A longitudinal observation of early pulmonary responses to cotton dust

X-R Wang, L-D Pan, H-X Zhang, B-X Sun, H-L Dai, D C Christiani

Aims: To examine early adverse pulmonary effects of exposure to cotton dust, and to identify potential risk factors, including atopy for pulmonary responses to cotton dust.

Methods: Spirometry, methacholine challenge testing, and questionnaire; performed among 101 non-smoking newly hired textile workers at baseline (prior to starting work), and at 3, 12, and 18 months after starting work. Concentrations of airborne cotton dust in various work areas were measured at each follow up survey using vertical elutriators.

Results: The incidence of non-specific respiratory symptoms was 8% at three months, then diminished afterwards. Substantial acute cross shift drops in FEV1, at each follow up survey, and longitudinal declines in FVC and FEV1, after 12 months of exposure were observed. Airway responsiveness to methacholine increased with follow up time, and was more pronounced among atotics. Increasing airway responsiveness was strongly correlated with cross shift drops in FEV1. In addition, one or more respiratory symptoms at three months was significantly, and pre-existing atopy marginally significantly, associated with cross shift drops in FEV1, after adjusting for other covariates and confounders.

Conclusion: Results suggest that non-specific respiratory symptoms, decreasing lung function, and increasing airway responsiveness are early pulmonary responses to cotton dust. In addition, the occurrence of respiratory symptoms and increasing airway responsiveness, as well as atopy, may be important predictors for acute changes in lung function among cotton textile workers.

Occupationally related exposure to cotton dust has been implicated in exacerbation of airway diseases including byssinosis, chronic bronchitis, and pulmonary function impairments. Most of the previous studies have focused on the typical syndrome of byssinosis, which is described as a feeling of chest tightness and shortness of breath that occurs on the first day of the working week, progressing to include other days in advanced stages. It has been known that attacks of typical byssinosis usually begin to appear after several years of exposure, and earlier pulmonary responses to cotton dust may be characterised by reversible respiratory symptoms and acute decrements in lung function.

Among the few studies that have assessed pulmonary responses to cotton dust in the early stages of exposure, Sepulveda and colleagues observed a significant decrement in FEV1 after exposure to 1.02 mg/m3 of elutriated cotton dust in model cardrooms for six hours in 226 healthy and non-asthmatic volunteers. The mean FEV1 decline, however, was provided a unique opportunity to observe relatively pure effects of exposure to cotton dust. The aims of the current analysis were to determine the changes in lung function, non-specific airway responsiveness, and respiratory symptoms caused by exposure to cotton dust, and to ascertain whether there is a difference in pulmonary responses between atopic and non-atopic persons.

SUBJECTS AND METHODS

Study subjects

The study was approved by the Institutional Review Boards of the Harvard School of Public Health and the First Hospital of the Shanghai Textile Industry. The original cohort was recruited from newly hired workers at three state owned cotton mills (mill 1–3) in Shanghai, China. A total of 240 workers who were assigned to the yarn preparation areas participated in the baseline survey conducted in March 1997. Among 15 excluded workers were nine males, five females with respiratory disease prior to work, and another one lacking a completed questionnaire. Therefore, the final cohort consisted of 225 female new workers without cardiorespiratory disease and respiratory symptoms. All workers were non-smokers with an average age of 18 years (range 16–29 years) at the outset, and not previously exposed to industrial dusts. Their socioeconomic status, geographical area, education level, and occupation were homogeneous.

The follow up surveys were carried out at 3, 12, and 18 months after the workers started to work in the cotton mills. A total of 194 (86%) and 136 workers (61%) of the original cohort were followed at 3 months and 12 months, respectively. The production and working conditions were stable over the period. After the 12 month survey, however, all of these workers were merged into one of the three cotton mills, because the...
other two were closed. There were 101 workers who participated in the last survey, representing 45% of the original cohort. The data of the workers who were followed at either 3 months or 12 months were analysed and reported separately. The current analysis focused on the subset data of 101 workers who were followed throughout the 18 month observation. Of these, 32 workers worked at mill 1, 46 at mill 2, and 23 at mill 3 before the mills were merged.

