ORIGINAL ARTICLE

Respiratory symptoms and cotton dust exposure; results of a 15 year follow up observation

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Aims: To determine chronic effects of long term exposure to cotton dust and endotoxin on incidence of respiratory symptoms and the effect of cessation of exposure.

Methods: Respiratory health in 429 Chinese cotton textile workers (study group) and 449 silk textile workers (control group) was followed prospectively from 1981 to 1996. Byssinosis, chest tightness, and non-specific respiratory symptoms were assessed by means of identical standardised questionnaires at four time points. Exposures to cotton dust and endotoxin were estimated using area samples collected at each survey. Incidence and persistence of symptoms were examined in relation to cumulative exposure and exposure cessation using generalised estimating equations (GEE).

Results: Among cotton workers, the cumulative incidence of byssinosis and chest tightness was 24% and 23%, respectively, and was significantly more common in smokers than in non-smokers. A high proportion of symptoms was found to be intermittent, rather than persistent. Among silk workers, no typical byssinosis was identified; the incidence of chest tightness was 10%. Chronic bronchitis, cough, and dyspnoea were more common and persistent in the cotton group than in the silk group. Significantly lower odds ratios for symptoms were observed in cotton workers who left the cotton mills; risk was also related to years since last worked. Multivariate analysis indicated a trend for higher cumulative exposure to endotoxin in relation to a higher risk for byssinosis.

Conclusion: Chronic exposure to cotton dust is related to both work specific and non-specific respiratory symptoms. Byssinosis is more strongly associated with exposure to endotoxin than to dust. Cessation of exposure may improve the respiratory health of cotton textile workers; the improvement appears to increase with time since last exposure.

Numerous studies have investigated the respiratory health effects of exposure to cotton dust.[1–5] The most conspicuous effects of exposure are clinical symptoms of bronchoconstriction together with a decline in expiratory flow over the work-shift. Byssinosis, characterised by a feeling of chest tightness on the first day of the working week that improves as week progresses, has been used to describe the acute and reversible response to exposure to cotton dust. The disease, however, may progress to a stage in which symptoms are present throughout the work week, and may eventually result in severe pulmonary disability as exposure continues.[1 2]

Previous cross sectional studies have reported a wide range in the prevalence of byssinosis. Length of exposure, cumulative or average dust concentration, past levels of dust exposure, and the "mill effect" that may be caused by grade of cotton, or degree of contamination with Gram negative microorganisms, have all been identified as possible causes of the development of byssinosis.[3–8] Gender, age, and ethnic group seem not to be important factors,[9] although gender and ethnicity may be associated with job and length of exposure. In some studies, smoking was found to be an important risk factor for byssinosis, but this has not been established clearly. Exposure to cotton dust has also been reported to be associated with chronic bronchitis, cough, and dyspnoea, which are regarded as non-specific respiratory symptoms.[4 10 11]

A limited number of longitudinal studies have assessed the relation between long term exposure to cotton dust and chronic changes in pulmonary function.[12–15] Fewer data exist with regard to the longitudinal occurrence of respiratory symptoms among populations occupationally exposed to cotton dust. The current 15 year prospective follow up study was undertaken among a group of Chinese cotton textile workers to provide additional information on the long term respiratory effects of exposure to cotton dust. Significantly accelerated chronic loss of pulmonary function in relation to airborne endotoxin exposure level was identified in these cotton workers.[16] The present analysis concentrates on both work specific and non-specific respiratory symptoms observed during the 15 years. The aim is to examine the incidence of respiratory symptoms occurring in these workers, and to evaluate their associations with cotton dust and endotoxin exposure, as well as cessation of exposure.

SUBJECTS AND METHODS

Study population

The study was approved by the Institutional Review Boards of the Harvard School of Public Health and the First Hospital of the Shanghai Textile Bureau. The study subjects were recruited from workers in the yarn preparation areas (opening, cleaning, carding, drawing, combing, roving, and fine spinning) of two cotton textile mills. Both mills were state owned and located in the same urban area of Shanghai, China. The baseline survey was conducted in 1981. All workers who had worked in the mills for a minimum of two years, and had no history of respiratory disease before hire were eligible for recruitment into the study. The initial cohort included 447 workers (mean age 37 years, and 52% female), representing 90% of the eligible subjects. At the same time, 472 silk textile workers (58% female) who worked for a minimum of two years in a silk thread processing mill located in the same city as the cotton mills were selected as a control group. As described previously,[16] the demographic features of the two groups were similar at baseline, with the exception that the proportion of smokers was greater in the cotton group than in the silk group (36% *v* 25%).

