third with first tertile) persisted after adjustment for nonstarch polysaccharides. With adjustment for the other foods and nutrients in Tables 2 through 4, the odds ratios for nonstarch polysaccharides, comparing extreme quartiles, ranged from 0.49–0.67 and remained statistically significant.

There was no appreciable difference in association between incident cough with phlegm and nonstarch polysaccharides by strata of median age (< 55 years), sex, dialect group (Hokkien or Cantonese), or median of body mass index (⩾ 23.1 kg/m^2) (data not shown). Although we observed a stronger association for nonstarch polysaccharide intake among ever smokers (OR = 0.45; 95% CI: 0.29, 0.70, comparing fourth with first quartile), an inverse association was still present among never smokers (OR = 0.70; 95% CI: 0.50, 0.97, comparing fourth with first quartile). There were no changes in the odds ratios for nonstarch polysaccharide intake when individuals who self-reported incident or prevalent asthma (n = 68 cases and 1,719 noncases) were removed (data not shown). *See* Table E6 in the online supplement for the frequency of asthma by incident cough with phlegm case status.

DISCUSSION

These prospective data support the role of diet in the etiology of cough with phlegm production. In particular, nonstarch polysaccharides, a major component of dietary fiber, and certain noncitrus fruits (e.g., apples, grapes) were independently associated

TABLE 2. ODDS RATIOS BY QUARTILE OF DAILY INTAKE OF NONSTARCH POLYSACCHARIDES, MAJOR CONTRIBUTORS TO NONSTARCH POLYSACCHARIDE INTAKE, AND RELATED NUTRIENTS IN RELATION TO INCIDENT COUGH WITH PHLEGM: THE SINGAPORE CHINESE HEALTH STUDY*

	Noncases	All Cases of Incident Cough with Phlegm		Cases with Symptoms for ⩾ 3 mo/yr	
	(*n* = *44,068*)	(*n* = *571*)	OR (*95% CI*)[¶]	(*n* = *359*)	OR (*95% CI*)[¶]
Total nonstarch polysaccharides, g					
Q1 (4.7)[†]	9,978	212	1.0 (ref.)	133	1.0 (ref.)
Q2 (6.6)	11,023	154	0.82 (0.66, 1.01)	94	0.81 (0.62, 1.06)
Q3 (8.5)	11,355	106	0.61 (0.48, 0.78)	73	0.69 (0.51, 0.93)
Q4 (11.6)	11,712	99	0.61 (0.47, 0.78)	59	0.60 (0.43, 0.82)
p Value for trend[‡]			< 0.001		0.001
Major contributors of nonstarch polysaccharides					
Total fruit and fruit juices, g					
Q1 (44.4)[†]	10,012	187	1.0 (ref.)	127	1.0 (ref.)
Q2 (127.1)	11,044	131	0.73 (0.58, 0.92)	83	0.70 (0.53, 0.94)
Q3 (210.9)	11,414	128	0.72 (0.56, 0.91)	74	0.64 (0.47, 0.87)
Q4 (377.0)	11,598	125	0.67 (0.52, 0.87)	75	0.64 (0.46, 0.88)
p Value for trend[‡]			0.006		0.010
All grain products, g					
Q1 (308.1)[†]	11,249	126	1.0 (ref.)	80	1.0 (ref.)
Q2 (449.7)	11,053	127	0.93 (0.72, 1.21)	88	1.08 (0.78, 1.49)
Q3 (546.8)	11,021	139	0.98 (0.74, 1.29)	79	0.98 (0.69, 1.41)
Q4 (858.0)	10,745	179	1.12 (0.80, 1.56)	112	1.32 (0.87, 2.00)
p Value for trend[‡]			0.301		0.133
Total vegetables and vegetable juices, g					
Q1 (51.7)[†]	10,090	151	1.0 (ref.)	95	1.0 (ref.)
Q2 (82.3)	11,087	148	0.98 (0.77, 1.23)	93	1.02 (0.76, 1.37)
Q3 (115.5)	11,358	130	0.87 (0.68, 1.12)	88	1.02 (0.75, 1.39)
Q4 (176.8)	11,533	142	0.92 (0.70, 1.21)	83	0.97 (0.69, 1.37)
p Value for trend[‡]			0.504		0.820
Related nutrients					
Vitamin C, mg[§]					
Q1 (32.1)[†]	10,011	183	1.0 (ref.)	115	1.0 (ref.)
Q2 (57.2)	10,992	157	0.95 (0.76, 1.18)	95	0.94 (0.72, 1.24)
Q3 (85.7)	11,361	124	0.79 (0.62, 0.99)	82	0.87 (0.65, 1.16)
Q4 (138.6)	11,704	107	0.73 (0.57, 0.94)	67	0.78 (0.57, 1.07)
p Value for trend[‡]			0.006		0.103
Vitamin E, mg[§]					
Q1 (3.9)[†]	10,118	187	1.0 (ref.)	111	1.0 (ref.)
Q2 (5.0)	10,994	139	0.83 (0.66, 1.04)	83	0.84 (0.63, 1.12)
Q3 (6.0)	11,318	133	0.87 (0.69, 1.09)	97	1.09 (0.82, 1.44)
Q4 (7.5)	11,638	112	0.78 (0.61, 0.99)	68	0.82 (0.60, 1.13)
p Value for trend[‡]			0.063		0.477
Total carotenoids, μg[§]					
Q1 (2,629.4)[†]	10,033	164	1.0 (ref.)	107	1.0 (ref.)
Q2 (4,098.3)	10,975	141	0.95 (0.75, 1.19)	85	0.90 (0.67, 1.20)
Q3 (5,629.0)	11,409	149	1.07 (0.85, 1.34)	97	1.10 (0.83, 1.46)
Q4 (8,493.8)	11,651	117	0.90 (0.71, 1.16)	70	0.87 (0.64, 1.19)
p Value for trend[‡]			0.567		0.586
β-Carotene, μg[§]					
Q1 (949.4)[†]	10,024	165	1.0 (ref.)	105	1.0 (ref.)
Q2 (1,524.1)	11,014	139	0.94 (0.75, 1.18)	91	0.99 (0.74, 1.31)
Q3 (2,140.1)	11,410	141	1.00 (0.80, 1.26)	91	1.05 (0.79, 1.40)
Q4 (3,371.3)	11,620	126	0.98 (0.77, 1.25)	72	0.92 (0.67, 1.25)
p Value for trend[‡]			0.998		0.626

