Respiratory effects of long-term exposure to cotton dust

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Traditionally, the concept of cotton dust-related disease focused on acute airway responses. A possible connection of long-term exposure to cotton dust with chronic obstructive airway disease was not addressed until the past two decades. This review summarizes the latest findings relevant to this topic that were observed from longitudinal cohort studies and discusses the relation between acute airway responses and chronic losses of lung function. Curr Opin Pulm Med 2003, 9:151–155

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Abbreviations

FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
LPS	lipoplysaccharide

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The relation between obstructive airway disease and exposure to cotton and other vegetable dusts has been an interesting topic in occupational health for several reasons: first, there is a large number of exposed working population in the world, particularly in developing countries; second, cotton dust is a good representative of vegetable dusts, exposure to which result in similar clinical manifestations, and probably share a common mechanism of disease development. Therefore, the research findings in linkage of cotton dust exposure to airway disease could be generalized to those induced by other kinds of vegetable dusts.

Historically, the concept of cotton dust-related disease focused on acute airway responses, expressed as Monday "mill" fever, chest tightness, cross-shift drops in forced expiratory volume in 1 second (FEV_1) and airway hyresponsiveness. These acute airway responses may even be observed in short-term exposed healthy volunteers in model cardrooms, while attacks of typical byssinosis syndrome usually begin to appear only after several years of exposure. Byssinosis, defined as an acute airway response, is characterized as chest tightness and shortness of breath, most typically pronounced on the first day of the workweek (Monday accentuation) and may progress to include other days in the advanced stages.

The precise etiology of airway disease caused by cotton dust and other organic dusts remains to be determined. However, increasing evidence indicates that cotton dust *per se* is not the causal factor, but dust contaminated with endotoxin is most likely the causative agent of byssinosis. Endotoxin is a component of the outer membrane of gram-negative bacteria, know as lipoplysaccharide (LPS) in its pure form. The lipid portion of LPS, lipid A, containing six fatty acids are important for the full bioactivity of LPS [1]. Liberation of endotoxin has been demonstrated from various genera of viable gram-negative bacteria *in vitro* and *in vivo* [2]. Endotoxin has now been found in large number of environments where organic dusts are present. A recent article described existing evidence showing important relations between exposure to endotoxin and disease [3]. Studies of experimental models *in vivo* showed rapid invasion of neutrophils in the lung and airways after LPS inhalation, taking place within hours of exposure. It is also indicated that the initiation of neutrophil migration requires only a very small amount of LPS, while high concentrations of LPS are required for the effects *in vitro* with isolated incubated cells. In humans, the number of polymorpho-

nuclear cells increases a few hours after acute inhalation exposure. Defense cells, particularly macrophages but also epithelial cells and dendritic cells, trigger inflammation, a major response to LPS. The production of inflammatory cytokines initiates reactions in the lung and in the body as a whole. A clinical outcome of inhaled endotoxin includes generalized symptoms, such as respiratory distress and fever, increased airway responsiveness, asthma-like symptoms, and decreased lung function and, in severe cases, shock and even death.

For many decades, research on adverse effects of exposure to cotton dust was largely restricted to acute respiratory responses and the prevalence of respiratory symptoms. The issue of whether long-term exposure to cotton dust leads to chronic airway disease was not investigated thoroughly, mainly because of the absence of longitudinally collected data. It is biologically plausible that long-term and repeated exposure to cotton dust may lead to chronic respiratory disease, but definitive evidence has been lacking. To obtain convincing evidence for the development and natural history of chronic diseases related to occupational exposures, more methodological requirements, including a prospective cohort design with long enough follow-up time, a large and stable study population for sufficient study power, and strict quality control of data gathered throughout the study are needed. More often than not, these methodological requirements are not easy to be reached simultaneously for one reason or another. Several longitudinal cohort studies have provided additional understanding of the relation between occupational exposure to cotton dust and obstructive airways disease. Recent efforts have been made to explore time course of disease onset. This article reviews relevant papers published during 2002 and introduces current findings. It was noted that the number of available papers focusing on addressing this topic was few during this time.

Studies in Chinese cotton textile workers

A 15-year longitudinal cohort study by Christiani *et al.* [4••] observing a group of Chinese textile workers directly addresses this review's topic. The original cohort consisting of cotton and silk workers (a control group) was established in 1981. Three follow-up surveys were conducted thereafter with intervals of 4 to 5 years. More than half of the subjects in both groups were women, of whom almost all were nonsmokers, making it possible to observe relatively pure effects of occupational exposure. The initial criteria for including study subjects were those who had worked in the yarn preparation areas for a minimum of 2 years and without obvious respiratory diseases/symptoms. The highest geometric mean dust exposure of the work area varied with time, as a result of blending synthetic fiber with cotton, decreasing from 1.6 mg/m^3 at the first period to 0.5 mg/m^3 at the last period.

