Longitudinal Changes in Pulmonary Function and Respiratory Symptoms in Cotton Textile Workers

A 15-yr Follow-up Study

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To evaluate the chronic effects of exposure to cotton dust, a 15-yr follow-up study in cotton textile workers was performed in Shanghai, China from 1981 to 1996. Testing occurred four times during the 15-yr period. The achieved follow-up rates were 76–88% of the original 447 cotton textile workers, and 70–85% of the original 472 silk textile workers (as a control group). Identical questionnaires, equipment, and methods were used throughout the study. The prevalence of byssinosis increased over time in cotton workers, with 15.3% at the last survey versus 7.6% at the baseline, whereas no byssinosis was found in silk workers. More workers in the cotton group consistently reported symptoms than in the silk group, although symptom reporting varied considerably from survey to survey. Cotton workers had small, but significantly greater, adjusted annual declines in FEV_1 and FVC than did the silk workers. Years worked in cotton mills, high level of exposure to endotoxin, and across-shift drops in FEV_1 were found to be significant determinants for longitudinal change in FEV_1, after controlling for appropriate confounders. Furthermore, there were statistically significant associations between excessive loss of FEV_1 and byssinosis, chest tightness at work, and chronic bronchitis in cotton workers. Workers who consistently (three or four of the surveys) reported byssinosis or chest tightness at work had a significantly greater 15-yr loss of FEV_1. We conclude that long-term exposure to cotton dust is associated with chronic or permanent obstructive impairments. Consistent reporting of respiratory symptoms, including byssinosis and chest tightness at work, is of value to predict the magnitude and severity of chronic impairments in textile workers.

Cotton workers are at risk for occupational lung disease, including byssinosis and chronic bronchitis. The initial phase of byssinosis is characterized by acute reversible symptoms, such as wheezing, chest tightness, shortness of breath, or cough, and is typically evident on the first day back to work after an absence of 48 h or more. These early symptoms are generally accompanied by reversible changes in pulmonary function (across-shift drops in FEV_1). With continued exposure, the disease may progress to a stage in which symptoms are present throughout the work week and may eventually result in severe pulmonary disability (1). In addition, excess nonspecific respiratory symptoms such as chronic cough, phlegm, and dyspnea were reported in cotton textile workers compared with nonexposed populations (2–4). Over the past several decades, a large number of cross-sectional studies have focused on acute airway response to cotton dust, have described a high prevalence of byssinosis, and have reported Monday across-shift declines in FEV_1. However, answers about whether chronic or permanent functional loss results from exposure to cotton dust remain unclear. Moreover, the relationship between byssinosis or work-related chest tightness and chronic changes in pulmonary function has not been well defined.

Longitudinal studies conducted in recent decades have produced conflicting results in understanding the chronic effects of exposure, especially with regard to functional impairments. Although some studies failed to find chronic effects (5–7), several studies observed accelerated annual decline in FEV_1 in cotton workers, with some reports relating Monday across-shift change in FEV_1, or byssinosis to long-term loss in FEV_1 (2, 8–10). Previous studies suggested that respiratory symptoms in cotton textile workers were reversible, and reporting symptoms varied substantially from survey to survey (5, 11, 12), whereas chronic symptoms persevered. Few studies, however, have examined the significance of respiratory symptom variability in relation to chronic functional loss. In a 5-yr follow-up study of cotton textile workers (13), consistent responders to either positive symptoms or across-shift FEV_1 decrements showed a 5-yr loss of FEV_1 at a greater rate. This suggests a relationship between chronic or permanent functional loss and the persistent reporting of symptoms in workers exposed to cotton dust. Weak or absent relationships have been found between respiratory symptoms, or average annual change in FEV_1, and average dust concentration, cumulative exposure, or length of exposure (5, 7, 10, 13, 14). Generally, follow-up studies to date have been limited by the short follow-up interval (10 mo to 5 yr), small data samples, and the absence or unsuitability of comparison groups.

To provide additional understanding of the chronic respiratory effects of exposure to cotton dust in terms of both pulmonary function and respiratory symptoms, we have extended the follow-up study to 15 yr in a large, stable group of cotton textile workers, and included both active and retired workers. The specific objectives of the present study were to determine the effects of long-term exposure to cotton dust on chronic respiratory impairments, and to evaluate the significance of respiratory symptom consistency for observed chronic functional changes.

METHODS

Study Population

The population-based, 15-yr longitudinal cohort study for respiratory disease among cotton textile workers was established in 1981. The study was approved by the Institutional Review Boards of the Harvard School of Public Health and Shanghai Medical University. The

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initial study population consisted of 447 cotton textile workers (52% female) in Shanghai, China. These represented 90% of workers who were employed more than 2 yr in the yarn preparation areas (opening, cleaning, carding, drawing, combing, roving, fine spinning) of two cotton textile mills, which are state owned and located in the same urban area. At the same time, 472 silk textile workers (58% female) who had worked for a minimum of 2 yr in a silk-thread processing mill in the same city were involved in the initial study as a comparison population. Subjects were excluded from the cohort if they had a history of active tuberculosis, of asthma, preceding entry into the textile workforce.

