Atopy, smoking, and chronic bronchitis

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SUMMARY The aim was to test the hypothesis that atopy increases the occurrence of chronic bronchitis. Relations between atopy, smoking, and chronic bronchitis were studied in farmers. The data were from two successive postal surveys and a skin prick tested subsample. The cross-sectional study consisted of 9017 farmers. Those 6899 farmers who did not have chronic bronchitis at the beginning and who continued farming were followed for three years. A sample of 150 farmers was skin-tested with 36 allergens. The prevalence of chronic bronchitis (rate per 1000), standardised for age and sex, was 41 in non-atopic non-smokers, 101 in atopic non-smokers, 106 in non-atopic smokers, and 257 in atopic smokers (effect of atopy: $p < 0.001$; effect of smoking: $p < 0.001$). The standardised incidence rates of chronic bronchitis (per 1000 farming years) were 14, 34, 36, and 50, respectively (atopy: $p < 0.001$; smoking $p < 0.001$). The relative risk of chronic bronchitis, calculated from the incidence data adjusting for the effects of age, sex, smoking or atopy by logistic regression analysis was 2.2 for atopy (95% confidence interval 1.8-2.7) and 2.3 for smoking (1.8-2.9). Only 20 farmers had chronic bronchitis in the skin-tested subjects; the results were consistent with the findings in the surveys but did not reach statistical significance for atopy. In conclusion, atopy and smoking have independent and additive effects on the occurrence of chronic bronchitis at least in dusty farming work.

Extensive follow-up studies by Fletcher and co-workers¹ revealed smoking to be an important determinant in the aetiology of chronic bronchitis. In the early 1960s, Orie and co-workers² proposed, on the basis of similarities between asthma and chronic bronchitis, that the two diseases may have a similar genetically determined pathogenesis. In the literature, this proposal concerning the development of chronic bronchitis is referred to as the Dutch hypothesis.¹ Reports on the possible role of asthma and atopy in the evolution of chronic bronchitis are conflicting. This study explores the possible association between atopy and chronic bronchitis in cross-sectional and follow-up material.

Materials and methods

The data were from the 'Farmers' occupational health programme' conducted in Finland during 1979-83. The programme, which has been described elsewhere,³ included postal surveys in October 1979 and October 1982, skin prick testing in 1980-81, and in selected

regions medical examinations in 1980-82.

The first questionnaire was sent to 13 231 active farmers in 14 municipalities in various farming regions of the country; 12 056 (91.1%) responded. After exclusions for incomplete data on respiratory diseases or smoking, 9464 questionnaires were available for the cross-sectional study.

The three-year follow-up study included only persons who had not had chronic bronchitis in the cross-sectional study. The follow-up was feasible only among farmers who continued farming for three years. The follow-up questionnaire was sent to 7985 persons still active in farming; 7425 (93.0%) responded. When farmers with incomplete data on respiratory diseases had been excluded, 7422 questionnaires remained for analysis.

The questionnaires were self-administered. They contained questions about the health, habits, work, and socioeconomic background of the farmers.

An individual was excluded from further analyses if he had answered 'yes' to the direct question 'Do you have asthma?' or had reported symptoms suggestive of

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farmer's lung. The subject was considered to have symptoms of farmer's lung if he had suffered from a prolonged cough, dyspnoea, or fever during October to May inclusive. In addition, the symptoms had to appear or worsen while the respondent took care of cattle, cleaned the cow house, or milled fodder grain.

After exclusion, 9017 farmers remained in the cross-sectional study, 4660 men and 4357 women. The mean age was 45.6 years, 44.8 years for men and 46.5 years for women. Age, sex, and social distributions of the sample were similar to those of the entire Finnish farming population of working age.

Those 3039 farmers who returned the first questionnaire but were not included in the cross-sectional study had the following (hierarchical) reasons for exclusion: incomplete data on chronic bronchitis (46.7%) or other respiratory diseases (31.5%), smoking information missing (7.1%), reported asthma or farmer's lung (14.7%). Information on atopy was available for 1138 excluded

farmers; 892 (78.4%) were atopic. For farmers with incomplete data on chronic bronchitis, information on atopy was available in 20.4% and information on smoking in 77.6%; 95.5% of these were atopic and 19.2% smokers. About half of those who had incomplete data on respiratory disease according to the cross-sectional survey yielded incomplete data on respiratory disease also according to the follow-up survey; 40.6% were healthy and 7.3% had chronic bronchitis. Formation of the cross-sectional study population is shown in the figure (a).

After exclusions due to asthma or farmer's lung, the follow-up study consisted of 6899 farmers, 3497 men and 3402 women. Their mean age at the beginning of the follow-up was 45.2 years, 44.2 years for men and 46.1 years for women.

