

Effect of grain exposure and smoking on the longitudinal changes in immediate skin reactivity

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Summary

The study was carried out to investigate the effect of occupational exposure and smoking on the longitudinal changes of immediate skin reactivity over 3 years in working populations. A total of 480 grain elevator workers and 707 transit and ferry (control) workers were included because they had allergy skin tests on both surveys. Skin-prick tests using three common allergens and a negative and histamine controls were administered during both surveys. The reaction was considered positive if the mean weal size was 3 mm or greater than that of the negative control. Conversion was defined as a change from the non-atopic state in the initial survey to the atopic state in the follow-up survey. Reversion was defined as a change from the atopic state in the initial survey to the non-atopic state in the follow-up survey. The findings showed that grain workers had two times risk of conversion than control workers. Recent smokers, who changed their habit from non-smoker/ex-smoker to smoker in the follow-up survey, were at a three times risk of conversion than non-smokers. The reversion of skin-test reactivity was not associated with age, smoking habits, or working exposure. When investigating studies of longitudinal changes in immediate skin reactivity, the effects of age, changes in smoking habit and occupational exposure should be considered.

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Introduction

Immediate skin reactivity has been used as an index of atopy status for a long time. The prevalence study of atopy, measured by skin-prick tests, ranged from 22 to 50% in different geographic adult populations [1–3]. It has been pointed out previously by Barbee *et al.* [4] that several factors affect skin-test reactivity such as the number of allergens used, the criteria for a positive response, the type and the potency of allergens, and the age distribution of the population.

There is some evidence that the incidence of atopy increased in different population studies [4–6]. Prospective studies showed the annual incidence rate of positive immediate skin reactivity was around 3–4% in school children [5,6]. Barbee *et al.* [4] showed an increase in the

prevalence of atopy by 27% over a mean period of 8.1 years in a follow-up study of 1333 subjects from 3 to over 75 years of age. Age was an important predictor on the longitudinal changes of allergen skin test in their study. The rate of change from negative to positive (conversion) skin-test reaction was found to be higher in subjects between 15 and 34 years of age and the rate of reversion in skin-test reactivity was found higher in those over the age of 55 years. Among those over the age of 35 years, smokers were less atopic in the initial survey and had a lower incidence rate over a period of 8 years follow-up. There has been no report on the trends of immediate skin reactivity in working population.

This is a study of longitudinal changes over a 3 year-period of immediate skin reactivity in workers in three industries: grain elevators, transit and ferry workers. The effects of age, changes in smoking habit, and exposure to grain dust on the longitudinal changes in immediate skin reactivity were examined.

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Materials and methods

Study population

White, male workers in five terminal grain elevators in British Columbia who took part in a surveillance programme during 1982 and 1985 [7] and workers in bus repair (transit) and ferry operations examined in another surveillance programme during 1986/1987 and 1990/1991 formed our study population. The latter two groups of workers were examined because of the possibility of exposure to low levels of asbestos at work; they were not exposed to other dusts, gases or fumes at work. They served as a control group. The participation rate was around 80%. Two hundred and forty-two (33.5%) of the 722 grain workers and 12 (5.9%) of the 719 transit and ferry workers (control group), who did not have allergy skin tests on both surveys, were excluded from analysis. The results of skin-test reactivity in 1187 white male workers were analysed.

The excluded grain workers were older (39.9 vs 37.2 years; $P = 0.007$) and had a higher proportion of current smokers (57% vs 41%; $P < 0.001$) than those included in the analysis. There was no difference in the prevalence of positive skin-test reaction during the first survey between grain workers included (14.8%) and those excluded (14.2%) from the analysis. There was no difference in the mean age, prevalence of positive skin-test reaction, and smoking habits between control workers who were excluded and those included in the analysis.