The follow up surveys were carried out during the same seasons in 1986, 1992, and 1996. The follow up rates ranged from 83–88% in the 1986 and 1992 surveys, to 77% for the cotton group and 72% for the silk group at the last survey. There were 88% of cotton workers and 83% of silk workers who took part in three or more surveys. Forty one workers (18 in the cotton and 23 in the silk group) who participated in the baseline survey, but did not return for any of the following surveys, were excluded from the analysis.

Exposure assessment

Environmental sampling was done with vertical elutriators (General Metal Works, Inc., Cleveland, OH, USA) in the various work areas during each survey period, as no personal samplers were available for cotton dust measurements. Airborne cotton dust and Gram negative bacteria endotoxins were measured using methods described previously.[17] Identical samplers, sampler locations, equipment, and methods were used throughout the study. Endotoxin assays were performed on the dust samples using the Limulus amoebocyte lysate assay, chromogenic method.[18] Production and general conditions were stable in the cotton mills between the first and second surveys. Geometric mean dust exposure of the work areas ranged from a low of 0.5 mg/m^3 to a high of 1.6 mg/m^3 during that time. Between the second and third surveys, the mills began to blend synthetic fibre with cotton, and pure cotton yarn production slowed.[19] The mean dust exposure for the highest area was reduced to 1.1 mg/m^3 at the third survey and to 0.5 mg/m^3 at the last survey. Environmental exposure measurements were not strikingly different between the two cotton mills, and endotoxin levels were moderately correlated with cotton dust levels for all periods.[19] Personal exposures to dust and endotoxin were calculated using geometric mean levels of environmental samples from four times multiplied by each time period of work in specific work areas. Vertical elutriated dust and endotoxin concentrations in the silk mill were identified as nearly zero over the observation period.

Questionnaires

A modified American Thoracic Society standardised respiratory symptom questionnaire[20] was administered to each subject on his or her return to work after rest at the end of rotation at each survey. The questionnaire was translated into Chinese and back translated into English to verify accuracy. The collected information included a complete work history, respiratory symptoms, and smoking history. The outcomes of interest in this analysis included byssinosis, chest tightness, chronic bronchitis, chronic cough, and dyspnoea. The questions on byssinosis were collected only in active workers. The questions on other respiratory symptoms were asked regardless of workers' retirement status.

Potential confounders

Subjects were initially classified as either smokers or nonsmokers on the basis of baseline survey, but changes in smoking habit were recorded in all follow up surveys. All but 10 female workers were non-smokers in the initial cohort, and five started to smoke during the follow up time. Smoking at each survey period was measured in unit of pack-years. Information was also gathered on exposure to indoor pollutants including cooking fuel type (coal, gas, and electricity), pets at home, regularly passive smoking either at home or at work area, and family medical history, focusing on respiratory diseases in parents (asthma, bronchitis, emphysema, and lung cancer).

Definitions of respiratory symptoms

- 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 colleagues.[21]
- Chest tightness: tightness or constriction of the chest occurring any time during the work shift and on any workday, without being worse specifically on the first day of the working week.
- Chronic bronchitis: sputum production occurring on most ($\geqslant$5) days a week for a minimum of three months a year for at least two consecutive years.
- Chronic cough: cough without sputum occurring on most ($\geqslant$5) days a week for a minimum of three months a year for at least two consecutive years.
- Dyspnoea (2+): having to walk slower than a person of the same age at an ordinary pace on level ground because of breathlessness.

Statistical analysis

The emphasis of the data analysis was on estimating the associations between work specific and non-specific respiratory symptoms, and exposure to cotton dust, endotoxin, controlling for smoking. Respiratory outcomes were measured by:

(1) *Cumulative incidence*, defined as newly developed cases during the follow up time among those asymptomatic at baseline.

