Atopy, non-allergic bronchial reactivity, and past history as determinants of work related symptoms in seasonal grain handlers

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ABSTRACT One hundred and five young subjects with little or no previous exposure to grain dust were studied before and after a seven week period of grain handling work to determine if there was an association between symptoms experienced at work and pre-employment respiratory symptoms, allergy skin test responses, and non-allergic bronchial reactivity. The incidence of work related symptoms was cough 18%, wheeze 13%, and dyspnoea 14%. The results showed that pre-employment history of respiratory symptoms, positive allergy skin test responses, and a high level of non-allergic bronchial reactivity were significantly associated with these symptoms. These measurements may be useful to predict symptoms associated with exposure to grain dust in new employees and the results suggest that these work related symptoms may be due to allergen induced asthma.

Prolonged exposure to grain dust causes cough and sputum, airflow obstruction,¹⁻⁶ and increased non-allergic bronchial responsiveness.⁷ These adverse effects have usually been noted after years of exposure. Nevertheless, symptoms and airflow obstruction have also been reported after shorter periods of exposure such as during a work shift⁸⁻¹⁰ and on resumption of work after a layoff period during winter,¹¹ suggesting that exposure to grain dust can provoke asthma. Furthermore, under laboratory conditions asthmatic responses have been provoked by the inhalation of grain dust,¹²⁻¹⁵ the pattern of immediate and delayed responses being similar to that after inhalation tests with common allergens.¹⁶ As grain dust contains many potential allergens¹⁷ it is logical to suspect that allergic status and the level of non-allergic bronchial reactivity may be determinants of grain dust asthma.¹²⁻¹⁴⁻¹⁸ An association between atopy and respiratory effects of grain dust in surveys of workers has been present in some studies¹⁻² but not in others.⁵⁻⁶ One explanation for the inconsistent results of different studies is that susceptible subjects develop allergic symptoms, as a result of which they leave the grain handling industry.

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We have studied a group of subjects with little or no previous exposure to grain dust before and after a short period of work at grain storage sites in Western Australia. We sought to document work related symptoms and to examine the relation between these symptoms and pre-existing respiratory symptoms, skin test responses, and the level of non-allergic bronchial reactivity. The aim was to determine how the pre-employment status of the worker determined the occurrence of respiratory symptoms when exposed to grain dust.

Methods

A sample of 127 consecutive recruits was examined at the beginning of the 1982-3 harvesting season in Western Australia. The sample was 40% of employees hired as temporary grain storage attendants at the Perth office of the co-operative company that handles the entire Western Australian harvest. Their mean age was 20 (range 15-30) and 20 of the subjects were women.

A questionnaire, based on the 1976 British Medical Research Council questionnaire was administered by a doctor or nurse. Questions were asked on a history of cough, sputum, breathlessness, or wheezing. Subjects were asked if they had ever been diagnosed as

of cough, sputum, breathlessness, or wheezing. Subjects were asked if they had ever been diagnosed as having bronchitis or asthma. The diagnosis of rhinitis was based on positive answers to questions on a history of sneezing or runny nose or on a history of hay fever. Subjects were also asked about cigarette smoking habits and previous work with grain dust.

Prick skin tests were performed with commercially available antigens from grain (wheat whole grain, wheat pollen, rye whole grain, oats whole grain, barley whole grain), fungi (*Aspergillus*, *Penicillium*, *Cladosporium*), common local grasses (canary grass, perennial rye grass, wildoats, Bermuda grass), animal danders (cat and dog), house dust, and house dust mite (*Dermatophagoides farinae*) (Hollister-Stier, USA). The antigens were prepared in 50% glycerine in a strength of 1:10 (wt/vol). The negative control was 50% glycerine and the positive control 1% histamine. A positive skin test was defined as a weal response of 3 mm or more greater than the negative control measured 15 minutes after inoculation. Atopy was defined as a positive reaction to one or more antigens.