Allergen skin test

Skin-prick tests using three common allergens (house dust mite, mixed Pacific grass pollen, epidermal antigen of cat) and a negative (saline) and positive (histamine) control were administered during each survey. The surveillance studies were always conducted at the same time of the year (October–January) to avoid seasonal influence. The same technicians performed the allergy skin-tests in both surveys. Although the batch numbers of allergen were different, they were supplied by the same laboratory for each survey (Bencard Allergy Labs, Ontario, Canada). Subjects who had taken antihistamine 2 weeks before the surveys were not skin tested. The weal diameters were measured on site by the same technicians as the mean of the largest diameter and its perpendicular diameter after 15 min of the test. The reaction was considered positive if the mean weal size was 3 mm or greater than that of the negative control. The use of 3 mm as a cut off value for positive skin reaction was arbitrary. Since there was no general

consensus about the cut off values and ≥ 3 mm has been suggested as cut off limit by some authors [8,9], we adopted the same criteria for the positivity of skin-prick tests in our study. Atopy was defined as the presence of a positive reaction to one or more of the three allergens. Conversion was defined as a change from the non-atopic state in the initial survey to the atopic state in the follow-up survey. Reversion was defined as a change from the atopic state in the initial survey to the non-atopic state in the follow-up survey. The reproducibility of the skin-prick testing on two consecutive days in our laboratory was 95%. This was carried out on two consecutive days on 20 subjects; 14 with positive and six with negative skin tests.

Smoking habit

Smokers were defined as subjects who smoked at the time of the survey. Ex-smokers were subjects who had been smokers and had quit smoking for at least 6 months prior to the survey. Non-smokers were those who did not smoke at all. Recent smokers were defined as subjects who were non-smokers or ex-smokers in the initial survey and had become smokers in the follow-up survey. Recent ex-smokers were defined as subjects who were smokers in the initial survey became ex-smokers in the follow-up survey.

Statistical method

The statistical analysis was performed with the Statistical Package for Social Science computer program (SPSS, Inc., Chicago, Ill, USA) on an Apple Macintosh PowerBook 170 computer (Apple Computer, Inc., Cupertino, Ca, USA). Multiple logistic regression models were used to obtain estimates of effect of age, smoking habits, and occupation on the changes of immediate skin reactivity. Two-sided 95% confidence intervals (95% CI) for odds ratio (OR) derived from the logistic regression model were calculated by the method of Schlesselman [10].

Results

Characteristics of workers

Table 1 shows the characteristics of the workers in the initial and the follow-up survey. The grain elevator workers was younger than the control workers. In the initial survey the prevalence of atopy was higher in control workers than grain workers. In the follow-up survey, there was no difference in the prevalence of

Table 1. The characteristics and prevalence of atopy by age group and smoking habits in grain workers and control workers

	n		Initial survey		Follow-up survey	
	Grain	Control	Grain	Control	Grain	Control
Number	480	707				
Age, years (SD)			37.2 (11.8)	44.7 (9.8)*	41.0 (11.7)	47.9 (9.8)*
Atopy, n (%)			71 (14.8)	186 (26.3)†	101 (21.0)	155 (21.9)
<i>Age at initial survey</i>						
< 25	77	2	23 (29.9)‡	0§	29 (37.7)‡	0¶
25-34	157	109	27 (17.2)	32 (29.4)	35 (22.3)	27 (24.8)
35-44	89	260	8 (9.0)	86 (33.1)	15 (16.9)	67 (25.8)
45-54	115	200	10 (8.7)	38 (19.0)	20 (17.4)	36 (18.0)
> 55	42	136	3 (7.1)	30 (22.1)	2 (4.8)	25 (18.4)
<i>Smoking habit</i>						
Non-smoker	126	237	25 (19.8)	67 (28.3)	30 (23.8)	58 (24.5)
Ex-smoker	142	263	18 (12.7)	79 (26.6)	24 (16.9)	60 (22.8)
Recent ex-smoker	46	49	5 (10.9)	14 (28.6)	10 (21.7)	10 (20.4)
Smoker	151	143	22 (14.6)	33 (23.1)	32 (21.2)	24 (16.8)
Recent smoker	15	15	1 (6.7)	2 (13.3)	5 (33.3)	3 (20.0)

* $P < 0.001$; difference between grain and control workers by Student *t*-test.

† $P < 0.0001$; difference between grain and control workers by chi-squared test.

‡ $P < 0.001$; relationship between age and prevalence of atopy in grain workers by chi-squared trend test.

§ $P < 0.05$; relationship between age and prevalence of atopy in control workers by chi-squared trend test.

¶ $P = 0.068$; relationship between age and prevalence of atopy in control workers by chi-squared trend test.

atopy. There were more current smokers among the grain workers in both the initial and the follow-up surveys. Workers ($n = 125$, 10.5%) had changed their smoking habits between the surveys; 30 from non-smokers or ex-smokers to smokers (recent smokers) while 95 stopped smoking (recent ex-smokers) by the follow-up study. There was no difference in the proportion of recent ex-smoker and recent smokers between grain and control workers.