Definition of abbreviations: CI = confidence interval; OR = odds ratio.

* Individuals (n = 4,498) with other symptom outcomes (incident cough or phlegm alone, prevalent cough and/or phlegm, and discordant incident/prevalent combinations) are not included, but their data concerning the foods and nutrients described here can be found in the online supplement (*see* Table E3).

[†] Food- and energy-adjusted nutrients were categorized into quartiles, based on the distribution of the entire baseline cohort. Median values within quartiles are presented in parentheses, and are based on the subjects included in these analyses.

[‡] Tests for trend were conducted using the median value for each quartile of the specified dietary factor analyzed as an ordinal variable in the regression models.

[§] Nutrient intake from food sources.

[¶] Models are adjusted for age, total energy intake, dialect group, sex, smoking status (never, former, current), age at starting to smoke (⩾ 20, 15–19, ⩽ 14 years), and cigarettes per day (⩽ 12, 13–22, ⩾ 23). These odds ratios are for individual dietary items without adjustment for the other items.

with reduced development of cough with phlegm. As in previous prospective studies of lung function (35) or chronic respiratory symptoms and disease (24, 36), we found modest inverse associations for fruit and vitamin C intake. However, these associations were eliminated after adjustment for nonstarch polysaccharide intake. The earlier prospective studies (24, 35, 36) did not consider the role of fiber, and therefore it is unclear whether the previously reported associations with fruit and vitamin C were independent of nonstarch polysaccharide intake.