(2) *Persistence of symptoms*, defined as the number of positive responses and measured as: 0, no symptom at any of four survey points; 1, symptom reported once; 2, symptom reported twice; and 3, symptom reported three or four times. The calculation of persistence of reporting symptoms was restricted to 303 cotton and 291 silk workers who participated in all of the four surveys.

(3) *Intermittent symptoms*, defined as absent symptom after positively reported at previous survey.

We considered two alternative statistical methods for modelling exposure-response. If we treated symptoms as chronic, persistent health effects, then we should model the data using a Cox proportional hazards model to estimate the effect of cumulative exposure on incidence. Alternatively, if we treat the symptoms as intermittent symptoms, then a generalised estimating equations (GEE) approach would be more appropriate to examine the association between more recent exposure and the incidence of recurring acute symptoms. After examining the results of our analysis regarding the persistence/intermittent nature of the response, we decided that the observed patterns of symptoms supported the use of GEE over a Cox model approach.

After considering alternatives, GEE models were applied to estimate effects of levels of exposure to dust and endotoxin, and to determine effect of cessation of exposure (in terms of retirement from the industry) on respiratory symptoms, taking repeated measure design into account. In a GEE model framework, logit link function was used to model the mean of binomially distributed outcome variables along with an exchangeable correlation structure to model the correlations between repeated measures of the outcome over 15 years for each individual. Repeated measures of respiratory symptoms were outcome variables in all GEE models. Personal exposures to cotton dust and endotoxin were measured as cumulative lifetime exposures or exposures during periods between surveys. Exposure was treated either as a continuous variable or as category variables with four levels—lowest, low, middle, and high—according to quartiles of individual exposure data. Age, years worked, and smoking status treated as time dependent factors were included in the models along with gender. In addition, other potential effects were also considered, including amount of smoking, history of parents' respiratory diseases, and exposure to indoor pollutants at home. Cessation of exposure (Y/N), in terms of previous retirement status (on/off work), and years since last worked (years of ceasing exposure) at each time point were also included to examine the effect of these factors on the occurrence of chest tightness and non-specific respiratory symptoms. Data analysis was performed with SAS personal computer software (version 8.2) (SAS Institute, Cary, NC, 1999).

RESULTS

Table 1 presents the characteristics of both cotton and silk workers at the final survey. Average age in both groups was 51 years. Overall 36% in the cotton group and 31% in the silk group smoked. Four females in the cotton group and one in the silk group started smoking during the follow up period. The mean number of years worked was 25 years for the cotton and 29 years for the silk group. By the end of the follow up, 48% of cotton workers and 54% of silk workers had retired, mostly in the past five years.

The cumulative incidence of byssinosis was 24.2% and chest tightness was 22.5% in the cotton group (table 2). Nearly 8% of these workers reported both byssinosis and chest tightness at the same time during the follow up surveys. No typical symptoms of byssinosis were identified in silk workers, but the incidence of chest tightness was 10%. The incidences of chronic bronchitis and cough were slightly higher in the cotton group than in the silk group. The overlapping reports of non-specific symptoms (bronchitis, cough, and dyspnoea) at the same survey were higher in silk workers than in cotton workers (4–5% *v* 1–2%).

Among those who reported symptoms, more than a half reported byssinosis and other symptoms only once out of four surveys (table 2). However, more persistent respiratory symptoms were seen in cotton workers than in silk workers. Ten per cent and 7% of cotton workers reported byssinosis and chest tightness twice, respectively; 5–7% reported chronic bronchitis, cough, and dyspnoea in three or four surveys, while far fewer silk workers reported symptoms multiple times. The differences in persistent trends between the two groups were highly statistically significant. In cotton workers, 51% of byssinotics (53 of 104) was classified as "intermittent", and 49% as non-intermittent, but the latter included 27 workers (26%) who reported byssinosis only at the last survey. Other symptoms also showed high intermittent proportions, which tended to be even higher in silk workers than in cotton workers.

When stratified by gender and smoking status, the incidence of byssinosis was significantly higher in smokers among male cotton workers (table 3). Smokers also had higher incidences of chest tightness and other symptoms. Among male silk workers, smokers had a higher incidence of chronic bronchitis. In the lifelong non-smoking females, all symptoms were more common in cotton workers than in silk workers, with a significant difference for byssinosis and chest tightness.