The forced expiratory volume in one second (FEV₁) and the forced vital capacity (FVC) were performed using a Wedge spirometer (Vitalograph S, Buckingham, England). The best FEV₁ from three technically satisfactory forced expiratory vital capacity manoeuvres was used for analysis.

Bronchial reactivity to methacholine was then measured using the method of Yan *et al.*¹⁹ Aerosols of physiological saline followed by methacholine solutions in increasing concentrations from 2.5 to 100 mg/ml were delivered at 90 second intervals from calibrated hand held De Vilbiss 40 nebulisers. FEV₁ was measured 60 seconds after the beginning of inhalation of each dose; one measurement was performed on each occasion unless the forced expiratory manoeuvre was technically unsatisfactory. Inhalations were continued until there was a 20% fall in FEV₁ or the maximum cumulative dose of methacholine (45 µmol) had been reached. The cumulative dose required to produce a 20% fall in FEV₁ (PD20) was taken from the log dose-response curve by linear interpolation of the last two points.

At the end of the season 105 of the subjects answered a questionnaire, administered by telephone, about their work experience and work related symptoms. They were asked: "Did the dust from the wheat bins cause any of the following: cough, wheeze, breathlessness, running nose or eyes, sneezing, rash?"

The statistical significance of differences in responses between groups was measured by unpaired *t* tests. Multiple linear regression analysis using dummy variables for nominal data was used to test

for significance of association between preseason measurements and the occurrence of symptoms at work.²⁰ The usefulness of measurements before work for prediction of symptoms at work was estimated by determining sensitivity, specificity, and positive and negative predictive values.²¹

Results

Of the 127 subjects studied before work, 44 (34.6%) had had previous seasonal employment with exposure to grain dust and 24 (18.9%) were current cigarette smokers. One quarter of the subjects had a history of wheeze unrelated to exposure to grain dust and 28% a history of rhinitis (table 1). Neither previous exposure to grain dust nor cigarette smoking was associated with significant differences in symptoms or responses to tests before work. FEV₁ was less than 90% predicted in only five subjects. There were significant associations between the level of bronchial reactivity and the frequency of wheeze and atopy.

Altogether 105 subjects (82.6%) answered the second questionnaire on the occurrence of respiratory symptoms at work. Their mean period of work was 6.6 weeks (SD 2.6 weeks). Three of the original group did not take up their employment and 20 subjects (15.7%) could not be contacted at the end of the study. There were no significant differences in age, smoking history or symptoms, previous exposure to grain dust, prick skin test responses, or PD20 between those who were contacted after work and those who were not. The frequency of symptoms at work was cough 17.1%, wheeze 14.3%, dyspnoea 14.3%, sneezing or runny nose 35.2%, and rash 12.4%. Ten subjects had cough, wheeze, and dyspnoea. Of these, three left work and six others sought medical treat-

Table 1 Pre-employment prevalence rates (127 subjects)

	No of subjects	Percentage of subjects
Questionnaire:		
Cough or phlegm	14	11
Wheeze	31	24
Shortness of breath	9	7
Chest tightness	17	13
Diagnosis of "asthma"	12	9
Diagnosis of "bronchitis"	11	9
History of rhinitis	36	28
Skin test positive:		
Any antigen	70	55
Whole grain antigens	19	15
Fungal antigens	36	28
Non-allergic bronchial reactivity (PD20 methacholine):		
≤ 4 µmol	13	10
> 4 ≤ 15 µmol	26	20
> 15 ≤ 45 µmol	31	24
> 45 µmol	57	45

Table 2 Association between measurements before work and symptoms at work (105 subjects)

Responses before work		Symptoms at work		
	Total	Cough (18)	Wheeze (15)	Dyspnoea (15)
History				
Cough and sputum	12	3	1	1
Wheeze	25	10*	11	10
Shortness of breath	8	3	4*	4*
Chest tightness	14	4	4	4
Asthma	11	4	5	5
Bronchitis	9	2	1	1
Rhinitis	33	8	8	7
Skin test positive				
Any	60	14	14	13
Grain	17	5	7	8
Fungi	31	9	11*	11*
PD20 methacholine $\leq 15 \mu\text{mol}$	26	8	11*	10*

*Significant associations ($p < 0.05$) by multiple linear regression analysis.

ment for these symptoms. There was no significant difference in the rate of symptoms between smokers and non-smokers and those who had had previous exposure to grain dust and those who had not.