Fruit, vegetable, and grain products were the major contributors

TABLE 3. ODDS RATIOS BY TERTILE OF DAILY INTAKE OF SPECIFIC FRUITS AND INCIDENT COUGH WITH PHLEGM: THE SINGAPORE CHINESE HEALTH STUDY*

	Noncases	All Cases of Incident Cough with Phlegm		Cases with Symptoms for ⩾ 3 mo/yr	
	(*n* = *44,068*)	(*n* = *571*)	OR (95% CI)[§]	(*n* = *359*)	OR (95% CI)[§]
Apples, g					
T1 (0.0)[†]	13,353	248	1.0 (ref.)	165	1.0 (ref.)
T2 (19.1)	10,796	125	0.75 (0.60, 0.93)	70	0.63 (0.47, 0.84)
T3 (47.8)	19,919	198	0.67 (0.55, 0.82)	124	0.64 (0.50, 0.82)
p Value for trend[‡]			< 0.001		0.001
Oranges, g					
T1 (0.0)[†]	14,019	238	1.0 (ref.)	153	1.0 (ref.)
T2 (21.4)	10,634	121	0.76 (0.61, 0.95)	70	0.69 (0.52, 0.92)
T3 (53.6)	19,415	212	0.79 (0.65, 0.96)	136	0.83 (0.65, 1.06)
p Value for trend[§]			0.026		0.201
Pears, g					
T1 (0.0)[†]	16,514	266	1.0 (ref.)	181	1.0 (ref.)
T2 (12.6)	15,057	178	0.84 (0.69, 1.02)	105	0.73 (0.58, 0.94)
T3 (25.2)	12,497	127	0.75 (0.60, 0.93)	73	0.65 (0.49, 0.86)
p Value for trend[§]			0.007		0.001
Grapes, g					
T1 (0.0)[†]	23,818	351	1.0 (ref.)	224	1.0 (ref.)
T2 (1.7)	9,703	122	0.94 (0.76, 1.16)	73	0.89 (0.68, 1.17)
T3 (5.8)	10,547	98	0.71 (0.57, 0.90)	62	0.74 (0.56, 0.99)
p Value for trend[§]			0.004		0.043

For definition of abbreviations *see* Table 2.

* Individuals (n = 4,498) with other symptom outcomes (incident cough or phlegm, prevalent cough and/or phlegm, and discordant incident/prevalent combinations) are not included, but can be found in the online supplement (*see* Table E4).

[†] Fruits were categorized into tertiles, based on the distribution of the entire baseline cohort. Median values within tertiles are presented in parentheses, and are based on the subjects included in these analyses. Tertiles rather than quartiles were used because consumption of any individual fruit is substantially less than that of total fruits.

[‡] Tests for trend were conducted using the median value for each tertile of the specified dietary factor analyzed as an ordinal variable in the regression models.

[§] Models are adjusted for age, total energy intake, dialect group, sex, smoking status (never, former, current), age at starting to smoke (⩾ 20, 15–19, ⩽ 14 years), and cigarettes per day (⩽ 12, 13–22, ⩾ 23).

of nonstarch polysaccharide intake in this population. Incidence of cough with phlegm was reduced with high intake of fruit, but not vegetable or grain products. The lack of an inverse association with vegetable intake may be due to its limited variation in our population, where the interquartile range was 2.6-fold smaller for vegetable than for fruit intake. The limited variation would give us much less power to find an association with vegetables than with fruit.

It is also possible that fiber from fruit may have physiologic effects that are more beneficial in reducing development of cough with phlegm than fiber from vegetables or grain products. In addition, to the extent that fiber from whole grains is important, we might not see this in our cohort because white rice is the major grain in the Asian diet, rather than the whole grains found in some Western diets (49). Fiber is a complex dietary component (47, 50) and may have beneficial effects on the lung such as reducing blood glucose concentrations (51–53), thereby reducing inflammation (54) and enhancing antioxidant processes (33, 34). The physiologic properties of fiber from fruits versus vegetables and grains in relation to lung disease have not been studied. However, in support of our finding for respiratory symptoms, fiber from fruit had the greatest inverse association with risk of coronary heart disease in a pooled analysis, compared with other sources of dietary fiber (55).

