Predictors of onset of wheezing in grain elevator workers

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P Pahwa, A Senthilselvan, HH McDuffie, JA Dosman. Predictors of onset of wheezing in grain elevator workers. Can Respir J 1998;5(3):200-205.

A longitudinal study of Canadian grain elevator workers over a 12-year period was conducted. Data on respiratory symptoms and pulmonary function tests were collected once every three years as part of the Grain Dust Medical Surveillance Program started by Labour Canada in 1978; each three-year interval was called a 'cycle'. Of workers who had two or more observations, 1848 subjects (67.2%) were free of respiratory symptoms (wheeze, dyspnea, cough or sputum) at the baseline (cycle II). Predictors of first episode of wheezing were examined in these symptoms-free grain workers.
Baseline mean age ± SD of the grain workers was 34.0±11.4 years and mean duration of work in the industry was 9.9±8.7 years. Of the 1848 symptoms-free grain workers at cycle II, 203 (11.0%) subsequently reported wheezing during the study. Cox's proportional hazards model for analysis of survival data was used to determine significant predictors of first episode of wheezing. Significant predictors for first episode of wheezing were current smoking (relative risk [RR] 2.33; 95% CI 1.63 to 3.33; P<0.0001) and baseline forced expiratory volume in 1 s to forced vital capacity ratio [RR 0.02; 95% CI 0.003 to 0.20; P<0.0001).
Baseline pulmonary function measurements and smoking habits appear to be important predictors of future development of asthma-like symptoms in grain elevator workers.

Key Words: *Grain workers, Longitudinal study, Pulmonary function, Wheezing*

Prédicteurs du développement du wheezing chez les travailleurs des silos à grain

RÉSUMÉ : Une étude longitudinale sur les travailleurs canadiens des silos à grain a été menée pendant une période de 12 ans. Des données sur les symptômes respiratoires et sur les épreuves de la fonction pulmonaire ont été recueillies dans des groupes environ à trois ans d'intervalle dans le cadre du Programme de surveillance médical sur la poussière du grain amorcé par Travail Canada en 1978 ; chaque intervalle de trois ans a été nommé «cycle». Des travailleurs qui ont été observés deux fois et plus, 1848 sujets (67,2 %) n'accusaient aucun symptôme respiratoire (wheezing, dyspnée, toux ou expectoration) à la période de référence (cycle II). Les prédicteurs du premier épisode de wheezing ont été examinés chez ces travailleurs du grain sans symptômes.
L'âge moyen à la période de référence ± EC des travailleurs du grain était de 34,0±11,4 ans et la durée moyenne du travail dans cette industrie de 9,9±8,7ans. Des 1848 travailleurs du grain sans symptômes au cycle II, 203 (11,0 %) ont par la suite signalé du wheezing pendant l'étude. On a utilisé le modèle des risques proportionnels de Cox pour analyser les données sur la survie afin de déterminer les prédicteurs significatifs du premier épisode de wheezing. Les prédicteurs significatifs pour le premier épisode de wheezing était la consommation courante de tabac (risque relatif [RR] 2,33 ; 95 % IC 1,63 à 3,33 ; P<0,0001 et le rapport du volume expiratoire maximum/seconde par la capacité vitale forcée de référence [RR 0,02 ; 95 % IC 0,003 à 0,20 ; P<0,0001).
Le mesures de base de la fonction pulmonaire et le tabagisme semblent être d'importants prédicteurs du développement futur de symptômes ressemblant à ceux de l'asthme chez les travailleurs des silos à grain.

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Farmers and grain handlers tend to show increased prevalence of respiratory symptoms and decreased lung function values compared with control subjects (1,2). Relationships between respiratory symptoms and reduced levels of pulmonary function test values have been documented in cross-sectional studies (1,3-6). Several longitudinal studies have investigated the relationship of respiratory symptoms to annual decline in pulmonary function test variables (7-10). Recently, it has been reported that working in the grain industry and exposure to ambient concentrations of endotoxin are associated with increased prevalence of respiratory symptoms and diminished measures of airway function (11). It has been reported that chronic wheeze is prevalent among dock and grain workers (12). Grain dust-induced asthma has been reported by several investigators (13-16). Wheeze and attacks of breathlessness are related to annual rate of decline in pulmonary function (17). In a longitudinal study from Montreal, Quebec onset of dyspnea and wheeze was significantly related to the annual rate of decline in forced expiratory volume in 1 s (FEV_1) among nonasthmatic subjects (18).