Environmental assessment

Environmental airborne cotton dust and Gram negative bacteria endotoxin in various work areas were measured at the 3 month survey. Cotton dust data for mill 1 were available at 12 and 18 months, and for mill 3 at 12 months. The methods used have been described previously. Vertical elutriators (General Metal Works, Inc., Cleveland, Ohio, USA) were used to take environmental samples using 37 mm PVC filters, over a full shift (minimum six hours). Endotoxin assays were performed on the dust samples using the Limulus amoebocyte lysate assay, chromogenic method.

Questionnaires

Questionnaires collecting information on complete work history, respiratory symptoms, and smoking history were administered at each survey. A modified American Thoracic Society (ATS/DLD) questionnaire was used. The questionnaire was translated into Chinese and back translated into English to verify accuracy. The symptoms of interest in the analysis included: usual cough with phlegm, usual dry cough, chest tightness, and dyspnoea. "Usual" was defined as a symptom occurring for more than five days a week. Work related nasal irritation, throat irritation, fatigue, and skin reactions were also observed.

Skin test

At baseline, each worker was given skin prick testing using standard methods. Briefly, the volar surface skin was cleaned with alcohol and allowed to dry. Twelve pricks were made in the skin approximately 2 cm apart with the Greer Scarifier (Greer Labs, Winston-Salem, NC). Subjects were tested with six common local antigens and six standard antigens, including ragweed, mould, standardised mite DF dermatophagoides farinae, mulberry silk, summer pollen, and house dust, along with a saline control. Erythema and induration were measured at 20 minutes by reading two perpendicular lines across the test site. Positive reactions were defined as induration at least 5×5 mm after subtracting diameters of negative control reactions. We reported the results of response to local antigens only, since the results of response to local antigens and to standard ones were almost identical. Atopy was defined as a positive reaction to two or more allergen extracts.

Lung function testing

Spirometric measurements were conducted by a trained technician using an 8 litre water sealed field spirometer (W.E. Collins Co., Braintree, MA) calibrated twice each day with a 3 litre syringe. At follow up surveys, forced expiratory spiromograms were performed before and after work shifts (cross shift) on the first day back to work after a two day rest. Each worker performed up to seven trials to produce three acceptable curves. The analysis of the study focused on indices of expiratory volume in one second (FEV1) and forced vital capacity (FVC). Acceptable FEV1, tracings were allowed to vary by no more than 5% or 100 ml, whichever was greater, and the best FEV1, 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 same techniques, instruments, and standardised methodology were used throughout the study.

Non-specific airway responsiveness

A test of non-specific airway responsiveness was performed at baseline, and at the 12 month and 18 month follow up surveys, respectively, using graded doses of inhaled methacholine. The methacholine challenge was done before work shift in the first day after a two day break at the 12 and 18 month surveys. Solutions were inhaled through a nebuliser (airflow 8 l/min, output 0.3 ml/min). The subjects inhaled the aerosol in a sitting position, at quiet breathing for two minutes through the nebuliser. They first inhaled phenol buffered saline alone to provide a control baseline spirometric value, then inhaled methacholine solution according to the following concentration schedule: 0.5, 1, 2, 5, 10, and 25 mg/ml. Spirometry was measured 60–120 seconds after each dose level inhalation. The test was terminated when a 15% decline in FEV1 from the post-diluent value occurred or when the methacholine concentration of 25 mg/ml was reached. Results were expressed as the decrease of FEV1, at the highest dose of methacholine given minus post-diluent value.

Total serum IgE measurement

Total serum IgE concentration using a modified classical radioimmunosorbent test was examined at baseline, and each follow up survey.

Statistical analysis

Data analysis focused on the changes in lung function and non-specific airway responsiveness over the 18 months after the workers started to work in the cotton mills. The possible impact of atopy on these changes was examined. The lung function data were expressed as longitudinal changes in FEV1, and FVC (using pre-shift values), and as acute changes (using cross shift drops in FEV1, ΔFEV1) over the follow up period. Changes in airway responsiveness were assessed as differences in decrease of FEV1, at the highest dose of methacholine (25 mg/ml) between follow up surveys and baseline survey. Personal exposure of individual workers during each follow up

<table>
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<tr>
<th>Table 1</th>
<th>Available environmental measurement data by mill</th>
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<td>Cotton dust [mg/m³]</td>
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<td>Endotoxin [µg/m³]</td>
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<td>3 months</td>
<td>42</td>
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Results expressed as geometric mean (SD).