In order to examine whether participation was related to the respiratory outcomes, GEE models were fit to examine the relation between symptoms and likelihood of participating in the next survey. Four measures of each respiratory symptom and participation status at three follow up surveys were included, along with age, years worked, and smoking habit. Retired status was also considered in the model for byssinosis, as it might interact with participating status on byssinosis. A higher odds ratio for periodically reported byssinosis was found in non-participating cotton workers, independent of retirement status (table 4), indicating that cotton workers reporting byssinosis were less likely to participate in the next survey. For the other symptoms, the non-participating cotton workers were less likely to have been symptomatic at the previous survey, but the difference was not significant. Similarly, non-participating silk workers were much less likely to have been symptomatic than participating silk workers, and the differences were statistically significant. Thus, byssinosis in these cotton workers was underestimated, and other symptoms were overestimated in both cotton and silk workers, but significantly so in silk workers. This may explain partly the apparent similarity in non-specific symptoms between exposed and non-exposed workers.

In the exposure-response analysis among cotton workers, dust or endotoxin exposure levels were first included as continuous and time dependent variables (measured in each period). No statistically significant contribution to the model was observed for either dust or endotoxin exposure. When quartiles were defined for cumulative exposures, an exposure-response trend was detected for byssinosis only (table 5). The results showed that risk for byssinosis was greater at

Table 1 Demographic features* of cotton and silk textile workers at last survey

	Cotton		Silk	
	n (%)	Mean (SD)	n (%)	Mean (SD)
Age (years)				
<40	74 (21.4)		70 (20.7)	
40–49	115 (33.2)		118 (34.9)	
50–59	63 (18.2)		57 (16.9)	
⩾60	94 (27.2)		93 (27.5)	
Gender, males	160 (46.2)		199 (41.1)	
Ever smokers	123 (35.5)		106 (31.4)	
Retired	165 (47.7)		183 (54.1)	
Years since last worked†		6.1 (4.1)		4.2 (3.9)
Smoking amount (pack-years)		15.8 (12.9)		14.4 (12.4)
Years working		24.8 (7.8)		28.5 (9.6)
Cumulative dust exposure, (mg/m^3.years)		17.0 (10.6)		–
Cumulative endotoxin exposure (Eu/m^3.years)		55315.4 (47405.2)		–

*Calculated based on 346 cotton and 338 silk workers who participated in last survey.
†Calculated among those retirees by last survey.

Table 2 Comparison of respiratory symptoms (%) between cotton and silk textile workers

		Persistence of report†			
	Cumulative incidence*	**Once**	**Twice**	**3 or 4 times**	**Intermittent symptom‡**
Byssinosis					
Cotton	24.2 (20.0 to 28.7)	23.1 (18.4 to 27.9)	9.9 (6.5 to 13.3)	1.3 (0.3 to 2.6)	51.0 (41.0 to 60.9)
Silk	0.0	0.0	0.0	0.0	0.0
p value	<0.0001			<0.0001	–
Chest tightness					
Cotton	22.5 (18.5 to 26.9)	20.8 (16.2 to 25.4)	7.3 (4.3 to 10.2)	1.3 (0.3 to 2.6)	83.1 (72.9 to 93.9)
Silk	9.9 (7.3 to 13.1)	8.9 (5.7 to 12.2)	1.7 (2.3 to 3.2)	0.0	83.9 (72.1 to 93.7)
p value	<0.0001			<0.0001	0.99
Chronic bronchitis					
Cotton	9.1 (6.5 to 12.2)	14.2 (10.3 to 18.1)	5.9 (3.3 to 8.6)	5.9 (3.8 to 8.6)	69.6 (58.3 to 79.5)
Silk	7.1 (4.6 to 10.4)	10.7 (7.1 to 14.2)	3.1 (1.1 to 5.1)	1.7 (0.2 to 3.2)	82.2 (67.9 to 92.0)
p value	0.32			<0.01	0.07
Chronic cough					
Cotton	9.0 (6.5 to 12.2)	14.5 (10.6 to 18.5)	5.0 (2.5 to 7.4)	5.3 (2.8 to 7.8)	74.7 (63.3 to 84.0)
Silk	6.6 (4.3 to 9.8)	9.3 (5.9 to 12.6)	4.5 (2.1 to 6.8)	1.7 (0.2 to 3.2)	86.7 (73.2 to 95.0)
p value	0.22			<0.01	0.20
Dyspnoea (+2)					
Cotton	27.7 (23.1 to 32.6)	24.1 (19.3 to 28.9)	9.2 (6.0 to 12.5)	7.3 (4.3 to 10.2)	67.5 (58.5 to 75.7)
Silk	26.4 (22.3 to 30.8)	23.4 (18.5 to 28.2)	5.8 (3.2 to 8.5)	1.4 (0.4 to 2.7)	71.9 (61.4 to 80.9)
p value	0.68			<0.001	0.08