There were significant associations between pre-employment symptoms of wheeze and dyspnoea, skin test responses to fungal antigens and bronchial responses to methacholine and the occurrence of cough, wheeze, and dyspnoea at work (table 2). When the significance of these associations was tested by multiple linear regression analysis, the variance of cough was least well explained by preseason measurements, the only significant determinant of cough at work was a history of wheeze; the co-efficient of determination (R^2) being only 0.15. The determinants of work related wheeze were a history of wheeze and dyspnoea, positive skin test to fungal antigens, and $\text{PD20} \leq 15 \mu\text{mol}$ ($R^2 = 0.34$). The determinants of dyspnoea at work were a history of dyspnoea, positive skin test responses to grain and fungal antigens, and $\text{PD20} \leq 15 \mu\text{mol}$ ($R^2 = 0.32$).

In the 60 atopic subjects there was a statistically significant association between bronchial reactivity at

the beginning of the season and frequency of work related symptoms; the lower the PD20 the more frequently were symptoms experienced (table 3).

The potential practical usefulness of these associations was examined by calculating the positive and negative predictive values of preseason history, skin test responses and PD20, singly and in combination, for the development of symptoms at work (table 4). Less than 15% of subjects with no history of wheeze, no evidence of atopy, and a PD20 of greater than $15 \mu\text{mol}$ complained of symptoms, a negative predictive value of $> 85\%$ for all work related symptoms. When prework tests were analysed separately the positive predictive values were low, between 22% and 53%. When subjects had a history of wheeze together with atopy and a PD20 equal to or less than $15 \mu\text{mol}$, however, the frequency of cough developing at work was 0.44, of wheeze 0.65, and of dyspnoea 0.56. Almost half the subjects with a history of wheeze, one or more positive skin tests, and a $\text{PD20} \leq 15$ had all three symptoms at work. The predictive values for cough were less than for wheeze or dyspnoea.

Discussion

The results of this prospective study of young subjects show that symptoms of cough, wheeze, and dyspnoea attributed to a short period of work place exposure to grain dust are significantly associated with a history of respiratory symptoms, atopy, and bronchial hyper-reactivity before starting work. This association suggests that these features may be useful to predict work related symptoms. If an individual has no history of wheeze, is non-atopic, and has a PD20 for methacholine greater than $15 \mu\text{mol}$, there is little risk of developing symptoms at work. Alternatively, if an individual has a history of wheeze, is atopic, and has

Table 3 Association between PD20 and symptoms at work in atopic subjects

PD20 (μmol)	No of atopic subjects	Atopic subjects with symptoms at work			
		Cough	Wheeze	Dyspnoea	Rhinitis
≤ 4	10	5	4	4	5
$> 4 \leq 15$	11	3	7	5	5
$> 15 \leq 45$	14	4	2	2	8
> 45	25	2	1	1	10
Total	60	14	14	13	28
p*		0.05	0.005	0.005	NS

*Chi-squared analysis.

Table 4 Predictive values of results of tests before work for the development of symptoms at work

Before work test result	Symptoms at work					
	Cough		Wheeze		Dyspnoea	
	PPV	NPV	PPV	NPV	PPV	NPV
History of wheeze	0.40	0.90	0.44	0.95	0.40	0.94
Skin test positive						
Any antigen	0.23	0.91	0.23	0.98	0.22	0.96
Whole grain antigens	0.29	0.85	0.47	0.91	0.53	0.92
Fungal antigens	0.29	0.88	0.35	0.95	0.35	0.95
PD20 $\leq$ 15	0.31	0.87	0.42	0.95	0.38	0.94
History of wheeze, atopy and PD20 $\leq$ 15	0.44	0.88	0.65	0.94	0.56	0.93

PPV = positive predictive value, the proportion of those with a positive test who had the symptom.