Those 2118 farmers who were included in the cross-sectional but not in the follow-up study had the following (hierarchical) reasons for exclusion: chronic bronchitis at the beginning of the follow-up (33.9%),

Formation of (a) cross-sectional, and (b) follow-up study populations. ← = questionnaire.

died (6.6%), retired (14.1%), stopped farming (14.8%), did not respond to the second questionnaire (5.8%), incomplete data on chronic bronchitis or other respiratory diseases (0.1%), reported asthma or farmer's lung (24.7%). Information on atopy was available for 1213 excluded farmers who did not have chronic bronchitis at the beginning of the follow-up: 426 (35.1%) were atopic. There was only one subject among excluded farmers with incomplete data on chronic bronchitis and he was an atopic smoker. Formation of the follow-up study population is shown in the figure (b).

In one of the municipalities, all farmers with any skin disease in the first survey and an equal number of randomly selected farmers without skin disease were skin-tested using the prick technique. After exclusions for asthma and farmer's lung, relevant data were available for 150 individuals, 63 men and 87 women. The mean age was 43.3 years, 43.7 years for men and 42.9 years for women.

The questions about chronic bronchitis were modified from the standardised Medical Research Council questionnaire on respiratory symptoms. The farmer was classified as having chronic bronchitis if he had brought up phlegm on most days for at least three months a year during at least two consecutive years.^{4,5} The validity and reliability of the questionnaire have been previously investigated.⁶ A random subsample of 194 farmers with chronic bronchitis, as defined by the questionnaire, participated in the medical examination. Four had either asthma or farmer's lung but not chronic bronchitis. Thus about 2% of the cases were falsely defined by the questionnaire as chronic bronchitis because they had other respiratory diseases.

A farmer was classified as a smoker if he had smoked at least one cigarette or the equivalent in another tobacco product per day for one year and smoked at the beginning of the follow-up. An ex-smoker had smoked similarly earlier; he was not asked when he had stopped smoking.

A farmer was classified as atopic if he presently suffered or previously had suffered from infantile eczema, atopic dermatitis, or hay fever or other allergic rhinitis. The data on atopy were missing for 1495 farmers in the cross-sectional study and for 1130 farmers in the follow-up study.

The allergen panel in prick tests included 36 common and farming related allergens: birch, alder, meadow foxtail, orchard, meadow fescue, rye grass, timothy, smooth meadow grass, mugwort, daisy, dandelion, house dust, fish, oat flour, barley flour, rye flour, wheat flour, house dust mite, horse epithelium, dog epithelium, cat epithelium, cow epithelium, pig epithelium, sheep wool, hen feathers, *Alternaria iridis*, *Candida albicans*, *Cladosporium herbarum*, *Aspergillus fumigatus*, *Aspergillus glaucus*, *Penicillium expansum*,

Aureobasidium pullulans, *Fusarium roseum*, *Trichophyton mentagrophytes*, as well as crude and dialysed fodder yeast extracts. The positive control was a glycerol solution of histamine chloride and the negative control a glycerol-saline diluent of the allergens. The allergens were applied onto the volar surfaces of both arms and pricked with disposable needles. An individual was considered to be skin test positive when the product of the two perpendicular diameters of the skin reaction (an estimate of the weal area) to at least one of the allergens was 6mm² or more.

The prevalence and incidence rates of chronic bronchitis were standardised for age and sex differences of the comparison groups by the direct method. The total sample was a standard population. For standardisation, sex-specific ten-year age groups were formed. Analysis of variance (ANOVA) was applied in statistical testing. Adjusted relative risks of chronic bronchitis for atopy and smoking were estimated by logistic regression models; other variables included were age (as such) and sex.

Relative risks of chronic bronchitis for specific symptoms and signs of atopy were calculated in the same way. Possible effects of incomplete information about atopy and smoking (originally a reason for exclusion from the study) on relative risks of chronic bronchitis were accordingly estimated. The group with incomplete data was successively included into one and another of the possible categories of the variable. The procedure was repeated in all possible permutations.

Results

In the cross-sectional study, 28% of the farmers had atopy and 18% smoked. The prevalence of chronic bronchitis was 80 per 1000. In the follow-up study, 26% had atopy and 16% smoked. The incidence of chronic bronchitis was 22 per 1000 farming years.

The farmers who had no data on atopy were put into the non-atopic group in further analyses. This was considered to be justified since the majority of farmers were non-atopic. One hundred and sixteen of them had and 84 developed chronic bronchitis. The standardised prevalence and incidence rates of chronic bronchitis among ex-smokers were almost identical with the rates among non-smokers in both non-atopic and atopic farmers. In further analyses ex-smokers were combined with non-smokers.