*Among those who were asymptomatic for each particular symptom at baseline.
†Among cotton and silk workers participating in all four surveys.
‡Among those who participated in all four surveys and reported a particular symptom one or more times.
95% confidence limits shown in parentheses.

higher levels of exposure to endotoxin in the whole group and stratified gender groups. The odds ratio in the highest quartile of endotoxin was statistically significant. An exposure-response trend for dust was less clear, suggesting that the occurrence of byssinosis is more closely related to exposure to endotoxin. Among other considered covariates, age and smoking were significantly associated with byssinosis. In addition, male cotton workers were found to be at a higher risk for byssinosis than females.

We also attempted to answer the question of whether cessation of exposure is related to improved respiratory health. Chest tightness and non-specific symptoms were significantly lower in both retired cotton and silk workers (table 6), after adjusting for age, years worked, and smoking status, suggesting a beneficial effect of retirement from the mills. Moreover, the variable of years since last worked was significantly related to symptoms among cotton workers: the more years since retiring, the more likely to be asymptomatic. For example, the odds ratios for any of the four symptoms were 0.9 after one year, 0.7 after two years, and 0.5 after five years since last worked. The results remained the same when exposure levels of endotoxin or dust were included in the GEE models. The association with the years after retirement, however, was not observed in silk workers.

DISCUSSION

Byssinosis was recognised and described in detail a half century ago, but the chronic effects of long term exposure on workers' health have not been elucidated clearly. The current study, based on a 15 year follow up observation and a stable occupational group, allowed us to investigate chronic respiratory effects. The results show that long term exposure to cotton dust is associated with the occurrence of byssinosis and chest tightness. Furthermore, the results suggested that workers exposed to cotton dust are more likely to develop non-specific respiratory symptoms, such as chronic bronchitis, chronic cough, and dyspnoea.

Few studies have estimated the incidence of byssinosis; most studies reported only prevalence. The prevalence of byssinosis varies widely in the literature on cotton textile workers, from 1.7%[22] to 47%.[23] This inconsistency in the results can be explained, in part, by great differences in environmental dust levels, grade of cotton being used, and degree of contamination with Gram negative microorganisms, referred to as the "mill effect".[8] In addition, selection bias or healthy worker effect may operate more strongly in some studies. Another potential reason for varying estimates is different criteria for diagnosing byssinosis used in different countries and across studies, as there is no universally

Table 3 Cumulative incidence of respiratory symptoms (%) by gender and smoking status† over 15 years

	Men				Women (non-SM)‡	
	Cotton		Silk			
	Ever-SM	**Non-SM**	**Ever-SM**	**Non-SM**	**Cotton**	**Silk**
Byssinosis	31.4 (23.1 to 40.5)**	11.7 (5.5 to 21.0)	0.0	0.0	25.1 (19.2 to 31.9)**	0.0
Chest tightness	23.1 (15.8 to 31.8)	18.2 (10.3 to 28.6)	5.7 (2.1 to 11.9)	8.3 (3.4 to 16.4)	24.6 (18.7 to 31.4)*	12.6 (8.5 to 16.9)
Chronic bronchitis	9.4 (3.5 to 16.6)	6.5 (2.8 to 15.9)	8.9 (5.6 to 12.4)	5.7 (4.2 to 15.2)	7.0 (3.8 to 11.7)	4.6 (2.3 to 8.1)
Chronic cough	9.0 (3.3 to 15.7)	5.5 (2.4 to 12.3)	7.6 (5.2 to 15.6)	9.2 (5.9 to 18.5)	5.5 (2.6 to 9.8)	5.3 (2.9 to 8.9)
Dyspnoea	26.2 (18.2 to 35.6)	17.1(9.2 to 28.0)	26.9 (18.7 to 36.4)	28.4 (18.9 to 39.5)	31.1 (24.3 to 38.5)	25.6 (20.3 to 31.5)

†The analysis was performed among those who were asymptomatic at baseline.
‡Fourteen smokers in cotton and one in silk groups were excluded from this analysis.
Ever-SM, ever smokers; Non-SM, non-smokers.
**p<0.001; *p<0.01 in comparison with smokers and non-smokers in the corresponding group among men, and cotton and silk workers among women (non-smokers).
95% confidence limits shown in parentheses.