Another hypothesis for why fruit, but not vegetable or grain, intake was inversely associated with cough plus phlegm is that components in fruit, in addition to fiber, such as individual flavonoids, may be important in protection against chronic productive cough. Flavonoids may protect the lung on the basis of their antioxidant (56) and antiinflammatory properties (22, 57). Flavonoid antioxidant mechanisms may involve direct free-radical scavenging and inhibition of nitric oxide synthase or xanthine oxidase (22, 58). In addition, flavonoid antiinflammatory mechanisms involve inhibitory effects *in vitro* on the cyclooxygenase and 5-lipoxygenase pathways of arachidonic acid metabolism (59, 60), including inhibition of protein kinases (61).

Flavonoids are a diverse group of polyphenols (56, 62). Although both fruits and vegetables are sources of flavonoids, particular classes of these compounds are more abundant in fruits (63, 64). Predominant flavonoids in the diet include quercetin, a flavonol primarily found in apples, berries, tea, and onions (65), and catechin, a flavonol primarily found in apples, pears, black grapes, tea, and apricots (66). In the Asian diet, with high intake of tofu, soy isoflavones are an important source of flavonoids (44, 67). Food composition databases to assess flavonoid intake have been developed for the United States (63, 65) and the Netherlands (64, 68, 69), but not for the diet of Asian countries. Thus we cannot evaluate total flavonoid intake in our study population at this time.

Our findings suggest that flavonoids may play a crucial role in the relation between fruit and soyfood intake and development of chronic cough with phlegm. We observed inverse associations between incident cough with phlegm and fruits high in flavonoids, such as apples, grapes, and pears (65, 66), and the associations with apples and grapes remained statistically significant after adjustment for total nonstarch polysaccharide intake. An inverse association between flavonoids and lung disease was first suggested by Miedema and coworkers on the basis of findings from a prospective study in which intake of apples and pears reduced the risk of chronic nonspecific lung disease; no

TABLE 4. ODDS RATIOS BY QUARTILE OF DAILY INTAKE OF SOYFOODS AND SOY ISOFLAVONES IN RELATION TO INCIDENT COUGH WITH PHLEGM: THE SINGAPORE CHINESE HEALTH STUDY*

	Noncases	All Cases of Incident Cough with Phlegm		Cases with Symptoms for ⩾ 3 mo/yr	
	(*n* = *44,068*)	(*n* = *571*)	OR (*95% CI*)¶	(*n* = *359*)	OR (*95% CI*)¶
Total soyfoods, g†					
Q1 (31.4)‡	10,457	163	1.0 (ref.)	102	1.0 (ref.)
Q2 (67.9)	11,080	147	0.89 (0.71, 1.12)	96	0.95 (0.71, 1.26)
Q3 (112.0)	11,284	136	0.80 (0.63, 1.02)	81	0.80 (0.59, 1.09)
Q4 (205.7)	11,247	125	0.69 (0.53, 0.90)	80	0.76 (0.55, 1.06)
p for trend§			0.005		0.085
Total soy isoflavones, mg					
Q1 (5.4)‡	10,483	183	1.0 (ref.)	112	1.0 (ref.)
Q2 (11.4)	10,987	156	0.91 (0.73, 1.13)	99	0.95 (0.72, 1.24)
Q3 (17.9)	11,188	126	0.76 (0.61, 0.96)	78	0.78 (0.58, 1.04)
Q4 (30.3)	11,410	106	0.67 (0.53, 0.86)	70	0.73 (0.54, 0.98)
p for trend§			0.001		0.022

For definition of abbreviations *see* Table 2.

* Individuals (n = 4,498) with other symptom outcomes (incident cough or phlegm, prevalent cough and/or phlegm, and discordant incident/prevalent combinations) are not included, but can be found in the online supplement (*see* Table E5).

¶ Models are adjusted for age, total energy intake, dialect group, sex, smoking status (never, former, current), age at starting to smoke (⩾ 20, 15–19, ⩽ 14 years), and cigarettes per day (⩽ 12, 13–22, ⩾ 23). These odds ratios are for individual dietary items without adjustment for the other item.

† Expressed in units of tofu equivalents (*see* METHODS for details).

‡ Food and energy-adjusted nutrients were categorized into quartiles, based on the distribution of the entire baseline cohort. Median values within quartiles are presented in parentheses, and are based on the subjects included in these analyses.