The strengths of this study include long-term observation, stable study population and low attritions of cohort, and the attention to quality control. Additionally, a special effort was made to collect environmental exposure data of cotton dust and endotoxin at each time period. This study provides additional information linking long-term exposure to cotton dust with adverse respiratory health outcomes in cotton textile workers.

Long-term exposure and chronic changes in lung function

The outcome measurements used to describe chronic effects included annual declines in FEV_1 and forced vital capacity (FVC). For each worker, cumulative dust and endotoxin were calculated on job history and periodic dust and endotoxin exposure. Of the 447 textile workers originally registered in the cohort, 392 (88%) provided three or more spirometric tests over the 15 years. In the control group, 394 of 472 (84%) did so. The annual declines in FEV_1 and FVC adjusted by age, height, sex, and smoking are shown in Table 1. Cotton workers were found to lose FEV_1 at a rate of 32 mL/y and FVC of 20 mL/y, which were slightly, but significantly greater than that observed in silk workers. The excessive loss of lung function was seen in both male and female cotton workers. In addition, smokers showed to have a greater annual loss in FEV_1 than nonsmokers among cotton workers, while this was not observed in silk workers.

Table 1. Annual changes in pulmonary function in cotton and silk textile workers

	FEV_1, mL/y		FVC, mL/y	
	Cotton	Silk	Cotton	Silk
Total	−32.3 (1.0)	−29.4 (1.0)*	−20.1 (1.2)	−15.3 (1.3)†
Men	−42.2 (1.8)	−38.0 (1.9)	−27.8 (2.1)	−23.6 (2.3)
Women	−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)

Values were adjusted by age at mid-point during follow-up period and heights at final survey (sex and smoking status were also adjusted in calculation of "Total"). Numbers in parenthesis indicate SE. *$P < 0.05$. †$P < 0.01$. ‡Calculated from male smokers at the final survey.

It is worthy to note that this analysis was conducted including active and retired cotton workers. Over 50% of the workers retired from the industry by the end of observation, and they were followed up, along with the active workers. Retired workers were included in the study to avoid potential bias resulting from health worker effects. Additionally, keeping retired workers in the cohort was useful to assess whether permanent cessation of exposure may lead to relieved airway obstruction and improved lung function in cotton textile workers. Unlike pneumoconioses that are caused by mineral dusts, such as silica and asbestos, vegetable-related airway diseases are not necessarily progressive after exposures cease. It becomes known that byssinosis is reversible in the early stage, and there has not been convincing evidence showing that chronic airway response to cotton dust is irreversible. If it is true that chronic airway obstruction is reversible or partially reversible, the annual declines in lung function in long-term exposed workers are likely to be underestimated when including the retired workers in the analysis. This supposition needs to be confirmed with additional analyses.

The study evaluated associations of chronic losses of lung function and cumulative dust and endotoxin exposure by multivariate analysis, using dichotomous variables (low or high level) of exposure. Although statistical significance was reached with exposure to endotoxin, the association was not strong enough to show a significant association with continuous variables, *ie*, a clear exposure-response relationship. Yet, the finding provides an etiologic clue, supporting evidence that the level of exposure to endotoxin plays a more important role than dust in producing chronic excess losses of lung function in cotton textile workers.

Long-term exposure and respiratory symptoms

The 15-year study described cotton dust-related respiratory symptoms: byssinosis, defined as chest tightness or shortness of breath at work occurring in the first or other days of the work week, and chest tightness at work which might occur anytime during the work shift and on any workday. Cotton workers were found consistently to report more respiratory symptoms at each follow-up survey than they did at baseline survey. The cumulative incidence of byssinosis and chest tightness was 24% and 23%, respectively, and was significantly more common in smokers than in nonsmokers. In silk workers, no byssinosis was observed, and the incidence of chest tightness was 10%. Furthermore, the prevalence of byssinosis in cotton workers tended to increase over time, with 19% at the third and 15% at the fourth survey verses 8% at baseline and 3% at the second survey. The increase in byssinosis over time cannot be explained by increase of cotton dust or endotoxin concentrations. On the contrary, measured concentrations of cotton dust and endotoxin were decreasing over time. This finding suggests that increased byssinosis is a function of length of exposure or work tenures, that is to say, long-term exposed workers are more likely to experience byssinosis than short-term exposed ones. This is supported by another recent study [5] that followed newly hired textile workers for 18 months and found no byssinosis and chest tightness.