Table 4 Odds ratios* for symptoms in relation to non-participation in follow up surveys for cotton and silk workers over 15 years

	Cotton	Silk
Byssinosis	1.6 (0.91 to 2.71)	–
Chest tightness	0.6 (0.41 to 1.02)	0.6 (0.32 to 1.20)
Chronic bronchitis	0.8 (0.46 to 1.25)	*0.4* (0.25 to 0.73)
Chronic cough	0.8 (0.49 to 1.41)	*0.5* (0.27 to 0.82)
Dyspnoea	0.8 (0.53 to 1.29)	*0.6* (0.38 to 0.90)
Any symptom†	0.7 (0.51 to 1.09)	*0.5* (0.37 to 0.77)

*The GEE analysis was modelled using all available data of 429 cotton and 449 silk workers over 15 years, with adjustment for age, years worked, and smoking habit.
†Positive report for any symptoms including chest tightness, bronchitis, cough, and dyspnoea.
Statistically significant odds ratios italicised. 95% confidence limits shown in parentheses.

acceptable diagnostic criterion for byssinosis. In this study, we applied a more commonly used criterion—that is, typical first day or "Monday" symptoms to define byssinotics.[21]

We observed that the cumulative incidence over the 15 years was 24% for byssinosis and 23% for chest tightness. In other words, as many as 40% of the cotton workers experienced work specific disorders during this period, taking 8% overlap of the two symptoms into account. The true incidence of byssinosis in these workers might actually be higher since the analysis showed that continued participation depended on the absence of byssinosis. Also we found that 11% and 9% of cotton workers reported byssinosis and chest tightness, respectively, in two or more surveys among those who took part in all of the four surveys, whereas 2% of silk workers reported chest tightness twice. Among those who missed at least one of the follow up surveys, 15% of cotton workers reported byssinosis once and 4% twice; 20% reported chest tightness once and 4% twice. These proportions were also significantly higher in comparison with silk workers in whom 8% of the non-participants reported chest tightness once.

Chronic bronchitis has been found to occur more commonly in coal miners,[24] foundry workers,[25] and steelworkers.[26] Some studies also reported an excess of chronic bronchitis or chronic cough in workers exposed to cotton dust.[4 10 11 27] In this study, we did not observe a significantly higher cumulative incidence of chronic bronchitis, cough, and dyspnoea in cotton workers than in silk workers. Although these symptoms were significantly more prevalent in cotton workers at baseline,[11] there was no apparent difference in cumulative incidences between the two groups. This result might be due to an overestimation of non-specific respiratory symptoms in the silk workers, which in turn might be due to two sources: a significant difference in the symptoms between participating and non-participating silk workers, and more overlap among non-specific symptoms reported by the silk workers. As shown in the data analysis (table 5), previously reported symptoms were significantly higher in the participating silk workers than in the non-participants in the follow up surveys. This may be due to the fact that the silk workers who had been symptomatic were more concerned with their own health status and were more likely to participate in the next medical examination. Furthermore, the higher overlap of bronchitis, cough, and dyspnoea in the same surveys reported by the silk workers (4–5%) than by the cotton workers (1–2%) might have resulted in an overestimated cumulative incidence of symptoms among the silk workers.

A few studies have investigated the persistence of respiratory symptoms in cotton workers, and reported that the symptoms varied substantially from survey to survey.[28–30] In this study, 10% of cotton workers reported byssinosis twice, and only 1% reported it three or more times, in contrast to 23% that reported it once. A similar trend was seen for other symptoms. The results suggest that byssinosis and other symptoms were reversible in most cases, while chronic symptoms persevered. This notion was also supported by the high proportions of intermittent symptoms shown in both cotton and silk groups. However, compared with the silk workers, the cotton workers had more persistent symptoms. There has been evidence showing that persistent reporting of respiratory symptoms is related to excess chronic functional loss.[16 17] These results further indicate the chronic effects of exposure to cotton dust.