The standardised prevalence rate of chronic bronchitis was 2.5 times larger in atopic than in non-atopic farmers among non-smokers (table 1). It was 2.4 times larger in atopic smokers than in non-atopic smokers. The rate was 2.6 times larger in smokers than in non-smokers among non-atopic farmers and 2.5 times larger in smokers than in

*Atopy, smoking, and chronic bronchitis*Table 1 *Prevalence of chronic bronchitis according to atopic status and smoking habits among 9017 farmers*

Smoking status	Non-atopic farmers*			Atopic farmers		
	Chronic bronchitis	Total group	Prevalence (per 1000)	Chronic bronchitis	Total group	Prevalence (per 1000)
Non-smokers†	212	5293	41	214	2088	101
Smokers	174	1198	106	117	438	257

ANOVA: Atopy, $p < 0.001$; smoking, $p < 0.001$; interaction of atopy and smoking, $p < 0.05$.

*1495 farmers with unknown atopic status included.

†Ex-smokers included.

In tables 1 to 3 the rates have been standardised for the effects of age and sex by the direct method.

non-smokers among atopic farmers. Atopy and smoking together increased the prevalence to 6.3-fold. The age and sex adjusted interaction of atopy and smoking on the prevalence of chronic bronchitis was statistically significant ($p < 0.05$).

The relative risk of chronic bronchitis in atopic farmers was 2.6 (95% confidence interval 2.2–3.0) with adjustment for differences between the groups in age, sex, and smoking habits by logistic regression analysis (the risk for non-atopic individuals was taken as 1.0). Relative risk of chronic bronchitis in smokers was 3.5 (2.9–4.1) after adjustment for age, sex, and atopy.

During the three-year follow-up period 452 farmers developed chronic bronchitis. The standardised incidence rate was 2.4-fold in atopic, non-smoking farmers compared to that in non-atopic farmers who did not smoke (table 2). It was 1.4 times larger in atopic smokers than in non-atopic smokers. Smoking

increased the rate to 1.5–2.6-fold. Atopy and smoking together increased the incidence to 3.6-fold. The age and sex adjusted interaction of atopy and smoking on the incidence of chronic bronchitis was statistically significant ($p < 0.01$).

The adjusted relative risk of chronic bronchitis for atopy was 2.2 (95% confidence interval 1.8–2.7) and for smoking 2.3 (1.8–2.9) when the effects of age and sex, smoking or atopy were controlled by logistic regression analysis.

This pattern of occurrence for chronic bronchitis according to smoking and atopy was consistent when atopy was broken down to specific symptoms and signs.

In the subgroup of 150 skin-tested farmers, only 20 had chronic bronchitis. Those with a positive skin test reaction against any of the 36 allergens had chronic bronchitis about two to four times as frequently as those with negative skin tests (table 3).

Table 2 *Incidence of chronic bronchitis according to atopic status and smoking habits among 6899 farmers (in 20 697 farming years)*

Smoking status	Non-atopic farmers*			Atopic farmers		
	Chronic bronchitis	Farming years	Incidence (per 1000 farming years)	Chronic bronchitis	Farming years	Incidence (per 1000 farming years)
Non-smokers†	176	12792	14	152	4689	34
Smokers	85	2439	36	39	777	50

ANOVA: Atopy, $p < 0.001$; smoking, $p < 0.001$; interaction of atopy and smoking, $p < 0.01$.

*1130 farmers with unknown atopic status included.

†Ex-smokers included.

Table 3 *Prevalence of chronic bronchitis according to skin reactivity and smoking habits*

Smoking status	Skin reaction negative ($< 6\text{mm}^2$)			Skin reaction positive ($\geq 6\text{mm}^2$)		
	Chronic bronchitis	Total group	Prevalence (per 1000)	Chronic bronchitis	Total group	Prevalence (per 1000)
Non-smokers*	4	65	63	9	66	134
Smokers	3	11	179	4	8	760

ANOVA: Skin reactivity, not significant; smoking, $p < 0.001$; interaction of skin reactivity and smoking, not significant.

*Ex-smokers included.

When the farmers with missing data on atopy were all considered atopic in the logistic regression analyses, the estimated relative risk of chronic bronchitis for atopy was 2.2 (95% confidence interval 1.9–2.6) in the cross-sectional material and remained unchanged in the follow-up material. The relative risks of chronic bronchitis for atopy remained unchanged regardless of whether all farmers with unknown smoking habits (otherwise excluded from the analyses) were considered to be smokers or non-smokers.

Discussion

A considerable proportion of patients with chronic bronchitis have never smoked.¹ The disease occurs also among persons without any relevant occupational exposure even in unpolluted areas of the world.^{7–9} There are several common characteristics in chronic bronchitis and asthma.² Controversial results of the possible role of asthma in the development of chronic bronchitis may have been caused by the fact that asthma represents an only partly atopic disposition. This study dealt with atopy as a predisposing factor in chronic bronchitis and with smoking as a known risk factor.