The follow-up surveys were conducted in 1986, 1992, and 1996, with eligibility for resurvey defined as membership in the original cohort, regardless of retirement from the industries. The numbers of participants who had left work and average years of retirement at each follow-up survey were 11 in the cotton group for 3 yr and 6 in the silk group for 2 yr at the 1986 survey; 27 in the cotton group for 4.5 yr and 25 in the silk group for 5 yr at the 1992 survey; and 191 in the cotton group for 6.1 yr and 196 in the silk group for 5.2 yr at the 1996 survey. Table 1 presents the number of participants in the following surveys. Overall, over 76–88% of the cotton workers and 70–85% of the silk workers in the original cohort performed either questionnaires or pulmonary function testing in the follow-up surveys.

Exposure Assessment

Airborne cotton dust and gram-negative bacteria endotoxins were measured using methods previously described (13). In brief, samples of work area were collected in each survey period using vertical elutriators in the various work areas. We used identical samples, sampler location handling techniques, and measurements for all four surveys. Endotoxin assays were performed on the dust samples using the *Limulus* amoebocyte lysate assay, chromogenic method, as previously described (15). A total of 802 air samples (130 at the first survey, 192 at the second survey, 408 at the third survey, and 72 at the last survey) were collected over the four surveys in the yarn preparation areas of the two mills. Between the first and second surveys, production and conditions were stable in the cotton mills. Geometric mean dust exposure of the work areas ranged from a low of 0.2 mg/m^3 to highs of 1.6 mg/m^3 during that time. However, 6 yr ago in 1994, between the second and third surveys, the mills began to blend synthetic fiber with cotton, and pure yarn production was slowed down. The mean dust exposure for the highest area was cut down to 1.1 mg/m^3 at the third survey and to 0.5 mg/m^3 at the last survey. As described in a previous study (16), environmental exposure measurements were not strikingly different between the two mills. There were no personal samplers available for cotton dust measurements. We developed cumulative dust and endotoxin variables for each person using geometric mean levels of dust and endotoxin exposure from the samplings of four time surveys multiplied by years of work in the various work areas. Endotoxin in the silk mill was identified as nearly zero over the period of follow-up study. Because we are interested in the effect of exposure to cotton dust, this exposure was zero for all silk workers.

Questionnaires

A modified version of the American Thoracic Society standardized respiratory symptom questionnaire (17) was used to collect information on a complete work history and medical history focusing on respiratory diseases and smoking history. All questionnaires were administered by a trained interviewer in the local dialect to each worker on his or her return to work after a 48-h rest period and before entering the production area. The workers were classified as either current smokers or nonsmokers according to their first interview in the study, as there were virtually no ex-smokers in the population. The changes in smoking habit were recorded in the following interviews. If someone had quit or started smoking for 3 mo during the follow-up period, he or she was classified as an ever-smoker and current smoker, respectively. Smoking amount was measured in units of pack-years. Symptoms of interest in the study were defined as follows:

Byssinosis (all grades): chest tightness or shortness of breath at work occurring in the first or other days of the work week according to criteria of Schilling and coworkers (18).

Chest tightness at work: tightness or constriction of the chest occurring anytime during the work shift and on any workday, without being worse specifically on the first day of the working week. Because the workers in the cotton mills worked continual rotating shifts on an 8-d cycle (4) with a 36-h rest at the end of rotation, we reported chest tightness at work separately from the typical byssinosis symptom.

Chronic bronchitis: sputum production occurring on most ($\geqslant$ 5) days a week for at least 3 mo a year for at least 2 consecutive years.

Chronic cough: cough without sputum for $\geqslant$ 5 d a week for at least 2 consecutive years.

Dyspnea 2+: having to walk slower than a person of the same age at an ordinary pace on level ground because of breathlessness.

TABLE 1. PARTICIPATING NUMBERS OF COTTON AND SILK TEXTILE WORKERS IN FOLLOW-UP SURVEYS

	Cotton Workers (*n* = *447*)		Silk Workers (*n* = *472*)	
	n	(%)	n	(%)
Questionnaire				
1986	384	(85.9)	403	(85.4)
1992	394	(88.1)	393	(83.3)
1996	346	(77.4)	338	(71.6)
Pulmonary function testing				
1986	356	(79.6)	374	(79.2)
1992	366	(81.9)	331	(70.1)
1996	339	(75.8)	336	(71.2)

Pulmonary Function Tests

In all surveys, pulmonary function tests were conducted by a trained technician at the participating mills. Forced expiratory spirograms were performed before and after work shifts (across-shift) on the first day back to work after a 2-d rest. In addition, all available retirees were also tested in the cohort follow-up surveys. An 8-L water-sealed field spirometer (W. E. Collins Co., Braintree, MA) calibrated twice a day with a 3-L syringe was used to record spirometric maneuvers throughout the surveys. Workers were asked to refrain from smoking for at least 1 h before performing the test. Each worker performed up to seven trials to produce three acceptable curves.