Risk factors for the occurrence of byssinosis and other respiratory symptoms in cotton workers have not been identified clearly. Specifically, the relation between exposure levels and respiratory outcomes has been a controversial

Table 5 Adjusted odds ratios* for byssinosis in relation to cumulative exposure levels† in cotton textile workers

	Exposure to endotoxin	Exposure to dust
Whole group (n = 429)		
Lowest	1.0	1.0
Low	0.6 (0.29 to 1.32)	1.6 (0.70 to 3.46)
Middle	1.4 (0.54 to 3.35)	1.0 (0.44 to 2.15)
High	*1.9* (1.02 to 3.51)	*1.8* (1.03 to 3.32)
Male (n = 203)		
Lowest	1.0	1.0
Low	0.5 (0.17 to 1.62)	2.5 (0.86 to 7.32)
Middle	2.5 (0.50 to 4.05)	0.8 (0.26 to 2.59)
High	1.9 (0.86 to 3.96)	*2.4* (1.13 to 5.10)
Female (n = 226)		
Lowest	1.0	1.0
Low	0.6 (0.18 to 1.95)	0.6 (0.17 to 1.84)
Middle	1.0 (0.25 to 3.71)	0.6 (0.20 to 1.97)
High	1.7 (0.48 to 5.64)	1.0 (0.37 to 2.66)

*The odds ratios were adjusted by age, years worked, smoking status, and gender (for whole group) in GEE models.
†Endotoxin exposure levels (Eu/m^3.years): lowest, <20616; low, 20616–48129; middle, 48129–80398; high, >80398. Dust exposure levels (mg/m^3.years): lowest, <9; low, 9–<14; middle, 14–<21; high, >21. The lowest levels of cumulative exposure were as reference.
Statistically significant odds ratios are italicised.

Table 6 Odds ratios* for respiratory symptoms associated with previous retirement from mills in cotton and silk workers over 15 years

	Chest tightness	Chronic bronchitis	Chronic cough	Dyspnoea (+2)	Any symptom†
Cotton workers (n = 429)					
Retirement from mills	*0.3* (0.11 to 0.97)	*0.3* (0.09 to 0.90)	*0.3* (0.11 to 0.89)	*0.2* (0.09 to 0.55)	*0.2* (0.11 to 0.48)
Years since last worked	*0.9* (0.86 to 0.98)	*0.8* (0.77 to 0.92)	*0.9* (0.81 to 0.96)	*0.9* (0.82 to 0.94)	*0.9* (0.80 to 0.92)
Silk workers (n = 449)					
Retirement from mills	*0.3* (0.10 to 0.86)	*0.1* (0.05 to 0.45)	*0.3* (0.09 to 0.78)	0.5 (0.24 to 1.01)	*0.4* (0.18 to 0.65)
Years since last worked	1.0 (0.92 to 1.15)	1.0 (0.86 to 1.04)	1.0 (0.86 to 1.06)	1.0 (0.91 to 1.03)	1.0 (0.91 to 1.01)

*The GEE analysis was performed using all available data of 429 cotton and 449 silk workers over 15 years, with adjustment for age, gender, years worked, and smoking status. Statistically significant odds ratios are italicised.
†Positive report for any of the symptoms including chest tightness, chronic bronchitis, cough, and dyspnoea.