Recurrent episodes of wheezing and dyspnea are related to asthma (19). The Normative Aging Study of middle-aged and older men (20) provided evidence that current smoking and increasing age are independent predictors of a new onset of wheezing. In the present paper, we report the results of a longitudinal study of Canadian grain elevator workers, in which we attempted to determine the predictors of a first episode of wheezing in apparently healthy and asymptomatic grain workers from baseline, and for whom we have at least two sets of observations. We report estimates of the magnitude of risk of developing a first episode of wheezing for predictors after adjusting for other factors.

SUBJECTS AND METHODS

A respiratory health surveillance program in grain elevator workers in Canada commenced in 1978 (21). Data on respiratory symptoms and pulmonary function tests were collected once every three years. Each three year interval was called a ‘cycle’. The periods of cycles were cycle I (October 1978 to September 1981) cycle II (October 1981 to September 1984), cycle III (October 1984 to September 1987); cycle IV (October 1987 to September 1990); and cycle V (October 1990 to September 1993). Details of the surveillance program are described elsewhere (8,9,22). Grain elevator workers with abnormal chest x-rays and/or the presence of any respiratory symptoms (wheeze, dyspnea, cough or sputum) and asthma at baseline (cycle II) were not included in this report. Information on wheezing was based on responses to two questions: “Does your chest ever sound wheezing or whistling?” and “Do you get this most days and nights?”. The presence of dyspnea was determined from the question: “Are you troubled by shortness of breath when hurrying on level ground or walking up a slight hill?”. The presence of cough and phlegm was determined if the symptom was present in the morning, or during the day or night for more than three months a year for two years. The development of a first episode of wheezing was the main interest of the present investigation, and only asymptomatic subjects at baseline were included in the analysis. Data from one province did not conform to the standards established by Labour Canada (22), and therefore these data were not included in the analysis. Data from cycle I were not included in this analysis because the follow-up between cycle I and cycle V was incomplete.

Study sample: At baseline (cycle II), 5493 male grain workers from 27 grain elevator companies participated in the study. Complete information was available on 4671 subjects. Of these subjects, 1919 participated only in cycle II and were excluded from the analysis. Significant differences were observed in age, height, forced vital capacity (FVC), FEV_1, ratio of FEV_1:FVC and smoking between subjects who were studied again in cycle III, cycle IV or cycle V (n=2752) and those who were excluded (n=1919). Among the former group (n=2752), 1848 subjects were symptom-free (asymptomatic) and 904 subjects (symptomatic) reported one or more respiratory symptoms (n=903), had abnormal x-rays (n=82) or had physician-diagnosed asthma (n=6). Table 1 shows the comparison of baseline characteristics between asymptomatic (n=1848) and symptomatic (n=904) subjects. Symptomatic subjects were significantly older, had a longer duration of employment, smoked more and had lower mean values for pulmonary function measurements in comparison with asymptomatic subjects. Only asymptomatic subjects were considered for the analysis to determine the predictors of first episode of wheezing.

Smoking behaviour: Smoking information available at baseline and end-point was used to define the smoking behaviour variable for statistical analysis. Subjects who were nonsmokers at baseline and at end-point were allocated to the lifetime ‘nonsmoker’ category. The ‘exsmoker’ category comprised subjects who reported smoking at the baseline and denied smoking at the end-point, subjects who were exsmokers at the baseline and at the end-point, and subjects who were exsmokers at the end-point. A subject who reported smoking at the end-point was considered a ‘current smoker’.

Statistical methods: Annual rate of decline in lung function was calculated for each subject by dividing the difference between the baseline and end-point lung function measurements by the time period between the baseline and end-point. Baseline characteristics of asymptomatic subjects who developed wheezing during 1981 to 1993 were compared with subjects who did not develop wheezing during this period. Two sample *t* tests were used to compare the continuous variables age, FEV_1, FVC, FEV_1:FVC ratio, and duration of follow-up. The χ^2 test was used for comparisons of the categorical variable smoking behaviour.