The analysis of the study was focused on indices of expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC). Acceptable FEV_1 tracings were allowed to vary by no more than 5% or 100 ml, whichever was greater, and the best FEV_1 and FVC were used regardless of whether they were on the same tracing. All values were corrected to conditions of body temperature and pressure saturated with water vapor (BTPS). The highest values for FEV_1 and FVC were used in subsequent analyses, provided that these values came from technically acceptable tests.

Chronic changes in pulmonary function were expressed in the consequent analyses as either annual changes or longitudinal changes (over 15-yr changes) using all available spirometric values obtained from each survey. Acute changes in pulmonary function were expressed as cross-shift change in FEV_1: $\Delta FEV_1 = FEV_1$ after shift $-$ FEV_1 before shift.

Statistical Analysis

Byssinosis, chest tightness at work, chronic bronchitis, cough, and dyspnea were the symptoms of primary interest in the analysis. Respiratory symptoms were categorized according to the consistency of subject reporting over the 15-yr study: 0—symptom was not reported at all four survey points; 1—symptom was reported once; 2—symptom was reported twice; 3—symptom was reported three times; and 4—symptom was reported all four times. In addition, reporting symptoms over the 15 yr were classified as dichotomous variables (0, 1) and analyzed in order to examine their associations with longitudinal changes in pulmonary function.

Average annual declines in FEV_1 and FVC for both cotton and silk workers were estimated by least-squares linear regression, using preshift data over the follow-up time. Potential confounders such as sex, height, and age at the mid-point between the first and last survey were adjusted to make the values comparable between the two occupational groups.

Statistical methods used in the study included the Student's *t* test, analysis of variance, Dunnett's test for multiple comparisons for continuous variables, and the chi-square test for category variables.

Generalized estimating equation (GEE) models (19, 20) were fitted to identify significant determinants for longitudinal changes in pulmonary function. The independent variables of interest included acute airway response (across-shift changes in FEV_1) and exposure terms, as well as symptoms occurring during the follow-up time. Because the outcome variables (FEV_1 and FVC) are continuous and approximately normally distributed, the identity link function and constant variance function were applied. The independence correlation structure, instead of the unstructured "working" correlation matrix, was used because of the varied number and spacing of the repeated measurements across subjects.

The procedure to fit regression models was as follows. First, age, height, smoking status, pack-year, years worked, and exposure terms were determined for possible interaction with follow-up time. As a result, both FEV_1 and FVC did not have time-dependent interacted covariates. The basic models were developed on the basis of a set of covariates and confounders of potential interest, including age, height, smoking status over the period of follow-up, status of exposure to cotton dust, sex, cumulative cotton dust exposure, cumulative endotoxin exposure, years worked, pack-year of cigarette smoking, and follow-up years. Across-shift changes in FEV_1 over the follow-up study were also included in the models to assess the relationship of acute changes in pulmonary function to longitudinal changes. Next, each symptom term was separately added to the models. At the same time, interaction between symptoms and follow-up year was determined, and only significant interaction terms were included in the final models. The data analysis was accomplished with SAS personal computer software (Version 8) (SAS Institute, Cary, NC, 1999).

RESULTS

Demographic and clinical characteristics of the initial cohort are shown in Table 2. Cotton and silk workers were similar in age, height, years employed, and sex proportion. The prevalence of smokers was higher in the cotton group, but average smoking amount was somewhat elevated in the silk group. There were 10 female smokers among the silk workers, and no female smokers among the cotton workers. The cotton group had a higher prevalence of respiratory symptoms, as well as larger cross-shift decrements in FEV_1 than the silk group.

There were 101 cotton workers and 134 silk workers from the initial cohort lost to follow-up at the last survey. A comparison of data at baseline between subjects followed and those lost to follow-up (Table 3) revealed them to be similar in demographic features and pulmonary function, with the exception that the lost to follow-up subjects had a significantly longer employed year in cotton workers. Although chronic bronchitis, cough, and dyspnea tended to be more prevalent in lost to follow-up subjects than in those followed for either cotton or silk workers, none of these differences was significant.

To identify whether those who had acute respiratory symptoms were more likely to leave work, the symptom prevalence of retired workers derived from the baseline survey, and the survey prior to their retirement as well, was compared with that of active workers. As a result, no significant differences were observed in acute respiratory symptoms such as byssinosis or chest tightness at work. In contrast, it was noted that chronic bronchitis, cough, or dyspnea was significantly more common among both retired cotton and silk workers.