§ Tests for trend were conducted using the median value for each quartile of the specified dietary factor analyzed as an ordinal variable in the regression models.

association was found for vitamin C or β-carotene (24). Two studies suggest that higher intake of apples and wine is associated with improved lung function (23, 70). In a cross-sectional study, Tabak and coworkers found intake of three classes of flavonoids (catechins, flavonols, and flavones) to be related to lung function, chronic cough, and breathlessness, but not to chronic phlegm (25). Solid fruit intake was associated with a decreased risk of all three symptoms (25).

Additional support for the importance of flavonoids comes from our finding of an inverse association with soyfoods and soy

TABLE 5. ODDS RATIOS FOR DAILY INTAKE OF SELECTED DIETARY FACTORS AND INCIDENT COUGH WITH PHLEGM, WITH AND WITHOUT ADJUSTMENT FOR TOTAL NONSTARCH POLYSACCHARIDES: THE SINGAPORE CHINESE HEALTH STUDY*

	OR (95% CI) for Dietary Factor‡: Adjusted for Covariates Only§		OR (95% CI) for Dietary Factor‡: Adjusted for Covariates§ and Nonstarch Polysaccharides	
Dietary Factor	All Cases of Incident Cough with Phlegm	Cases with Symptoms for ⩾ 3 mo/yr	All Cases of Incident Cough with Phlegm¶	Cases with Symptoms for ⩾ 3 mo/yr¶
Total fruit	0.67 (0.52, 0.87)	0.64 (0.46, 0.88)	1.06 (0.74, 1.52)	0.89 (0.57, 1.39)
Apples	0.67 (0.55, 0.82)	0.64 (0.50, 0.82)	0.79 (0.64, 0.98)	0.74 (0.56, 0.97)
Pears	0.75 (0.60, 0.93)	0.65 (0.49, 0.86)	0.86 (0.69, 1.09)	0.73 (0.54, 0.98)
Grapes	0.71 (0.57, 0.90)	0.74 (0.56, 0.99)	0.79 (0.62, 0.99)	0.81 (0.61, 1.09)
All grain products	1.12 (0.80, 1.56)	1.32 (0.87, 2.00)	0.89 (0.63, 1.26)	1.08 (0.70, 1.67)
Total vegetables	0.92 (0.70, 1.21)	0.97 (0.69, 1.37)	1.23 (0.91, 1.65)	1.27 (0.87, 1.85)
Vitamin C†	0.73 (0.57, 0.94)	0.78 (0.57, 1.07)	1.16 (0.82, 1.65)	1.30 (0.84, 2.02)
Vitamin E†	0.78 (0.61, 0.99)	0.82 (0.60, 1.13)	1.08 (0.81, 1.43)	1.16 (0.81, 1.67)
Total soyfoods	0.69 (0.53, 0.90)	0.76 (0.55, 1.06)	0.83 (0.62, 1.10)	0.91 (0.64, 1.30)
Total soy isoflavones	0.67 (0.53, 0.86)	0.73 (0.54, 0.98)	0.80 (0.62, 1.04)	0.86 (0.62, 1.19)
Nonstarch polysaccharides	0.61 (0.47, 0.78)	0.60 (0.43, 0.82)	—	—

For definition of abbreviations *see* Table 2.

* Individuals (n = 4,498) with other symptom outcomes (incident cough or phlegm, prevalent cough and/or phlegm, and discordant incident/prevalent combinations) are not included, but can be found in the online supplement (*see* Table E6).

† Nutrient intake from food sources.

‡ Odds ratios (ORs) and 95% confidence intervals (CIs) for fourth versus first quartile of daily intake for all specified dietary factors, except for apples, pears, and grapes, where ORs and CIs are for third versus first tertile of daily intake.

§ Covariates include age, total energy intake, dialect group, sex, smoking status (never, former, current), age at starting to smoke (⩾ 20, 15–19, ⩽ 14 years), and cigarettes per day (⩽ 12, 13–22, ⩾ 23).