Survival analysis techniques were used to determine the risk factors for a first episode of wheezing. The time of origin for survival analysis was cycle II, and the end-point was either cycle III, cycle IV or cycle V, depending on when the subject last participated in the surveillance program. Survival time is the period from cycle II to the cycle in which the subject reported an episode of wheezing. Censoring occurred in this study when a subject did not report an episode of wheezing at any cycle. Censoring time was defined as the period

TABLE 1
Baseline characteristics of asymptomatic and symptomatic grain workers who continued to work at the beginning of cycle II

Characteristic	Asymptomatic at cycle II (n=1848), mean (SD)	Symptomatic at cycle II (n=904), mean (SD)
Age (years)	34.0 (11.4)	38.3 (12.2)*
Years in industry	9.9 (8.7)	13.7 (9.8)*
FEV_1 (L)	4.2 (0.7)	3.9 (0.8)*
FVC (L)	5.3 (0.8)	5.1 (0.9)*
FEV_1:FVC ratio	80.2 (6.6)	76.6 (8.1)*
Smoking status, n (%)		
Nonsmokers	635 (34.4)	151 (16.7)
Exsmokers	526 (28.5)	204 (22.6)
Current smokers	687 (37.2)	549 (60.7)**

**P<0.0001; **P<0.001. Cycle II Measurements taken from October 1981 to September 1984; FEV_1 Forced expiratory volume in 1 s; FVC Forced vital capacity*

TABLE 2
Proportions of respiratory symptoms among grain workers who were symptomatic at cycle II (n=904)

Symptom	Cycle II (n=904) n (%)	Cycle III (n=691) n (%)	Cycle IV (n=366) n (%)	Cycle V (n=337) n (%)
Wheeze	375 (41.5)	239 (34.6)	51 (13.9)	37 (11.0)
Dyspnea	318 (35.2)	158 (22.9)	60 (16.4)	44 (13.1)
Cough	441 (48.7)	244 (35.3)	105 (28.7)	83 (24.6)
Sputum	439 (48.5)	256 (37.1)	95 (26.0)	67 (19.9)

Cycle II Measurements taken from October 1981 to September 1984; Cycle III Measurements taken from October 1984 to September 1987; Cycle IV Measurements taken from October 1987 to September 1990; Cycle V Measurements taken from October 1990 to September 1993

from cycle II to the last cycle in which the subject participated without a report of wheezing.

The variables considered in the analysis were age, exposure years in the grain industry, height, smoking behaviour and FEV_1:FVC ratio at baseline. Exposure years in the grain industry were divided into three categories: less than 10 years; 10 or more years but less than 20 years; and 20 years or more. Two dummy variables for exposure years were used in the analysis.

Cox's proportional hazards model (24) is of the form:

$$\log[h(t|x)/h_0(t)]=\exp(\beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_4 x_4 + \beta_5 x_5 + \beta_6 x_6 + \beta_7 X_7)$$

where $h(t|x)/h_0(t)$ is the hazard ratio and five variables in the model represent age at baseline (x_1), dummy variable for exposure years 10 years or more but less than 20 years (x_2), dummy variable for exposure 20 years or more (x_3), height at baseline (x_4), dummy variable for exsmokers (x_5), dummy variable for current smokers (x_6) and ratio FEV_1:FVC at baseline (x_7). One important assumption of the hazards model is that different individuals have hazard functions that are proportional to one another. The validity of the assumptions made in Cox's model was tested by fitting the interaction between time and significant predictor variables (age and FEV_1:FVC ratio) one at a time (23). For example, to test the proportionality assumption for age, a Cox's model with age and the product of age and survival time as predictor variables were fitted.

Survival analysis techniques were used in a similar manner as above to examine the predictors for first episode of dyspnea, cough or sputum.