The prevalence of respiratory symptoms at each follow-up survey was consistently higher in the cotton group than in the silk group. In comparison with the initial survey, the prevalence of byssinosis in the cotton group tended to increase over time, with 19.0% at the third survey and 15.3% at the fourth survey versus 7.6% at baseline and 3.1% at the second survey, whereas the prevalences of other symptoms were not increased over time for both groups. Symptoms were categorized by consistency (Table 4) and proportions of symptoms reported one or more times were higher in cotton workers than in silk workers. Among those reporting any particular symptom, most subjects reported them once. No typical byssinosis was identified in silk workers, and 20% and 8% of cotton workers reported byssinosis symptoms once and twice, respectively. Fewer reported byssinosis three or four times (the two categories were combined

TABLE 2. DEMOGRAPHIC AND CLINICAL DATA OF THE STUDY POPULATION AT BASELINE*

	Cotton Workers (*n = 447*)	Silk Workers (*n = 472*)
Age, yr	37.4 ± 10.6	36.2 ± 10.7
Male, %	47.7	42.2
Height, cm	163.9 ± 7.5	162.5 ± 7.3
Years worked, yr	16.4 ± 10.4	17.1 ± 11.8
Cumulative dust exposure, mg/m^3 yr	13.5 ± 12.1	—
Cumulative endotoxin exposure, EU/m^3 yr	23825.7 ± 31096.2	0
Current smoker, %	35.6	25.0
Pack-year	8.5 ± 9.7	9.2 ± 9.9
Pulmonary function testing		
FEV_1, L	2.92 ± 0.73	2.88 ± 0.67
FVC, L	3.53 ± 0.78	3.44 ± 0.75
ΔFEV_1†, L	−0.06 ± 0.15	−0.001 ± 0.141
Respiratory symptoms, n (%)		
Byssinosis	34 (7.6)	0 (0.0)
Chest tightness at work	35 (7.8)	1 (0.2)
Chronic bronchitis	96 (21.5)	36 (7.6)
Chronic cough	87 (19.5)	33 (7.0)
Dyspnea (+2)	67 (15.0)	18 (3.8)

* Mean and SD were indicated unless otherwise stated.
† ΔFEV_1 = across-shift change in FEV_1.

TABLE 3. COMPARISON OF SYMPTOM PREVALENCE AND PULMONARY FUNCTION VALUES AT INITIAL SURVEY BETWEEN SUBJECTS FOLLOWED UP AND LOST TO FOLLOW-UP

	Cotton Workers		Silk Workers	
	Follow-up	Lost to Follow-up	Follow-up	Lost to Follow-up
Number	346	101	338	134
Age, yr, mean	36.9	38.9	36.6	35.2
Years worked, mean	14.7	16.2*	16.4	13.7
Male, %	46.2	52.5	41.1	44.8
Current smokers, %	35.5	35.6	23.7	28.4
Pack-year, mean	7.9	10.4	8.6	10.3
Symptoms, %				
Byssinosis	7.2	8.9	0	0
Chest tightness at work	7.5	8.9	0.3	0.0
Chronic bronchitis	20.8	23.7	6.5	10.4
Chronic cough	19.4	19.8	5.9	9.7
Dyspnea (2+)	13.9	18.8	3.0	6.0
Pulmonary function†				
FEV_1 L	2.92 ± 0.70	2.90 ± 0.79	2.88 ± 0.65	2.90 ± 0.71
FVC, L	3.51 ± 0.76	3.58 ± 0.83	3.44 ± 0.75	3.45 ± 0.75
ΔFEV_1, L‡	−0.06 ± 0.15	−0.06 ± 0.15	−0.003 ± 0.130	0.003 ± 0.167

* $p < 0.05$ when compared with followed subjects.
† Mean and SD were indicated.
‡ ΔFEV_1 = across-shift change in FEV_1.

TABLE 4. CONSISTENCY OF RESPIRATORY SYMPTOMS DURING 15 yr FOLLOW-UP IN COTTON AND SILK TEXTILE WORKERS*

	Cotton Workers (*n* = *447*)				Silk Workers (*n* = *472*)			
	0	1	2	⩾ 3	0	1	2	⩾ 3
Byssinosis	317 (70.9)	91 (20.4)	35 (7.8)	4 (0.9)	472 (100.0)			
Chest tightness at work	301 (67.4)	102 (22.8)	38 (8.5)	6 (1.3)	413 (87.5)	53 (11.2)	6 (1.3)	0 (0.0)
Chronic bronchitis	327 (73.2)	71 (15.9)	29 (6.5)	20 (4.4)	398 (84.3)	49 (10.4)	19 (4.0)	6 (1.3)
Chronic cough	337 (75.4)	72 (16.1)	21 (4.7)	17 (3.8)	401 (85.0)	44 (9.3)	21 (4.4)	6 (1.3)
Dyspnea (2+)	279 (62.4)	101 (22.6)	42 (9.4)	27 (5.6)	340 (72.0)	105 (22.3)	22 (4.7)	5 (1.0)

* The differences between cotton and silk workers were significant ($p < 0.01$) for all symptoms (Chi-square test for trend).

due to a small number). A similar trend was observed for chest tightness at work. For both cotton and silk workers who reported a particular respiratory symptom two or three times, 71% to 82% reported the same symptom at consecutive times. Overall, the prevalence of each symptom was significantly different ($p < 0.01$) between cotton and silk workers.