As expected, smoking was associated with chronic bronchitis in all of the studied materials. Atopy was also associated with chronic bronchitis. Both the prevalence and incidence of chronic bronchitis were about twice as large among atopic as among non-atopic individuals. The relative risks of chronic bronchitis were virtually the same for those with atopy as for those who smoked. Atopy and smoking had an independent and additive effect on the occurrence of chronic bronchitis.

The results of the two cross-sectional studies and of the follow-up study were consistent, and the quantitative estimates for the associations were of the same magnitude.

Atopy is not an unequivocal entity.¹⁰ It has been suggested that, regardless of symptoms, a person should be classified as atopic if specific IgE antibodies to common allergens are found either serologically or by positive reactions in skin tests.¹¹ Such a definition is not easy to apply in an extensive epidemiological study. In this study, the presence of symptoms generally accepted as atopic manifestations¹⁰ were applied to define atopy. The independent examination of atopy by skin tests confirmed the relation between atopy and chronic bronchitis.

In this study, chronic bronchitis was defined according to criteria presented by the Ciba Guest Symposium⁴ and the American Thoracic Society.⁵ The questionnaire method is not, however, reliable for diagnosing chronic bronchitis when the individual also has asthma or farmer's lung. Therefore, it was

considered necessary to exclude these individuals from the analyses. In a validation study based on the remaining material, only about 2% of the farmers classified to have chronic bronchitis but not asthma or farmer's lung were misclassified due to asthma or farmer's lung. Thus the results are not explained by the simultaneous presence of other chronic respiratory diseases common in farming populations in the farmers defined as having chronic bronchitis, nor are they explained by the misclassification of individuals with previously undiagnosed asthma or farmer's lung into the group of farmers with chronic bronchitis.

The possibility of bias due to differences in the way individuals with and without atopic symptoms replied to the survey questions concerning symptoms of chronic bronchitis cannot be totally excluded. In particular, symptoms of allergic rhinitis could have been confused with symptoms of chronic bronchitis. Nevertheless, it is not likely that the bias would have been large enough to account for the observed results. This is supported by the finding that, even in the absence of allergic rhinitis, different signs of atopy, such as allergic conjunctivitis, infantile eczema, and atopic dermatitis, were all associated with chronic bronchitis.

Incomplete information on atopy and smoking could not have been the reason for the observed associations. Even an extreme selection bias had not changed the results, as shown by the specific analyses on the effects of the missing data.

Some subjects in the cross-sectional study were lost because there was no information on chronic bronchitis. The main reason for incomplete data apparently was that the questionnaire was rather extensive (142 questions). It is possible that the response to the questioning was related to the presence of either atopy or chronic bronchitis. Even if it was, the results could have been explained only by heavy under-reporting of the farmers with chronic bronchitis when they did not have atopy. Similar bias could have been caused by under-reporting of the atopic farmers when they did not have chronic bronchitis. Either possibility is not likely.

Similar considerations apply to the losses of follow-up in the longitudinal study. Here also, effective selection bias is not probable. Farmers cannot easily change their occupation and leave the land. The results can be explained only by a hypothetical situation in which healthier persons give up farming and sick persons continue.

In an epidemiological study, Burrows and co-workers¹² showed that symptoms suggestive of chronic bronchitis were more common among skin test positive than among skin test negative individuals. This association was present in only a small subgroup of 10- to 14-year-olds. Later, Burrows *et al.*¹³ found

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that the occurrence of chronic bronchitis was associated with the level of serum IgE.

Among 569 Canadian workers exposed to grain dust, there was no significant difference in the prevalence of respiratory symptoms between atopic and non-atopic subjects.¹⁴ Only wheezing was consistently more common among atopic than among non-atopic individuals. Atopy was defined by a positive skin prick test reaction to mixed grass pollen or to house dust mite. In another series of 18 skin test positive and 18 skin test negative grain elevator workers, there was no association between positive skin test reaction and respiratory symptoms or pulmonary function.¹⁵ Other studies have also failed to identify any association between chronic bronchitis and atopy in grain workers.¹⁶⁻¹⁸

The conflicting results on the relation between atopy and chronic bronchitis in the studies cited may be explained by the small samples, self-selection of hyperreactive individuals from grain elevator work, or the use of few or mixed allergens in skin testing. The relatively weak association between atopy and chronic bronchitis observed in the current study could easily have been missed in a small sample.

The observed predisposing effect of atopy on the occurrence of chronic bronchitis might be due to the work environment of the farmers. Farmers are known to be frequently exposed to organic dusts. This exposure may favour the development of both chronic bronchitis and symptoms of atopy in subjects with an atopic predisposition. The relation of chronic bronchitis and atopy calls for further studies in different exposure conditions.

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