TABLE 3
Distribution of first episode of wheezing and censoring during follow-up

Follow-up	Baseline* symptom-free	Cycle III wheeze	Cycle IV wheeze	Cycle V wheeze	Censoring at end-point
Cycle II to cycle V	808	46	17	32	713
Cycle II to cycle IV	358	25	14	–	319
Cycle II to cycle III	682	69	–	–	613
Total	1848	140	31	32	1645

Cycle II Measurements taken from October 1981 to September 1984; Cycle III Measurements taken from October 1984 to September 1987; Cycle IV Measurements taken from October 1987 to September 1990; Cycle V Measurements taken from October 1990 to September 1993

TABLE 4
Characteristics of grain workers who reported wheezing compared with those who did not report wheezing during the study period

Characteristic	Wheezing reported, mean (SD) (n=203)	No wheezing reported, mean (SD) (n=1645)
Age (years)	35.5 (11.4)	33.8 (11.4)
Height (cm)	175.6 (6.8)	174.9 (6.5)
Duration of follow-up (years)	4.4 (2.1)	6.0 (2.6)**
FEV_1		
Baseline (L)	4.15 (0.8)	4.23 (0.7)
End-point (L)	3.85 (0.9)	4.04 (0.8)***
Annual rate of decline (mL)	85.3 (143.3)	39.3 (97.4)**
FVC		
Baseline (L)	5.32 (0.9)	5.26 (0.8)
End-point (L)	5.00 (1.0)	5.08 (0.9)
Annual rate of decline (mL)	88.2 (155.1)	40.0 (114.7)***
FEV_1:FVC ratio		
Baseline (%)	78.0 (7.1)	80.5 (6.5)**
End-point (%)	76.6 (8.5)	79.7 (7.0)**
Annual rate of decline (%)	0.4 (1.6)	0.1 (1.2)****
Smoking behaviour† n (%)		
Nonsmokers	45 (22.2)	539 (32.8)
Exsmokers	59 (29.1)	627 (38.1)
Current smokers	99 (48.8)	479 (29.1)*

**P<0.0001; **P< 0.001; ***P< 0.01; ****P< 0.05; †Smoking behaviour was calculated from all cycles (refer to Subjects and methods section). FEV_1 Forced expiratory volume in 1 s; FVC Forced vital capacity*

RESULTS

Table 2 shows the proportions of symptoms (wheeze, dyspnea, cough and sputum) in cycle III, cycle IV and cycle V among 904 workers who were symptomatic at cycle II.

TABLE 5
Proportional hazard regression analysis to identify predictors for development of any symptom in grain workers

	Symptom							
	Wheeze		Dyspnea		Cough		Sputum	
Variable	Odds ratio	95% CI	Odds ratio	95% CI	Odds ratio	95% CI	Odds ratio	95% CI
Age	1.01	1.00-1.03	1.06	1.04-1.09	1.01	1.00-1.03	1.02	1.00-1.04
Years in industry								
≥10 and <20	1.06	0.73-1.52	1.06	0.68-1.66	1.00	0.68-1.45	0.86	0.58 -1.28
≥20	1.06	0.62-1.83	1.23	0.70-2.17	0.82	0.44-1.52	0.88	0.48-1.61
Height	1.02	0.99-1.04	1.02	1.00-1.05	1.00	0.98-1.02	1.01	0.99-1.03
Exsmoker	0.93	0.62-1.38	1.11	0.68-1.81	1.14	0.70-1.86	1.16	0.73-1.03
Current smoker	2.33	1.63-3.33	2.15	1.32-3.48	4.68	3.08-7.11	3.63	2.42-5.46
FEV_1:FVC ratio	0.02	0.003-0.20	0.17	0.01-2.56	0.06	0.006-0.62	0.07	0.007-0.78

FEV_1 Forced expiratory volume in 1 s; FVC Forced vital capacity

At cycle II, 41.5% reported wheeze, followed by 34.6% at cycle III, 13.9% at cycle IV and 11.0% at cycle V. Fewer subjects reported dyspnea at cycle II (35.2%) and cycle III (22.9%). There was a decreasing trend for all symptoms over the study period suggesting a 'healthy worker' effect.

Table 3 shows the distribution of the first episode of wheezing and censoring during the study period from cycle II to the end of the study.