*Significantly lower (p<0.05) in comparison with mill 2 or mill 3 (F test).
†Filter numbers.

Available environmental measurement data by mill

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<td>12 months</td>
<td>56</td>
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<td>18 months</td>
<td>56</td>
<td>0.47 (0.33)</td>
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<td>Endotoxin [µg/m³]</td>
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<tr>
<td>3 months</td>
<td>42</td>
<td>0.22 (0.51)</td>
<td>48</td>
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Results expressed as geometric mean (SD).

*Significantly lower (p<0.05) in comparison with mill 2 or mill 3 (F test).
†Filter numbers.

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period was assigned to high or low level according to the median values of dust (or endotoxin) concentrations of their work area measured at each time.

A paired $t$ test was used to compare the differences between baseline and follow up data, and Student’s $t$ test, Wilcoxon rank sum test, or Fisher’s exact test to compare the differences for continuous variables and Fisher’s exact test for category variables included atopic status, exposure level, respiratory symptoms, and serum IgE concentrations. In addition, age, height, and mill at 3 and 12 months were also considered as covariates. The GEE models were fitted using all available spirometric and airway responsiveness measurements taken from all surveys (time varying dependent variables). Cotton dust exposure level and IgE concentrations were time varying independent variables. Time fixed independent variables included age, height, and atopic status at baseline, respiratory symptoms and exposure to endotoxin at 3 months. Serum IgE concentrations were logarithmically transformed (log10) for the analysis because of highly skewed distribution. Data analysis was carried out with SAS personal computer software (version 8, SAS Institute, Cary, NC, 1999).

**RESULTS**

Table 1 shows the environmental measurement data throughout the follow up period. According to the available data, dust concentrations were highest in mill 3, whereas dust level in mill 1 was stable during the 18 months. There was a large difference in endotoxin among the three mills, of which a significantly lower level was in mill 1. Irrespective of mill or survey, the dust concentrations were highest in carding, followed by drawing, and lowest in the spinning area. The trend was similar for endotoxin. Spearman correlation coefficient between dust and endotoxin measured at 3 months was moderately high ($r = 0.73; p < 0.0001$). The majority of the workers remained in the same work area until the 12 month follow up survey. After the mills were merged by the 18 month survey, more workers joined in carding and drawing areas where the concentration of cotton dust was relatively higher. The total median concentrations of cotton dust (all three mills) were 0.35 mg/m$^3$ at 3 months, 0.27 mg/m$^3$ (mills 1 and 3) at 12 months, and 0.28 mg/m$^3$ (mill 1) at 18 months. The median concentration of endotoxin at 3 months was 0.037 μg/m$^3$.

To examine a potentially differential loss to follow up that may be a source of selection bias, demographic features, and health status for the analysed subset of 101 workers and the dropouts at 18 months were compared using Student’s $t$ test for continuous variables and Fisher’s exact test for category variables included atopic status, exposure level, respiratory symptoms, and serum IgE concentrations. In addition, age, height, and mill at 3 and 12 months were also considered as covariates. The GEE models were fitted using all available spirometric and airway responsiveness measurements taken from all surveys (time varying dependent variables). Cotton dust exposure level and IgE concentrations were time varying independent variables. Time fixed independent variables included age, height, and atopic status at baseline, respiratory symptoms and exposure to endotoxin at 3 months. Serum IgE concentrations were logarithmically transformed (log10) for the analysis because of highly skewed distribution. Data analysis was carried out with SAS personal computer software (version 8, SAS Institute, Cary, NC, 1999).
variables. Wilcoxon rank sum test was also applied to compare cross shift changes in FEV1, because of a skewed distribution of the variable with the large standard deviation. As table 2 shows, the demographic data were comparable, but the dropout subset had a slightly higher proportion of respiratory symptoms at either 3 or 12 months and a significantly greater cross shift change in FEV1, at 12 months. The proportion of atopy in followed up workers (31%) was close to that in dropouts (30%). The data suggested that dropouts at 18 months had a poorer respiratory condition than the 101 workers followed throughout the 18 months.