Effect of age and smoking on the prevalence of atopy

The prevalence of positive skin reaction in both surveys was inversely associated with age. In grain workers, the prevalence of positive skin reaction decreased with age (Table 1). The same trend was found in control workers during both surveys, but was not statistically significant ($P = 0.068$) in the follow-up survey.

There was no association between smoking habits and the prevalence of positive skin reaction in both the initial and the follow-up survey among both groups of workers.

Longitudinal changes in immediate skin-test reactivity

During the follow-up survey, 10% of the grain workers and 4.8% of the controls changed their immediate skin-test reactivity from negative to positive (conversion) while 15.5% of grain workers and 30.1% of controls changed their immediate skin-test reactivity from positive to negative (reversion) (Table 2). The conversion rate of skin-test reactivity was significantly higher in grain workers than in controls. In contrast, the reversion rate was significantly higher in the controls.

House dust mite allergen was the most common allergen that showed conversion in both groups of workers. Among grain workers, four showed conversion of all three allergens and five to two allergens simultaneously. Among controls, one showed conversion to all three allergens while seven only to two allergens. Among grain workers, reversion of skin-test reaction to house dust mite allergen was also most common, followed by grass pollen and cat allergen. Two grain workers showed reversion to two allergens. Among controls, reversion of skin-test reaction occurred with equal frequency to all three allergens. Eight control

Table 2. Allergens responsible for conversion and reversion in grain and control workers

	Grain workers n (%)	Control workers n (%)
<i>Conversion</i>	41 (10.0)*	25 (4.8)
Houset dust mite	28 (6.8)*	16 (3.1)
Cat	13 (3.2)†	6 (1.2)
Grass pollen	13 (3.2)	12 (2.3)
<i>Reversion</i>	11 (15.5)*	56 (30.1)
House dust mite	9 (12.7)	28 (15.1)
Cat	1 (1.4)*	26 (14.0)
Grass pollen	3 (4.2)*	30 (16.1)

* $P < 0.05$; difference between grain and control workers by chi-squared test.

† $P = 0.053$; difference between grain and control workers by chi-squared test.

workers showed reversion to three allergens and 12 to two allergens.

Effect of age and smoking habits on change in immediate skin-test reaction

Table 3 shows that while the rate of conversion was not associated with age, there was a trend of an increase in

Table 3. Changes in skin-test reaction by age and smoking habit in grain and control workers

	Conversion, n (%)		Reversion, n (%)	
	Grain (n = 41)	Control (n = 25)	Grain (n = 11)	Control (n = 56)
<i>Age at initial survey</i>				
< 25	6 (11.1)	0	0*	0
25-34	15 (11.5)	4 (5.2)	7 (25.9)	9 (28.1)
35-44	8 (10.0)	6 (3.5)	1 (12.5)	25 (29.1)
45-54	11 (10.4)	9 (5.6)	1 (10.0)	11 (29.0)
> 55	1 (2.6)	6 (5.6)	2 (66.7)	11 (36.7)
<i>Smoking habit</i>				
Non-smoker	8 (7.9)	10 (5.9)	3 (12.0)	19 (28.4)
Ex-smoker	9 (7.3)	11 (5.7)	3 (16.7)	21 (30.0)
Recent ex-smoker	6 (14.6)	1 (2.9)	1 (20.0)	5 (35.7)
Smoker	14 (10.8)	2 (1.8)	4 (18.2)	11 (33.3)
Recent smoker	4 (28.6)	1 (7.7)	0	0

* $P = 0.055$; relationship between age and reversion rate in grain workers by chi-squared trend test.

the rate of reversion with age in both groups of workers. Consistent smoking habit was not associated with the rate of conversion and reversion. Among grain workers, recent smokers had the highest conversion rate. For all strata of smoking habit, the rate of conversion was consistently higher in grain workers than the controls; in contrast, the rate of reversion was consistently higher in control workers than in grain workers.

The determinants of conversion of immediate skin-test reactivity were analysed using a logistic regression model adjusting for the effects of age, smoking habits and work exposure simultaneously (Table 4). Grain workers showed a significantly higher risk of converting than controls. Recent smokers were three times more likely to become converted compared with non-smokers. Age was not associated with the risk of conversion. Analysis was also carried out on the determinants of reversion of immediate skin-test reactivity. The reversion of skin-test reactivity was not associated with age, smoking habits, or work exposure (data not shown).