Table 4 shows demographic, smoking and lung function test values in the asymptomatic grain workers at baseline, who subsequently reported an episode of wheezing during the study period compared with those who remained wheeze-free. The proportion of current smokers was significantly higher among those who reported wheezing (48.8%) than among those who did not report wheezing (29.1%). Baseline and end-point FEV_1:FVC ratios were significantly higher for those who did not report wheezing compared with those who reported an episode of wheezing. Crude annual decline in FEV_1, FVC and FEV_1:FVC ratio were significantly higher for those who reported wheezing than for those who did not report wheezing. Similar trends were observed for annual declines in FVC and FEV_1:FVC ratio.

Table 5 shows the results of fitting Cox's proportional hazards model to identify predictors for development of wheezing, dyspnea, cough and sputum in the grain workers. Because age and years in grain industry were highly correlated (Pearson's correlation coefficient = 0.776, P<0.001), models were fitted with and without including age. When age was included in the model, relative risk for years in industry was reduced, so age was kept in the model. Baseline FEV_1:FVC ratio and smoking behaviour during the study period were significant predictors of first episode of wheezing after adjusting for height. Those who had higher FEV_1:FVC ratio at baseline experienced a protective effect (relative risk [RR] 0.02; 95% CI 0.003 to 0.20) against developing wheezing in the multivariate model. Current smokers were at increased risk (RR 2.33; 95% CI 1.63 to 3.33) of developing wheeze after controlling for age, height, FEV_1:FVC ratio and exsmoking status. Significant predictors for first episode of dyspnea were age and current smoking. For first episode of cough or first episode of sputum, significant predictors were current smoking and baseline FEV_1:FVC ratio. A similar analysis was conducted to examine the predictors for development of wheezing and dyspnea together in grain workers. Years in the industry, current smoking and FEV_1:FVC ratio were significant predictors of first episode of wheezing and dyspnea in the absence of age in the model. A dose-response relationship was also observed between years in the industry and the first episode of wheezing and dyspnea. When age was included, years in industry was not significant. Similar analyses were conducted for cough and sputum together. Years in the grain industry was not a significant predictor for first episode of cough, sputum, or cough and sputum. Smoking and FEV_1:FVC ratio were significant predictors for cough and sputum together.

'Years in the grain industry' was used as a surrogate for personal dust exposure. However, personal dust samples were available for 17 of the grain elevator companies that participated in the study. The dust samples were collected by the Labour Canada regional inspectional staff in response to specific complaints and at the discretion of the inspectors. A total of 340 grain dust samples was available from 14 terminal elevators and 190 samples from three primary elevators from 1980 to 1983. No identifiers were available, maintaining confidentiality. Therefore, dust level measurement data were not matched with symptoms and lung function test values. However, analysis of the 530 grain dust samples showed that workers in certain job classifications were exposed to higher dust levels than were others. Based on this analysis three job categories were created: mean dust levels greater than 10 mg/m^3 (highest exposed group); mean dust levels 10 mg/m^3 or less but more than 5 mg/m^3 (moderately exposed group); and mean dust levels 5 mg/m^3 or less (lowest exposed group). The 1849 workers from 27 companies were grouped into the three job categories based on the information obtained about these companies. This categorization was used as a surrogate index of dust exposure. When two dummy variables were included as indicators of three job categories in Cox's model with other predictors, the dummy variables were not statistically significant.

Figure 1 shows wheeze-free survival probability curves stratified by smoking behaviour and FEV_1:FVC ratio. Nonsmokers with FEV_1:FVC ratio 70% or more had the lowest risk of developing wheeze during the study period, and current smokers with FEV_1:FVC ratio less than 70% had the highest risk of developing wheeze. The validity of the proportionality assumption of the predictor variables, age and ratio of FEV_1:FVC were tested by fitting time-dependant variables in the model. The time-dependant variables were not significant in the model, indicating that the proportionality assumption was valid for these variables.

DISCUSSION

The objectives of the statistical analysis in this paper were to observe determinants of first episode of wheezing and to determine the magnitude of the risk of developing first episode of wheezing for particular predictors adjusting for other factors. Several conclusions can be drawn from this analysis of longitudinal data of grain workers who participated in any one or more surveillance cycles over a 12-year period. The group of nonsmokers with an FEV_1:FVC ratio 70% or greater had the best survival function for not developing wheeze compared with nonsmokers with an FEV_1:FVC less than 70% and smokers with FEV_1:FVC greater or less than 70%. The risk of the onset of wheezing also increased with age.