Adjusted annual declines in FEV_1 and FVC showed a small, but significant difference between cotton workers and silk workers (Table 5). Both male and female cotton workers lost pulmonary function at a faster rate than did their counterparts. When stratified by smoking status, greater functional decrements were found in smoking cotton workers than in smoking silk workers. Among cotton workers, smokers tended to have a greater annual loss in FEV_1 than nonsmokers, but no such trend in silk workers was seen.

Annual changes in FEV_1 and FVC stratified by consistency of each symptom showed a gradient with greater declines related to more consistently positive symptoms in both the cotton and silk groups (data were not shown). Declines in FEV_1 by 42 ml/yr and in FVC by 25 ml/yr were observed in cotton workers who always reported positive byssinosis (category > 3), compared with 33 ml/yr for FEV_1 and 20 ml/yr for FVC in those who never reported byssinosis (category 0). Significant differences ($p < 0.05$) were found in FVC between always positive and always negative reporting for chronic bronchitis in both groups, for dyspnea in cotton workers, and for cough in silk workers.

Significant independent determinants of longitudinal changes in FEV_1 and FVC were identified using GEE models. In this analysis, cumulative dust and endotoxin exposure were defined as dichotomous variables, that is, low or high level with cut-points of the median cumulative dust exposure (14.2 mg/m^3 years) and median cumulative endotoxin exposure (48,000 EU/m^3 years) in cotton group. As shown in Table 6, a significant effect of high level of exposure to endotoxin on FEV_1 was observed in two group-combined models. Furthermore, when analysis was restricted to the cotton group, high level of exposure to endotoxin was a significant determinant of excessive longitudinal losses of both FEV_1 and FVC. In addition, years worked had significantly adverse effects on both FEV_1 and FVC in cotton group models, but not in silk group models, suggesting that longer work in cotton mills was associated with greater functional losses. Exposed status (0, 1) and high level of exposure to cotton dust were not observed to be significantly associated with changes in pulmonary function. Across-shift drops in FEV_1 (ΔFEV_1) measured from four surveys strongly correlated with FEV_1 and FVC in cotton workers, and such an association was absent in silk workers. Even after symptom terms were added to the models, the strong relationship remained, indicating that across-shift drop in FEV_1 in cotton workers is a strong predictor for long-term accelerated loss of lung function. Sex and smoking status were found to be synonymous and are virtually interchangeable as independent variables, because there were so few female smokers (n = 10).

TABLE 5. ANNUAL CHANGES* IN PULMONARY FUNCTION IN COTTON AND SILK TEXTILE WORKERS

	FEV_1 (*ml/yr*)		FVC (*ml/yr*)	
	Cotton	Silk	Cotton	Silk
Total	−32.3 (1.0)†	−29.4 (1.0)‡	−20.1 (1.2)	−15.3 (1.3)§
Male	−42.2 (1.8)	−38.0 (1.9)	−27.8 (2.1)	−23.6 (2.3)
Female	−24.8 (1.6)	−22.4 (1.5)	−14.7 (1.6)	−9.0 (1.6)
Smokers‖	−43.7 (2.0)	−39.3 (2.1)	−27.5 (2.5)	−24.3 (3.1)
Nonsmokers	−40.4 (3.2)	−40.1 (2.5)	−27.5 (4.0)	−23.6 (3.7)

* The values were adjusted by age at mid-point during the follow-up period and height at final survey (sex and smoking status were also adjusted in calculation of "Total").
† Numbers in parentheses indicate SE.
‡ $p > 0.05$.
§ $p < 0.01$.
‖ Calculated from male smokers at final survey.

For respiratory symptoms, chronic bronchitis, chronic cough, dyspnea, and chest tightness at work were significantly associated with excessive 15-yr loss of FEV_1 in the analysis including both groups. Chronic bronchitis interacted with follow-up years was seen in both cotton and silk groups, and indicates that FEV_1 decreased significantly more over time in those with chronic bronchitis. In the models restricted to the cotton group alone, the relationship of accelerated loss in FEV_1 to byssinosis was significant ($p < 0.01$). FEV_1 loss in relation to chest tightness at work and dyspnea reached marginal significance ($p = 0.05$ and 0.06, respectively). In the silk worker models, statistically significant associations with chronic bronchitis and cough, but not with chest tightness, were observed.

The GEE model describing longitudinal changes in pulmonary function in relation to consistency of reporting symptoms in cotton workers is presented in Table 7. Potential confounders, such as sex, height, age, years worked, and across-shift changes in FEV_1 over the follow-up time, were adjusted. In contrast to subgroups reporting no symptoms in all four surveys, there was little change in FEV_1 or FVC for reporting symptoms once, whereas excessive loss in FEV_1 was observed in those reporting symptoms twice or more. Greater losses of FEV_1, however, were found in subgroups reporting symptoms consistently, that is, three or four times, with the exception of dyspnea, for which reporting at least twice led to a greater loss in both FEV_1 and FVC. Consistently reporting either chest tightness or byssinosis was associated with greater declines in FEV_1 and FVC, relative to other consistently reported symptoms, which is suggestive of a stronger relationship between these two (work-related) symptoms and longitudinal function losses among the cotton workers.