Discussion

In this study we found that during the initial survey grain workers had a lower prevalence of atopy than control workers. This is not surprising since grain workers with a history of allergy have been excluded from the industry during pre-employment examination. Moreover, those with atopy and entered the industry probably leave their job within the first few weeks because of the irritating effect of grain dust [1].

In the longitudinal analysis, however, we found that grain workers had a higher rate of conversion of immediate skin-test reactivity than the controls. We believe that the higher rate of skin-test conversion in grain workers is likely to be due to grain dust exposure. Extracts of grain dust have been shown to release histamine and leukotrienes from human lung fragment [12], and to induce production of interleukin-1 by macrophage [13]. Exposure to grain dust might induce airway inflammation associated with an increase in mucosal permeability resulting from mediator release, thus allowing aeroallergens to go through the mucosa more readily [14].

Other reasons for the higher rate of conversion of immediate skin-test reactivity should be discussed. One obvious reason is differences in technique and methodology of skin testing and the allergens used between the studies. We have ensured that the same technicians performed skin tests in all the studies using the same methods and the same allergens purchased from the same laboratory. The reproducibility of skin testing on two consecutive days was found to be very good, 95%. It is

Table 4. Multiple logistic regression of age, occupation, and smoking status, as predictors of conversion of skin-test reactivity ($n = 930$)

	β	<i>P</i> -value	Odds ratio	95% CI
Age, (every 10 years)	-0.09	0.44	0.91	0.72-1.16
Grain workers	0.71	0.011	2.04	1.18-3.54
Smoking status				
Ex-smoker	-0.00007	0.99	1.00	0.50-1.99
Recent ex-smoker	0.23	0.62	1.27	0.50-3.18
Smoker	0.091	0.80	0.91	0.45-1.86
Recent smoker	1.12	0.047	3.06	1.02-9.23

β . Regression coefficient. 95% CI. 95% confidence interval. Recent smoker. Non-smokers or ex-smokers in first skin-test become smokers in the follow-up survey. Recent ex-smoker. Smokers in first skin test become ex-smokers in the follow-up survey. Dummy variables: occupation—grain workers compared with control workers. Smoking status—ex-smokers, recent ex-smoker, smokers, and recent smoker compared with non-smoker.

unlikely that our findings of conversion and reversion of skin-test reaction were due to methodological differences. The factor of selection should be considered as about one-third of the grain workers who took part in the first survey was no longer present in the follow-up study. This is an unlikely reason for a higher rate of skin-test conversion in grain workers as one would expect those with atopy would have selected themselves out of the industry. The other possibility could be a cohort effect as the grain workers were studied in 1982 and 1985 while the controls were studied in 1986 and 1991. This is also a rather unlikely reason as the control workers were 7 years older than the grain workers during the first survey even though they were studied later. One other possibility could be the controls might be exposed to contaminants that would inhibit immediate skin-test response. The opposite is true as some of the controls might be exposed to diesel exhaust because of their job in bus repair. Diesel exhaust particulates have been shown to enhance sensitization in animals [11]. We found, on the contrary, that the controls had a lower rate of conversion of skin-test reactivity.

Age has been shown to be related to the longitudinal changes of skin-test reaction. Barbee *et al.* [4] found that the age at the time of the first skin testing was related to subsequent changes of immediate skin reactivity; the young age group was associated with a higher rate of conversion while the old age group was associated with higher rate of reversion. In this study, we could not demonstrate the effect of age on changes of skin-test reactivity. The discrepancy in the findings may be due to the differences in age of the study populations. Subjects in this study were from working populations age ranged

from 18 to 76 years while those in Barbee's study were derived from general population with an even wider age range (3 to over 75 years). In addition, the number of allergens and the type of allergens used were different; three allergens were used in our study and five in Barbee's study. The mean interval between skin testing was different: 3.4 years in our study and 8.1 years in Barbee's study.