Of 101 workers, 31 (31%) were designated as atopic subjects, and the remaining 70 as non-atopic ones according to the results of skin prick test at baseline. As a whole group, the average age was 18.5 years and height 160.5 cm at baseline. There were no differences in age, height, baseline FVC, or FEV1 for atopic and non-atopic workers, while the drop in FEV1, at the highest methacholine dose at baseline was slightly greater in the non-atopics (87 ml) than in the atopics (58 ml). Forty seven per cent of workers of the whole group were assigned into being exposed to higher dust level at 18 months, while only 16% were so classified at 3 months and 22% at 12 months. The proportions of exposure to higher dust level were significantly higher in the non-atopic subgroup at 12 (p = 0.04) and 18 months (p = 0.02).

Table 3 shows the acute and longitudinal changes in spirometry, changes in FEV1, at the highest methacholine concentration, and log[IgE] after initiating work in cotton mills. As a whole group, no decrements in FVC and FEV1 were found at 3 months, in comparison with baseline values. At 12 months, however, statistically significant declines in both parameters were observed. On the other hand, substantial cross shift drops in FEV1, were noted at the 3 month survey, and similar drops remained at the following surveys. Even at 3 months, 16% of workers were found to have an acute drop of 5% or more. Atopic and non-atopic workers showed similar declines in longitudinal changes in FVC and FEV1, since 12 months, but the atopics appeared to have a greater cross shift drop in FEV1, at each follow up survey. Moreover, the proportion of acute drop by 5% or more tended to increase with the time in the atopics, whereas no such a trend was seen in the non-atopics.

Overall, FEV1 at the highest methacholine dose dropped by 26 ml at 12 months, and by 16 ml at 18 months, when compared with the baseline values. Atopics had greater drops at 12 and 18 months than did the non-atopics, and the value at 18 months was statistically significantly different from that at baseline (p < 0.05). Log[IgE] was significantly increased at 3 months and almost returned to the baseline level at 12 and 18 months for all the workers. Both atopic and non-atopic workers had significantly increased log[IgE] at 3 months, while the atopics had an insignificantly higher log[IgE] than did the nonatopics at 3 months.

Eight of 101 workers (8%) reported either cough with phlegm or dry cough at 3 months; an additional three had nasal irritation, and two throat irritation, in spite of the fact that none of the workers had respiratory disease or symptoms at baseline. The frequency of the respiratory symptoms reported at the following two surveys was 2% and 1%, respectively, which was less than at 3 months. Atopic workers did not report more symptoms than non-atopic workers. No bbyssinosis was observed among these workers during the observation time.

Dose-response characteristics of methacholine challenge testing done at baseline, 12 months, and 18 months were compared. As a whole group, airway responses to methacholine increased with time—that is, the lowest at baseline and the highest at 18 months. The average drop in FEV1, at the highest methacholine dose (25 mg/ml) was 97 ml at 18 months. A trend for the change with time was seen more distinctly in the atopics than in the non-atopics (fig 1). In the former, the FEV1 drops in response to each dose were greater at 18 months than at baseline and 12 months, reaching 124 ml of the average drop at the highest dose. This trend, however, was not evident in the non-atopics, whose airway responsiveness at 18 months was less than at 12 months.

Pearson correlation analysis including all the workers showed that changes in airway responsiveness were significantly correlated with the cross shift changes in FEV1, (r = 0.25, p < 0.0001), but not significantly with the longitudinal changes in either FVC or FEV1, (r = 0.09, p > 0.05 for both).