DISCUSSION

Cotton Dust Exposure and Chronic Loss of Pulmonary Function

Pulmonary function testing in cotton workers is essential to determine the frequency, severity, and pattern of airway dis-

TABLE 6. INDEPENDENT DETERMINANTS OF LONGITUDINAL CHANGES IN PULMONARY FUNCTION*

	FEV_1 (*L*)		FVC (*L*)	
	Estimate (SE)	p Value	Estimate (SE)	p Value
Cotton and silk combined				
Sex, male	0.548 (0.162)	<0.001	0.695 (0.244)	<0.001
Height, cm	0.046 (0.007)	<0.001	0.060 (0.007)	<0.001
Age, yr	−0.046 (0.008)	<0.001	−0.017 (0.004)	<0.001
Endotoxin exposure, high	−0.281 (0.130)	<0.05	—	
ΔFEV_1, L	−0.732 (0.135)	<0.001	−0.380 (0.157)	<0.05
Symptoms				
Chronic bronchitis	−0.189 (0.081)	<0.05	—	
Chronic cough	−0.212 (0.073)	<0.01	—	
Dyspnea (2+)	−0.161 (0.081)	<0.05	—	
Chest tightness at work	−0.235 (0.116)	<0.05	—	
Bronchitis × year†	−0.198 (0.066)	<0.01	—	
Cotton only				
Sex, male	0.530 (0.188)	<0.001	0.693 (0.250)	<0.001
Height, cm	0.045 (0.010)	<0.001	0.060 (0.009)	<0.001
Age, yr	−0.044 (0.014)	<0.001	−0.014 (0.012)	<0.05
Years worked, yr	−0.035 (0.005)	<0.05	−0.027 (0.011)	<0.05
Endotoxin exposure, high	−0.334 (0.125)	<0.01	−0.308 (0.142)	<0.05
ΔFEV_1, L	−0.916 (0.150)	<0.001	−0.678 (0.2.3)	<0.001
Symptoms				
Byssinosis	−0.336 (0.118)	<0.01	—	
Chest tightness at work	−0.181 (0.093)	0.05	—	
Dyspnea (2+)	−0.194 (0.104)	0.06		
Bronchitis × year	−0.140 (0.057)	<0.05	—	
Silk only				
Sex, male	0.446 (0.079)	<0.001	0.589 (0.078)	<0.001
Height, cm	0.036 (0.005)	<0.001	0.048 (0.052)	<0.001
Age, yr	−0.034 (0.003)	<0.001	−0.028 (0.004)	<0.001
Symptoms				
Chronic bronchitis	−0.397 (0.128)	<0.01	—	
Bronchitis × year	−0.138 (0.064)	<0.05	−0.205 (0.106)	0.05
Chronic cough	−0.340 (0.144)	<0.05	—	

* Covariates considered in the GEE models include height, age, years worked, smoking status, and across-shift change in FEV_1 over 15 yr and sex, exposed status, smoking pack-years, cumulative exposure level to cotton dust and endotoxin (high, low), and follow-up year.

† Interaction between chronic bronchitis and follow-up years.

ease resulting from dust exposure. In early studies of byssinosis, ventilatory tests were not used, until Schilling and coworkers (18) included spirometric testing before and after the work shift in an attempt to better characterize the disease. These investigations revealed that acute across-shift airway obstruction occurred in some, but not all, workers with the symptoms of byssinosis (10). Since the 1970s, a few follow-up studies focusing on chronic changes in ventilatory function have been conducted in populations exposed to cotton, hemp and other organic dust. Fox and coworkers in a 2-yr study (5) found 23 ml/yr loss of FEV_1 in 866 cleaning and card-room workers, which was no greater than that expected due to age alone. This study was limited by the absence of a control group and the short follow-up interval. Berry and coworkers (7) in a 3-yr study found no relationship of annual declines in FEV_1 to present dust level, dust bioactivity, byssinosis, or Monday across-shift drop in FEV_1. Similar results were reported by Larson and Barman (6), in which annual change in FEV_1 for cotton gin workers followed over 4 yr was less than that observed for control subjects.

By contrast, Beck and coworkers (9) in a 6-yr follow-up study reported significantly greater annual declines in FEV_1 in active and retired cotton workers compared with control subjects from another community, but the appropriateness of the control group has been questioned. A 5-yr study of cotton mill workers in India (21) reported very large annual declines in FEV_1 for both cotton workers and control subjects, possibly an artifact caused by changing the spirometric equipment after the first survey. In a recent 10-yr two-point study, Zuskin and coworkers demonstrated an accelerated mean annual decline in FEV_1 among a small cohort of 66 remaining active workers of an original group of 116 (22).