The effect of smoking habits on the prevalence of atopy was less clear. While Burrows *et al.* [15] showed that smokers were less atopic than non-smokers in a general population, Chan-Yeung *et al.* [1] found that smoking had no association with the prevalence of atopy in industrial populations. In this study we demonstrated that recent smokers had about three times the risk of becoming atopic than non-smokers. Persistent smokers were not found at a higher risk of conversion than non-smokers in this study. The reason why only recent smokers were at higher risk of being converted was not clear. It has been shown that serum IgE level was higher in smokers than in non-smokers [16, 17]. And IgE levels was closely related to immediate skin reactivity [18]. But these findings could not explain why we did not find an increase of conversion rate in smokers in both groups. Information about whether recent smokers have a higher serum IgE level than consistent smokers is needed.

In conclusion, we have demonstrated that grain workers and recent smokers had a higher risk of conversion of skin-test reaction. This observation also suggests an annual 1.6 and 3.3% incidence rate of new skin-test reactivity in grain and control workers respectively. When investigating studies of longitudinal changes in

immediate skin reactivity, one must consider the effect of changes in smoking habit and occupational exposure in addition to age factor.

References

- 1 Chan-Yeung M, Vedal S, Lam S, Enarson D. Immediate skin reactivity and its relationship to age, sex, smoking, and occupational exposure. *Arch Environ Hlth* 1985; 40:53-7.
- 2 Haahtela T, Björkstén F, Heiskala M, Suoniemi I. Skin prick test reactivity to common allergens in Finnish adolescents. *Allergy* 1980; 35:425-31.
- 3 Barbee R, Lebowitz M, Thompson H, Burrows B. Immediate skin-test reactivity in a general population sample. *Ann Intern Med* 1976; 84:129-33.
- 4 Barbee R, Kaltenborn W, Lebowitz M, Burrows B. Longitudinal changes in allergen skin test reactivity in a community population sample. *J Allergy Clin Immunol* 1987; 79:16-24.
- 5 Peat J, Salome C, Woolcock A. Longitudinal changes in atopy during a 4-year period: relation to bronchial hyper-responsiveness and respiratory symptoms in a population sample of Australian schoolchildren. *J Allergy Clin Immunol* 1990; 85:65-74.
- 6 Kuehr J, Karmaus W, Frischer T et al. Longitudinal variability of skin prick test results. *Clin Exp Allergy* 1992; 22:839-44.
- 7 Chan-Yeung M, Dimich-Ward H, Enarson DA, Kennedy SM. Five cross-sectional studies of grain-elevator workers. *Am J Epidemiol* 1992; 136:1269-79.
- 8 Dreborg S. Skin tests used in type I allergy testing: Position paper. *Allergy* 1989; 44 (Suppl 10):36.
- 9 Bernstein L. Proceedings of the task force on guidelines for standardizing old and new technologies used for the diagnosis and treatment of allergic diseases. *J Allergy Clin Immunol* 1988; 82:487-526.
- 10 Schlesselman JJ. *Case-Control Studies: Design, Conduct, Analysis*. New York: Oxford University Press, 1982:248.
- 11 Takafuji S, Suzuki S, Koizumi K. Diesel exhaust particulates inoculated by the intranasal route have an adjuvant activity for IgE production in mice. *J Allergy Clin Immunol* 1987; 79:639-45.
- 12 Chan-Yeung M, Chan H, Salari H, Wall R, Tse K. Grain dust extract induced direct release of mediators from human lung tissue. *J Allergy Clin Immunol* 1987; 80:279-84.
- 13 Keller GI, Lewis D, Olenchock S. Demonstration of inflammatory cell population changes in rat lung in response to intratracheal instillation of spring wheat dust using lung enzymatic digestion and centrifugal elutriation. *Comp Immunol Microbiol Infect Dis* 1987; 10:219-26.
- 14 Lebowitz S, Salvaggio J, Schwartz H. An hypothesis for the development of atopic allergy in man. *Clin Allergy* 1972; 2:237-46.
- 15 Burrows B, Lebowitz M, Barbee R. Respiratory disorders and allergy skin test reactions. *Ann Intern Med* 1976; 84:134-9.
- 16 Burrows B, Halonen M, Barbee R, Lebowitz M. The relationship of serum immunoglobulin E to cigarette smoking. *Am Rev Respir Dis* 1981; 124:523-5.
- 17 Taylor R, Gross E, Joyce H, Holland F, Pride N. Smoking, allergy, and the differential white blood cell count. *Thorax* 1985; 40:17-22.
- 18 Loeffler J, Cawley L, Moeder M. Serum IgE levels: correlation with skin test reactivity. *Ann Allergy* 1973; 31:331-6.

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