In GEE analysis, longitudinal changes in FVC, FEV1, or airway responsiveness were not predicted by atopy, symptoms, exposure level, or IgE level (data not shown). However, for cross shift drops in FEV1, over the follow up period, respiratory symptoms reported at 3 months were found to be a significant predictor and atopy to be a marginally significant predictor (table 4). In addition, exposure to high dust levels was negatively associated with greater acute drops in FEV1, though not statistically significant. When the term of exposure to high endotoxin at 3 months was added, as shown in model 2, exposure to high dust contributed more to cross shift drops in FEV1.
Early pulmonary responses to cotton dust

(−28 ml) in comparison with that (−20 ml) in model 1 without the term of exposure to high endotoxin. This might reflect an interactive effect of exposure to cotton dust and to endotoxin, as their measurements were significantly correlated. When exposure to dust was removed from model 2, exposure to high endotoxin at 3 months turned to be negatively related to cross shift FEV\(_1\) (−8 ml), suggestive of an adverse effect of endotoxin on the outcome variable.

Working at mills 2 and 3 was found to be significantly associated with a greater drop in FEV\(_1\), than working at mill 1, which was consistent with the result that mill 1 was lowest in concentrations of both dust and endotoxin. Age and height at baseline were also considered in all of the models. They were significantly related to longitudinal changes in FEV\(_1\), and FVC, but not to the cross shift drops in FEV\(_1\). These two variables were removed from the final models to improve the model fitting. When airway responsiveness to methacholine (drops in FEV\(_1\), at highest doses) over the 18 months was added to either model 1 or 2, it was strongly associated with the cross shift drops in FEV\(_1\), (p < 0.001), while atopy and respiratory symptoms were not. This finding suggests a stronger relation between cross shift changes in FEV\(_1\), and increasing airway responsiveness in these workers.

**DISCUSSION**

This study observed pulmonary responses to cotton dust during the first 18 months of exposure. The cohort was made up of same gender, lifelong non-smoking and previously non-exposed newly hired workers, with no pre-existing cardiorespiratory diseases and/or chest symptoms. Our results need to be interpreted in light of some limitations. There was a great attrition of the original cohort, especially after one year, largely because of a merger of the cotton mills (from three mills to one), leading to a number of workers leaving from the industry. The dropout workers at 18 months was found to have more respiratory symptoms at either 3 or 12 months, and a significantly greater drop in cross shift FEV\(_1\), at 12 months in comparison with the followed workers. It suggests that the dropouts were likely to be more predisposed to the effects of cotton dust. Hence, this study could be subject to a “healthy worker effect”, leading the health outcomes related to cotton dust exposure being underestimated. In spite of that, the findings of this study are informative and helpful in further understanding the natural history of pulmonary responses to exposure to cotton dust at the earliest stage of exposure.

We showed a remarkable change in lung function, not only reflected in acute drops, but also in longitudinal declines. A substantial cross shift drop in FEV\(_1\), was seen at each follow up point since the workers started to work in the cotton mills. This acute drop was most likely explained by the effects of exposure to cotton dust, as observed in healthy volunteers. Nevertheless, few epidemiological studies could assess a longitudinal change in airway responsiveness in cotton textile workers. In this study, we found that increasing methacholine responsiveness was strongly associated with the

**Table 4** GEE analysis for cross shift changes in FEV\(_1\), over 18 month observation

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<th>Model 1</th>
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<tr>
<td></td>
<td>Estimate (SE) p value</td>
<td>Estimate (SE) p value</td>
</tr>
<tr>
<td>Intercept</td>
<td>13.37 (15.09) 0.37</td>
<td>13.21 (15.09) 0.38</td>
</tr>
<tr>
<td>Atopy</td>
<td>−23.39 (13.06) 0.07</td>
<td>−23.29 (12.93) 0.07</td>
</tr>
<tr>
<td>Symptoms*</td>
<td>−36.91 (16.47) 0.02</td>
<td>−37.02 (16.47) 0.02</td>
</tr>
<tr>
<td>Exposure to high dust</td>
<td>−19.89 (16.43) 0.23</td>
<td>−27.77 (19.30) 0.15</td>
</tr>
<tr>
<td>Log(IgE), log mg/dl</td>
<td>3.84 (9.66) 0.69</td>
<td>3.46 (9.29) 0.71</td>
</tr>
<tr>
<td>Mill 2 v mill 1 †</td>
<td>−53.95 (14.84) 0.000</td>
<td>−56.56 (15.58) 0.000</td>
</tr>
<tr>
<td>Mill 3 v mill 1 †</td>
<td>−33.98 (17.02) 0.05</td>
<td>−33.82 (17.01) 0.05</td>
</tr>
<tr>
<td>Exposure to high endotoxin‡</td>
<td>8.88 (11.26) 0.45</td>
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*Including either cough with phlegm or dry cough reported at three months.
†Working mill at 3 and 12 months.
‡Endotoxin data measured at 3 months only.
cross shift drops in FEV₁, in response to cotton dust. This finding is in agreement with that observed in volunteers in the model cardroom and suggests that airway hyperresponsiveness is both a risk factor for, and a respiratory effect of exposure to cotton dust. Non-specific airway responsiveness is also associated with airway inflammation, which may explain its relation to the cross shift drop in FEV₁, induced by cotton dust exposure.