In our 5-yr follow-up study, the mean unadjusted annual decline in FEV_1 among cotton workers (39.5 ml) was significantly greater than that (30.6 ml) for silk workers. The current study showed that cotton workers had small, but significantly greater, annual losses in FEV_1 and FVC in comparison with the silk workers, after taking into account age, sex, height, and smoking status. The adjusted annual declines were 32.3 ml in FEV_1 and 20.1 ml in FVC for the cotton workers versus 29.4 ml in FEV_1 and 15.3 ml in FVC for the silk workers. Sex-specific annual declines in FEV_1 among the cotton workers showed 42.2 ml in males and 24.8 ml in females. Smoking cotton workers tended to be greater in annual loss in FEV_1, but no such trend was observed in the silk workers.

In accordance with our previous study (10), the strong relationship between across-shift drops in FEV_1 and longitudinal losses of pulmonary function is reconfirmed in the current study. Across-shift changes in FEV_1 were associated with a loss of 916 ml in FEV_1 and 678 ml in FVC over 15 yr among the cotton workers, irrespective of respiratory symptoms, and the changes were significant. It is assumed that across-shift drops in FEV_1 and chronic airway obstruction are not a causal relationship, and both may be a consequence of exposure to cotton dust.

In addition, we found a significant correlation between chronic loss of pulmonary function and length of exposure (years worked in cotton mills). More importantly, the functional losses were significantly associated with cumulative en-

TABLE 7. EFFECTS OF CONSISTENCY OF RESPIRATORY SYMPTOMS ON LONGITUDINAL CHANGES IN PULMONARY FUNCTION ESTIMATED FROM GEE MODELS* IN COTTON TEXTILE WORKERS

	FEV_1 (*L*)		FVC (*L*)	
	Estimate (SE)	p Value	Estimate (SE)	p Value
Byssinosis†				
1	0.039 (0.090)	NS	0.109 (0.095)	NS
2	−0.118 (0.154)	NS‡	−0.224 (0.132)	NS
⩾ 3	−0.414 (0.064)	<0.001	−0.142 (0.173)	NS
Chest tightness at work				
1	−0.068 (0.092)	NS	−0.015 (0.089)	NS
2	−0.069 (0.143)	NS	−0.016 (0.134)	NS
⩾ 3	−0.924 (0.292)	<0.01	−0.549 (0.097)	<0.001
Chronic bronchitis				
1	0.001 (0.089)	NS	0.001 (0.094)	NS
2	−0.066 (0.111)	NS	−0.016 (0.121)	NS
⩾ 3	−0.281 (0.149)	<0.05	−0.027 (0.134)	NS
Chronic cough				
1	−0.062 (0.081)	NS	0.013 (0.107)	NS
2	−0.111 (0.123)	NS	0.018 (0.158)	NS
⩾ 3	−0.373 (0.555)	<0.05	−0.070 (0.144)	NS
Dyspnea (2+)				
1	0.129 (0.089)	NS	0.134 (0.106)	NS
2	−0.496 (0.127)	<0.05	−0.139 (0.064)	<0.05
⩾ 3	−0.116 (0.193)	NS	−0.037 (0.142)	NS

Definition of abbreviations: GEE = generalized estimating equation; NS = not significant.

* Sex, age, height, years worked, cumulative exposure to endotoxin, and across-shift changes in FEV_1 were simultaneously adjusted.

† Categories 1, 2, and ⩾ 3 versus category 0 (all negative), respectively.

‡ $p > 0.05$.

dotoxin exposure. The workers with a higher level of cumulative endotoxin exposure had significantly greater losses of FEV_1 and FVC than did those with a low level. Conversely, a relationship of cumulative cotton dust exposure was not detected in the workers. Both experimental and epidemiological studies have suggested that endotoxin, other than cotton dust, is a potent inflammatory stimulus that causes acute airway obstruction and transient bronchial hyperresponsiveness after acute exposure in populations exposed to organic dust (23–28). Other studies have hypothesized that microorganisms or their constituents (notably gram-negative bacterial endotoxin) may be key factors in the etiology of cotton dust lung disease (29, 30). The positive relationship detected in this study provides a clue to the long-term airway effect of inhaled endotoxin.

Relationship between Chronic Functional Impairments and Respiratory Symptoms

In this study, respiratory symptoms were always more prevalent in the cotton workers than in the silk workers, whereas the prevalence of nonspecific symptoms was not increased over the follow-up period. The prevalence of byssinosis, however, was observed to increase over time, reaching 15.3% at the last survey compared with 7.6% at baseline. This cannot be explained by either the increase of cotton dust or endotoxin concentrations, or technical problems. In fact, the concentrations had decreased, rather than increased, since the second survey (1986), and identical questionnaires and definitions were used throughout the study. The finding demonstrates that prevalence of byssinosis is a function of length of exposure, or work tenures (31, 32). On the other hand, respiratory symptoms varied greatly from survey to survey, as reported in several other studies (13, 33). Among the 447 cotton workers, one-fifth reported symptoms once, 5–9% reported symptoms twice, and a smaller proportion reported symptoms more consistently during the 15-yr four-point observation. It is reasonable to presume that the inconsistent subgroups (reporting once) included both those who became symptomatic and those who became asymptomatic during the follow-up time, whereas the consistently reporting subgroups were those whose symptoms persisted. The latter was confirmed by the fact that most of the repeated symptoms including byssinosis were reported at two or three consecutive survey times. A small proportion of the population (about 20%) who reported symptoms at alternate times might include those whose symptoms cleared and then recurred at a later survey, or failed to report at consecutive times because of nonparticipation in one or more follow-up surveys. Based on the results, the term “chronic byssinosis” may be used to refer to cases in which typical symptoms of byssinosis or chest tightness at work are persistently present.