The incidence of first wheeze was highest in cycle III (the first cycle after the baseline) and was followed by a decreasing trend. A similar trend was observed for the incidence of wheezing and dyspnea. This could be the result of a number of factors. There may have been a healthy worker effect (24) in the populations, and the population that was followed up after cycle III might be healthier than those who were lost to follow-up. Other factors may include improved working conditions and job seniority, which could lead to less dusty working conditions for more senior workers.

The association between first onset of respiratory symptoms and occupational exposure has been investigated in other industries (25). Kongerud and Samuelson (25) in a prospective study of respiratory health in aluminium potroom workers found that 8.1% of workers reported dyspnea and wheezing during follow-up. Our results showed that 11.0% of asymptomatic grain workers developed wheezing during an observation period of nine years. During the study period, 11.5% of grain workers reported wheezing or dyspnea and 3.6% reported a combination of wheezing and dyspnea (data not shown). Konegerud and Samuelsen (25) used a proportional hazards analysis to determine the predictors of the development of dyspnea and wheezing. They found that smoking and total fluoride exposure were the most important predictors. They reported that the risk of developing dyspnea and wheezing among smokers was two to three times higher than that for nonsmokers. Our data show that the risk of developing wheezing among current smokers was 2.3 times that of nonsmokers.

In a prospective study of middle-aged and older men who initially denied any history of wheezing and asthma, current smoking was the strongest independent predictor of an onset of wheezing (20). We also found that current smoking was a risk factor for a first episode of wheezing.

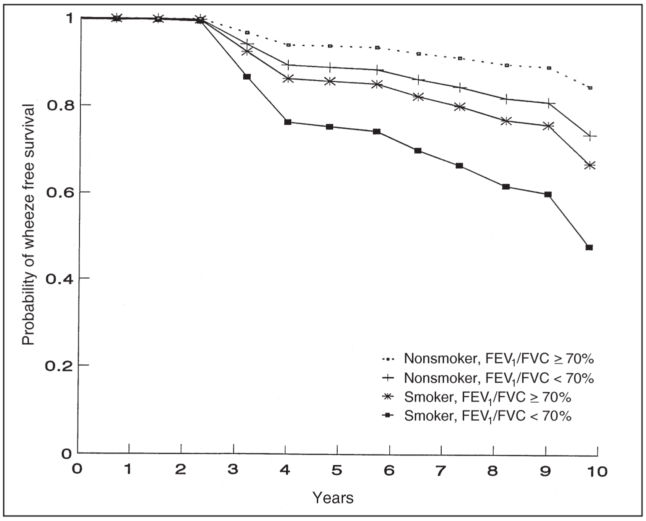

Figure 1) *Wheeze-free survival probabilities categorized by smoking behaviour and the ratio of forced expiratory volume in 1 s to forced vital capacity (FEV_1:FVC)*

McDuffie et al (8) reported on the respiratory health status of 3098 Canadian grain workers studied longitudinally at two different time point, 1981 to 1984 (cycle II) and 1984 to 1987 (cycle III). The frequency of chronic sputum production and chronic wheeze changed significantly from cycle II to cycle III. Obstructive lung dysfunction was more prevalent and increased from cycle II to cycle III. In the present analysis we found that grain workers with lower lung test values were at increased risk of developing wheeze.

A limitation of our study was that dust concentrations in the grain elevators at the work place could not be matched to individual workers and, therefore, could not be used as predictors for a first episode of wheezing.

Our analysis was aimed at evaluating predictors for the development of wheeze among initially symptom-free grain workers studied longitudinally. This study provides evidence that among Canadian grain elevator workers independent predictors of future development of wheezing are current smoking and baseline FEV_1:FVC ratio; independent predictors of future development of dyspnea are age and current smoking; independent predictors of future development of cough are current smoking and baseline FEV_1:FVC ratio; and independent predictors of future development of sputum are current smoking and baseline FEV_1:FVC ratio.

ACKNOWLEDGEMENTS: This study was supported by Labour Canada. The writers thank the physicians, scientists and a number of occupational health services, primarily in grain companies who collected the information on this project across Canada, according to the guidelines established by Labour Canada.

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