The importance of increased non-specific airway responsiveness in the development of chronic airflow limitation in cotton textile workers remains unclear. In this study, there was no direct evidence linking non-specific airway responsiveness with longitudinal changes in lung function. Atopy appeared to interact with exposure to cotton dust, reflecting in both increasing non-specific airway responsiveness and increasing acute drops in lung function. In consideration of a reported positive relation between acute drops and chronic declines in lung function, there is a reason to assume that atopic workers may be at a greater risk for chronic airflow limitation at these exposure levels.

Non-specific respiratory symptoms appeared to be the earliest pulmonary response to cotton dust. There was no difference in the incidence (at 3 months) or prevalence (at 12 or 18 months) of symptoms between the atopics and non-atopics, suggesting that both atopic and non-atopic workers experienced an inflammatory airway response to cotton dust. In contrast to the changes in lung function and airway responsiveness, the reported symptoms did not increase with longer exposure time. There were fewer subjective symptoms reported one year after than at three months. This phenomenon may partly be explained by the reversibility of the symptoms. The symptoms occur as a rapid response to the onset of exposure, and then tolerance develops with continued exposure, as observed in the early stage of byssinosis, and in organic dust toxic syndrome. In addition, the finding of fewer symptoms with time might be affected, more or less, by subject selection of this study, as the dropouts had slightly more symptoms than followed workers at either 3 or 12 months. No matter which circumstance, however, it is interesting to find that the early occurring symptoms may be an important risk factor for subsequent decrement of lung function.

Average IgE was found to be increased at three months, with a higher level in the atopics, and it returned to the pre-exposure level after 12 and 18 months, irrespective of atopic status. The IgE level was not related to lung function changes, suggesting that IgE level might not be the basis for the airway obstruction observed in cotton workers. A clear exposure-response relation was not observed for either acute or longitudinal pulmonary responses, though exposure to high dust was negatively related to lung function. Several possible explanations were considered. Firstly, the lack of exposure-response relation may be a result of exposure misclassification. Although considerable effort was made to measure dust concentrations of the working place at each follow-up survey, no detailed personal exposure information or personal samples were available. Secondly, the limited sample size and great cohort attrition in this study might lead to lack of power to observe a clear exposure-response relation. Thirdly, current knowledge suggests that bacterial endotoxin, rather than cotton dust itself, may be a major causative agent in vegetable dust induced lung disease, as shown in cotton workers and agricultural workers, as well as in animal experimental studies. It was impossible to assess the causative importance of endotoxin with the current limited data. We found a strong milk effect on the changes in lung function, and mills 2 and 3 had a significantly higher endotoxin level than mill 1 at 3 months, while their dust levels were similar. Correspondingly, a significantly greater drop in lung function was seen in working at mill 2 or 3 than at mill 1. This finding indicates an exposure-response relation with endotoxin.

In summary, our findings show that exposure to cotton dust was associated with acute and longitudinal changes in lung function and increasing airway responsiveness among healthy newly hired non-smoking workers. Atopic and respiratory symptoms occurring at the earliest time of exposure may be important risk factors for an acute drop in lung function induced by cotton dust. The results also suggest that non-specific airway responsiveness is both a risk factor for acute drops in lung function and a response to cotton dust.

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REFERENCES


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