The 15-year study also examined persistence of reported respiratory symptoms and its significance to the chronic changes in lung function. Cotton workers more persistently reported either specific or nonspecific symptoms than silk workers, and the differences were statistically significant. Twenty percent of cotton workers reported byssinosis once, and 8% reported it twice; 23% reported chest tightness at work once, and 9% reported it twice. There were fewer workers reporting the symptoms three or more times. Among the men, significantly more persistent specific and nonspecific symptoms were observed in smoking than nonsmoking cotton workers, but their difference was not seen in silk workers, indicating a synergetic effect between cotton dust exposure and smoking. Additionally, female cotton workers showed significantly more persistence of specific and nonspecific symptoms than did silk workers, though they all were lifelong nonsmokers. This suggests that exposure to cotton dust is a potent factor in producing airway disease. Subjects who were lost to follow up possibly resulted in an underestimation of persistent symptoms, but the respiratory symptoms varied greatly from survey to survey, indicating that these symptoms were reversible in most of the cases, even in the long-term exposed workers. Nonetheless, there remained a small proportion of workers whose symptoms persisted. It is unknown which factors determine reversibility or irreversibility of the symptoms. It is assumed that cessation of exposure might be one of the favorable factors for reversibility of symptoms, based on the fact that half of the workers retired from the industry over the observation time.

The results of analysis of relating persistent symptoms to longitudinal changes in lung function are shown in Table 2. Those who reported persistently respiratory symptoms had significantly greater losses of FEV_1 in comparison with those who never had symptoms. It is not surprising that chronic bronchitis or chronic cough may result in or aggravate chronic airway obstruction. A more interesting point is that the study revealed a significant connection of repeated attacks of byssinosis with excessive lung function loss, which had not been documented clearly to date.

Relationship of acute airway response to chronic losses of lung function

Since chronic respiratory effects of cotton dust exposure were suggested by those studies, the possible link of the acute airway responses to cotton dust and the develop-

Table 2. 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

*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. GEE, generalized estimating equation; NS, not significant ($P > 0.05$).

ment of chronic airway obstruction was questioned and examined. The 15-year cohort study suggested a strong relation by the multivariate analysis using repeated measurements (Table 3), showing that cross-shift drops in FEV_1 was highly significantly related to longitudinal losses in FEV_1 and FVC after adjustment for appropriate confounders and covariates. Furthermore, byssinosis was found to be associated with a significantly greater loss of FEV_1. Although "chronic byssinosis," expressed as persistent presence of byssinosis, existed in a small proportion of the workers, most of the byssinosis cases were regarded as being acute or reversible. It appeared that chronic losses of lung function were related not only to cross-shift drops in FEV_1 but also to acute byssinostic symptoms.

Are the acute airways responses and chronic changes in lung function each related to the exposure independently, or are they causally related; is the first a causal factor for the second? It is possible that both mechanisms are involved in the development of chronic changes in lung function. However, current findings showing a strong relation of chronic lung function change to acute airway responses and a weak relation to cumulative exposure levels imply that the recurrent acute airway changes may play a more important part. Acute inflam-

Table 3. Independent determinants of longitudinal changes in pulmonary function among cotton textile workers*

	FEV_1, L		FVC, L	
	Estimate (SE)	*P* value	Estimate (SE)	*P* value
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, y	−0.044 (0.014)	< 0.001	−0.014 (0.012)	< 0.05
Years worked, y	−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	–	–

*Covariates considered in the GEE models include height, age, years worked, smoking status, and across-shift change in FEV_1 (ΔFEV_1) over 15 years 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.

matory airways reactions, as a response to cotton dust exposure, developing and being sustained by continued exposure, may be a common pathway leading to chronic inflammatory process and chronic airway obstruction. This hypothesis was also supported by the studies of newly hired textile workers [5,6].

The newly hired textile worker study, aimed at observing the natural history of cotton dust-related disease at the early stage, followed a group of new workers, who were previously unexposed and healthy, at 3, 12, and 18 months after the exposure began. At 3 months, 21 of 194 (11%) workers were found to have over 5% of cross-shift drop in FEV_1, and 20 (10%) workers reported reversible respiratory symptoms. Longitudinal changes in FEV_1 and FVC were not detectable until 12 months. Interestingly, the analysis revealed that respiratory symptoms reported earlier were not only associated with cross-shift drops in FEV_1, but also related to greater longitudinal changes in FEV_1. Although the study focuses on the natural history of the cotton dust-related disease at the earliest stage, it provides some evidence that acute airway responses, such as reversible respiratory symptoms, may be a risk factor for subsequent development of chronic conditions in long-term exposed workers. For that reason, it makes sense to consider the acute airway responses to cotton dust exposure as a step in the pathway for chronic changes in lung function. If this notion is confirmed, cross-shift drops in FEV_1 and/or byssinostic symptoms could be used to monitor exposed populations and evaluate environmental controls.

In conclusion, recent findings derived from cohort studies have provided evidence that workers who were exposed to cotton dust long-term may develop chronic airway obstruction. The mechanism(s) of the chronic airway disease remain unclear. To date, there is no strong evidence of a direct exposure-response relation between chronic airway obstruction and cumulative dust or endotoxin exposure levels. Given the strong evidence showing a close connection of longitudinal changes in lung function with acute airway responses, recurrent acute airway responses may be a major contributor to chronic airway obstruction. Additional data are warranted to verify this hypothesis, including special efforts to explore an exposure-response relation with endotoxin, as well as further efforts to observe a time course of cotton dust-related airway disease.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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