issue. Several studies suggested an exposure-response relation,[3–5] whereas others reported weak or absent relations between respiratory symptoms, or pulmonary function, and average dust concentration, cumulative exposure, or length of exposure.[6 12 31] Nevertheless, growing evidence has indicated that cotton dust *itself* is not a causative agent, and endotoxin considered as bioactive agent is a possible cause of byssinosis. Endotoxin is known to cause a variety of pulmonary responses, such as alveolar-macrophage activation, neutrophil chemotaxis, complement activation, and mast cell release of histamine.[32–34] Also, epidemiological studies have suggested Gram negative bacteria or associated endotoxins as a possible cause of respiratory symptoms and pulmonary function abnormalities among cotton workers[35–37] and agricultural workers.[38] Moreover, dose-response relations between endotoxin levels and the presence of symptoms of byssinosis and decreased pulmonary function were suggested by several human experimental studies.[39 40] Our data showed that quartile levels of cumulative exposure to endotoxin predicted byssinosis better than dust levels, suggesting the relative importance of endotoxin in the occurrence of byssinosis. However, the current data were unable to show a definitely quantitative exposure-response when using continuous cumulative exposure or periodic exposure variables. A definite exposure-response relation was not shown in other respiratory symptoms either. Despite the considerable effort made to develop quantitative exposure estimates for cotton dust and endotoxin for individual workers in this study, it is likely that the exposure estimates did not reflect correctly actual biological potency of endotoxin or dust due to a lack of personal samples. An alternative explanation is that there may be some other interactive factors or biological mechanisms involved that modify the dose-response relation in cotton related disease.

Cessation of exposure (that is, retirement from the industry) was found to have a significant protective effect on respiratory health, independent of age, years worked, and smoking habit. This result implies reversibility of cotton related symptoms after the exposure ceases. Interestingly, a similar result was also observed in the silk workers, suggesting that the working environment in the silk mill may be responsible for workers' respiratory symptoms. However, unlike the cotton workers, symptoms were not related to years since last work, implying that respiratory symptoms might disappear once they stopped working in the mills. In cotton workers, removal from exposure predicted respiratory symptoms; subjects were less likely to be symptomatic with increasing years after retirement. The odds ratio for being symptomatic was 0.9, if the workers were removed from exposure for one year, and it was 0.5 after five years. These results, in turn, further indicate the biologically potent effects of exposure to cotton dust for non-specific respiratory symptoms, as well as for byssinotic symptoms.

The role of smoking in the development of byssinosis has not been established definitely. The difference between smokers and non-smokers was observed in some studies, but not in others.[9 41] Bouhuys and colleagues[42] and Fox and colleagues[30] reported in their early work that byssinosis was significantly more prevalent in current smokers than non-smokers, even when varying dust exposures were taken into consideration. Berry and colleagues[4 12] also found that smoking influenced byssinosis prevalence and suggested an additive effect between smoking and cotton dust exposure. Similar to these studies, our findings showed a significant difference between smokers and non-smokers in the incidence of byssinosis. Incidences of other symptoms were also higher in smoking cotton workers. However, the differences in the symptoms other than chronic bronchitis could not be detectable between smoking and non-smoking silk workers. One explanation for the lack of a smoking effect in silk workers may be due to the difference in age: smokers were significantly younger than non-smokers: 53.5 versus 60.1 years ($p<0.01$) for the male silk workers according to the last survey data. This was also the case for the cotton workers (52.1 years for smokers and 59.2 years for non-smokers; $p<0.01$). In spite of the similar gap in age, a more pronounced smoking effect was seen in the cotton workers, indicating a synergistic effect between smoking and exposure to cotton dust. On the other hand, higher incidences of either work specific or non-specific symptoms were shown in the female cotton workers when compared with their silk counterparts, who were all lifelong non-smokers. The result further indicates a potent effect of dust on cotton workers' respiratory health.

There is no convincing evidence that gender is a risk factor for byssinosis. It was reported previously that byssinosis was more common in males,[4] but this was believed to be due to the fact that male operatives tended to work in the more heavily exposed dust occupations. A similar explanation is applicable to our finding showing that males were more likely to be at risk for byssinosis than females. Compared to the females, the male workers were found to have a significantly higher cumulative exposure levels for either endotoxin or dust (42 964 *v* 67 950 Eu/m^3.years, and 13 *v* 21 mg/m^3.years, respectively; $p<0.05$). In addition, the male workers, on average, were four years older than the females, while age was indicated to be one of the risk factors for byssinosis. Hence, gender per se cannot be considered a significant risk factor for byssinosis based on the current data.

In conclusion, this study shows chronic respiratory effects of long term exposure to cotton dust, reflected not only by byssinotic symptoms but also by non-specific respiratory symptoms. Endotoxin, rather than dust *itself*, is a more important determinant for byssinosis, which can be accentuated by cigarette smoking. The results also indicate that respiratory symptoms related to cotton dust exposure may be reversible after removal from exposure, with decreasing risk with increasing year since exposure cessation.

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