NPV = negative predictive value, the proportion of those with a negative test who did not have the symptom.

a PD20 equal or less than 15 μ mol, there is a two thirds chance of developing wheeze at work and a 50% chance of cough, wheeze, and dyspnoea on exposure to grain dust at work.

The use of pre-employment health surveys as a condition for employment is controversial. Atopy has been considered a contraindication to work with proteolytic enzymes and the complex salts of platinum.²² This contrasts with the conclusion of a symposium on the effects of grain dust on health which suggested that a pre-employment medical examination should be performed before entering the industry but that the information should not be used to prevent employment of an individual who would normally be considered fully employable.¹⁷ The results of our study, however, do suggest that useful advice may be given to potential workers in the grain industry on the basis of a simple questionnaire and prick skin tests and measurement of bronchial reactivity. Also, Gerrard and colleagues found that non-atopic, non-smoking men could work in grain elevators without developing respiratory problems²³ although non-allergic workers had increased bronchial reactivity.⁷

The association between work related symptoms, particularly dyspnoea and wheeze, and pre-existing atopy and increased bronchial reactivity suggests that exposure to grain dust may provoke asthma by an allergic mechanism¹⁸ and this is supported by previous observations.¹²⁻¹⁴ The occurrence of cough at work was associated only with a pre-employment history of wheeze and was less well predicted by measurements before work than wheeze and dyspnoea. Do Pico and colleagues in a study of long term grain handlers during a work shift found the prevalence of cough to be almost four times that of wheezing or dyspnoea.⁹ These findings suggest that the mechanism of cough resulting from exposure to grain differs from that of wheeze and dyspnoea and is com-

patible with cough being due to non-specific effects whereas wheeze and dyspnoea may be manifestations of allergen induced asthma. Laboratory evidence also indicates that cough and wheeze can be separate responses to inhaled aerosols.²⁴

Some studies of grain workers have not found an association between symptoms and atopy.^{5,6} Those studies involved long time workers and the difference suggests that they were affected by selection and each involved survival populations; atopic workers having developed symptoms and left the grain industry or that chronic or recurrent symptoms, or both, have a non-allergic mechanism. We studied a healthy young population, most of whom had no previous exposure to grain dust, for a relatively short period at work. The prevalences of a history of wheeze, a diagnosis of asthma, atopic state, and a PD20 < 15 μ mol were similar to that of a nearby general population sample.²⁵ The incidence of work related respiratory symptoms in this group during the period of employment was between 14.3% for wheeze and dyspnoea and 17.1% for cough, with 9.5% complaining of all three symptoms. As there was no unexposed control group for comparison the relative rate of these symptoms cannot be stated. The main purpose of the study, however, was not to determine the overall incidence of the various work related symptoms for comparison with another (unexposed) population but to examine the associations between pre-season characteristics of the subjects and exposure related symptoms within the group. Knowledge of these associations may provide an understanding of the mechanisms of the respiratory symptoms and a practical method of predicting an adverse response to grain dust exposure in an individual.

Positive skin test responses to fungal antigens (*Aspergillus*, *Penicillium*, and *Cladosporium*) were one of the determinants of work related wheeze and

dyspnoea. Fungi abound in wheat dust from Western Australia and the predominant varieties identified include those for which commercial skin testing material was obtained for this study (R McAleer, personal communication). These findings suggest that fungal allergens may be important in Western Australian grain. Sensitisation to storage mites and grain weevils is unlikely as they are uncommon and because the water content of the grain is low.

The conclusions of this study are based on a history of symptoms at work obtained by telephone questionnaire. The significance of these symptoms needs to be assessed by measurements of the effect of work on lung function and bronchial reactivity. Observations of change in allergic status may also help clarify the mechanism of responses.

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