¶ Odds ratios for nonstarch polysaccharide intake in each model were statistically significant and ranged from 0.49–0.67.

isoflavones. We are not aware of any previous epidemiologic data on soyfoods and nonmalignant lung disease. A role for soy is plausible, because genistein, a soy isoflavone, acts *in vivo* as an antiinflammatory agent by inhibiting protein tyrosine kinase (30) and nuclear factor-κB (31). Daily tea drinking, a source of flavonoids, had a weak inverse association with cough plus phlegm (data not shown). Wine, another source of flavonoids that may have beneficial effects on the lung (70, 71), cannot be assessed in our population because only 0.8% drank at least one glass of (red or white) wine annually.

A limitation of observational studies is the potential for differential recall bias of usual diet by case status. With specific reference to our population, traditional Chinese medicine recommends that individuals with cough, wheeze, and/or excess phlegm avoid "Yin" foods, or foods with "cold" properties (72, 73). Most fruits and vegetables are considered Yin (72). Although we prospectively assessed cough with phlegm, we considered the possibility that individuals may have avoided certain foods, which could cause a false protective association. However, after removing individuals who reported onset of symptoms within the first year after the baseline diet interview, we observed no differences in the odds ratios for total fruit or total nonstarch polysaccharide intake with cough plus phlegm (data not shown). Further, if this bias were operating, we would have expected to see an inverse association with vegetable intake, which we did not. We concluded that our findings could not be explained by avoidance of Yin foods due to early symptoms. This possible bias was not relevant to soy, which is considered "neutral" or without Yin and Yang characteristics.

One possible concern is that the presence of cough with phlegm may be due to infectious causes. It should be noted that the period of symptom ascertainment (July 1999–August 2003) preceded a severe acute respiratory syndrome outbreak. Further, previous diagnosis of tuberculosis was rare among our case group (2.3%, with an average age at diagnosis of 37 years).

The objection may be raised that a diet high in fiber, fruit, and soy might be a marker of a healthy lifestyle, including lower smoking (74, 75). We carefully adjusted for smoking, although eliminating residual confounding is difficult to guarantee. However, we found a protective effect of nonstarch polysaccharide intake in both smokers and nonsmokers, suggesting that the protective effects of nonstarch polysaccharides are not due to correlations with smoking behavior.

We had follow-up data on respiratory outcomes for 84.2% of the Singapore Chinese Health Study participants. We would expect that some differences would exist between those with and without respiratory outcome data, some of whom are deceased (*see* Table E1 in the online supplement). However, for loss to follow-up to have created the inverse association we observed, we would have had to disproportionately lose either cases with higher fiber intake, or noncases with low fiber intake. Although we obviously lack respiratory data on those who have yet to complete the follow-up interview or who died before completion, when we compare the dietary data at baseline among participants with and without follow-up, participants without outcome data have similar to slightly lower intakes for all the key nutrients (*see* Table E1 in the online supplement). Thus, it is not plausible that the lack of follow-up data in this cohort could be responsible for the observed inverse associations between diet and incident cough with phlegm.

The strengths of this study include its prospective design, which allows us to have greater confidence that associations we observe between diet and symptoms reflect effects on incidence rather than recall bias or dietary changes due to symptom development. We acknowledge that for symptoms of cough and phlegm, subjects will have some difficulty reporting the exact number of years they have had the symptoms and thus there will be some misclassification between the prevalent and incident categories. However, on average, individuals who we classified as "incident" are much more likely to have initiated symptoms after the baseline dietary interview compared with individuals we classified as "prevalent."

Other advantages of the study include high-quality dietary data, specifically the use of a 165-item food frequency questionnaire, developed for and validated in this population, and extensive smoking and other lifestyle data to adequately adjust for potential confounding effects. A unique aspect of these analyses was the Asian population that enabled us to examine foods less common in a Western-style diet, such as soy. Vitamin supplement use was also low compared with U.S. populations, enabling us to better examine effects of food intake.

Preventing the initiation of smoking is still the most important primary prevention method for chronic respiratory symptoms and chronic obstructive pulmonary disease in general, not only because it is the major risk factor for development of the conditions, but also because adverse effects on lung parenchyma remain long after cessation (76, 77). However, our data from the Singapore Chinese Health Study provide evidence that promoting a diet high in sources of fiber and flavonoids, such as fruit and soy, may be an important contribution to primary prevention strategies for chronic respiratory symptoms, both in smokers and nonsmokers.

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