The relationship between longitudinal changes in lung function and byssinosis, or other symptoms, has been less well documented. Several short-term follow-up studies (5–7, 11) investigated the relationship, and found that symptoms were not associated with the rate of FEV_1 deterioration between surveys. In a 10-yr two-point study of workers exposed to coarse-grade cotton dust by Zuskin and Valic (8), an accelerated mean annual decline in FEV_1 was greater in workers with byssinosis than those without byssinosis, although the study observed only a small number of subjects ($n = 66$). In this study, we observed that there was an accelerated loss of FEV_1 associated with byssinosis and chest tightness at work. Among the symptoms, byssinosis contributed to a greater 15-yr loss of FEV_1 (336 ml, $p < 0.01$) in the cotton workers versus silk workers, indicating a close link of byssinosis to irreversibly and progressively chronic obstructive impairments. It also suggests that an interval of longer than 5 yr is necessary to identify the relationship between byssinosis and chronic respiratory impairments.

Another striking finding of the study is that the extent or magnitude of chronic functional losses was apparently affected by the consistency of reporting respiratory symptoms. There was a gradient in either annual declines or 15-yr losses with consistency of reporting symptom. More consistent presence of symptoms correlated with greater declines in FEV_1 and FVC. In contrast to consistently negative reporting, only the consistent presence of symptoms led to significantly greater chronic functional declines. Interestingly, “chronic byssinosis” and “chronic chest tightness at work” were found to be associated with greater chronic declines in FEV_1 and FVC than other respiratory symptoms in the cotton workers. This result implies a stronger relationship between chronic specific cotton-related disease and longitudinal declines in lung function, which is independent of smoking and aging. In other words, the persistent presence of byssinosis or chest tightness at work is related to chronically irreversible ventilatory impairments.

Possible Biases and Limitations

Longitudinal studies of respiratory health in occupational cohorts are not common. This study has been the longest prospectively follow-up study, to date, in a large group of cotton workers. The followed rates reached 76–88% for cotton workers and 70–85% for control workers. Silk textile workers were selected as a control group, instead of synthetic fiber mill workers, because at the time of the study, all synthetic fiber mills in Shanghai were converted cotton mills. We used identical methods of recruitment in cotton and silk workers and chose both populations from the same districts of a large industrial city. The silk and cotton workers were similar in respect to socioeconomics (urban environment, job selection criteria, family income status, etc.). We made an effort to follow-up both active and retired workers to avoid the biases due to "healthy workers' effect," which may lead to underestimating the chronic effects of cotton dust exposure. Although no significant difference was found in the prevalence of acute respiratory symptoms between the active and retired workers, retired workers reported more chronic symptoms. In determining a potential selection bias caused by dropouts in the follow-up study, the data showed significantly longer employment years and a higher prevalence of chronic bronchitis and dyspnea in lost to follow-up cotton workers, though the differences were not statistically significant. It is likely that the rates of functional losses in cotton workers, to some extent, were underestimated due to the dropout, as years worked in the cotton mills and respiratory symptoms were identified as significant factors for chronic functional losses.

The absence of personal sampling data may be a major limitation of the study. The absence of personal sampling data likely results in exposure misclassification. Moreover, although this study used information incorporating periodic measurements of airborne gram-negative bacterial endotoxin over the length of the study, air sampling was not taken throughout the entire periods of follow-up. It is possible that exposure measurements during our sampling periods do not accurately reflect actual exposure levels. However, a relationship between cumulative endotoxin exposure and longitudinal declines in pulmonary function was observed, which is suggestive of an exposure–response relationship and is in line with the current understanding of the mechanisms of cotton-related diseases. Because endotoxin is measured from dust samples, it is unlikely that exposure misclassification would differentially affect endotoxin more than dust concentrations. Therefore, the exposure data provide valuable information to estimate exposure–response relationship in cotton-related respiratory impairments.

In conclusion, based on the 15-yr follow-up study, accelerated chronic loss of pulmonary function in relation to airborne endotoxin exposure was observed. The chronic functional losses were significantly associated with across-shift drops of FEV_1 and byssinosis or chest tightness at work. Although reporting symptoms apparently varied from time to time, the consistency of respiratory symptoms may provide important information regarding permanent obstructive impairments in cotton workers. Further study is required to identify the factors that determine the consistent presence of cotton dust-related syndromes.

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