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Influence of hay and animal feed exposure on respiratory status: a longitudinal study

Authors: I. Thaon (1, 2), A. Thiebaut (1), L. Jochault (3), A. Lefebvre (3), J.J. Laplante (4), and J.C. Dalphin (2,3)

(1) Occupational Diseases Department, University Hospital of Besançon, Besançon, F-25000 France ;
(2) UMR 6249 CNRS/Université de Franche-Comté, Laboratoire Chrono-environnement, F-25030 Besançon, France.
(3) Chest Diseases Department, University Hospital of Besançon, Besançon, F-25000 France.
(4) Mutualité Sociale Agricole of Besançon, France

Correspondence and requests for reprints should be addressed to Prof. Jean-Charles Dalphin, Dept. of Chest Diseases, CHU - Hôpital Jean Minjoz, Boulevard Fleming, 25030 Besançon CEDEX, France. Fax: (33) 3 81 66 88 11. Phone: (33) 3 81 66 82 04. E-mail: jean-charles.dalphin@univ-fcomte.fr.

Short title: Respiratory status in farmers

Abstract:

Objectives: To study respiratory symptoms and lung function decline in farmers with particular attention to the influence of handling hay, straw and animal feed.

Methods: From a cohort constituted in 1993-94, 219 dairy farmers (82.6%), 130 non-dairy agricultural workers (62.5%) and 99 controls (66.4%) were re-evaluated in 2006. They answered medical and occupational questionnaires, underwent spirometric tests at both evaluations and pulse oxymetry in 2006.

Results: Dairy and non-dairy agricultural workers showed an increased risk for usual morning phlegm (respective adjusted odds ratio and 95% confidence intervals 4.27 (1.41-12.95) and 3.59 (1.16-11.10). Animal feed handling was associated with increased risks of wheezing (p=0.01) and usual morning phlegm (p=0.04), as was hay or straw handling with wheezing (p=0.008). Adjusted for smoking, age, height, gender and altitude, dairy farmers had greater declines in FEV_1/FVC (p=0.01) than controls. An increased decline in FEV_1 for all agricultural workers was associated with animal feed handling both measured as a categorical value (currently handling versus never handling p=0.05) or quantitative value (years of exposure during the survey period p=0.03).

Conclusions: Hay, straw or animal feed handling represents a risk factor of bronchial symptoms and, for animal feed only, of accelerated decline in expiratory flows.

Key words: asthma – chronic bronchitis – farming – longitudinal studies – respiratory function tests

Introduction

An increased risk of chronic bronchitis has been demonstrated in various agricultural groups [1] notably in swine confinement workers [2, 3], poultry workers [4, 5] and dairy farmers [6-9]. Several cross-sectional studies have reported lung function impairment in agricultural workers [10, 11] - including dairy farmers [8, 9]. An accelerated decline in lung function has been suggested in swine confinement workers [12, 13] and in grain handlers [14]. The results of two controlled longitudinal studies we conducted in French dairy farmers in 1986 and 1994 were discordant. In the 1986-cohort, we found an accelerated decline in forced vital capacity (FVC), and forced expiratory volume in one second (FEV_1), in dairy farmers at five-year follow-up [15], but these results were not confirmed at the second follow-up, twelve years after inclusion [16]. This may be due to an improvement in working conditions leading to a decrease in agricultural exposure over time, as suggested by studies in grain elevator workers [17]. In the 1994-cohort, dairy farmers showed an accelerated decline in FEV_1/FVC at six-year follow-up when compared with controls [18]. Hence, the present study aimed to compare lung function decline for a 12-year follow-up period in the 1994-cohort between dairy farmers, non-dairy agricultural workers and controls and to explore the influence of two situations that engender exposure to organic dust – hay or straw handling and animal feed handling – in dairy and non-dairy agricultural workers.

METHODS

Population

The study population consisted of three groups of both genders, aged 16 to 66 (at baseline), living in the same rural area in the Doubs province. Subjects were selected from the Doubs Mutualité Sociale Agricole (MSA) (Agricultural Health Insurance Mutual) medical files. Every five years, the MSA medical unit organizes free medical examinations for all affiliated members. For the 1993-1994 examinations, we opened recruitment to 353 dairy farmers, 278 non-dairy agricultural workers (poultry farmers, swine workers, fish farmers, beekeepers, herdsmen, cattle inseminators, cheesemakers, forestry workers) and 189 controls (administrative employees from agricultural companies). From February 1993 to May 1994, 265 dairy farmers, 208 non-dairy agricultural workers and 149 controls participated in the first investigations (T1). The T1 results, which compared dairy farmers and controls, were published in 1998 [9]. In 1999 (T2), identical investigations were conducted on the same farmers and controls [18].

In 2006 (T3), we decided to re-evaluate respiratory symptoms and lung function in this 1994-cohort including non-dairy agricultural workers. An explanatory letter concerning the objectives practical value of the study and was sent to all surviving 1993-94 participants (16 subjects had died). Those who agreed to participate were re-evaluated at the same time of year (winter or spring) as for the two previous analyses. Subjects who agreed to participate but could not come to the medical examination (having moved to another province, for example), were asked to answer the questionnaires and return them by mail. The protocol comprised a medical and occupational questionnaire, spirometric tests in 1994 and 2006 and a non-invasive measure of blood oxygen saturation ($Sp0_2$) in 2006 only.

This study respects the ERS principles for research involving humans and was approved by the local ethics committee.

Questionnaires

Occupational and medical questionnaires were sent by mail 10 days before the scheduled medical examination and were collected during the check-up examination. The medical questionnaire was based on the American Thoracic Society (ATS) questionnaire [19] and on the long version of the European Community Respiratory Health Survey questionnaire [20]. Chronic bronchitis was defined as cough and expectoration for 3 months of the year or more for at least two consecutive years. Questions on smoking habits, respiratory symptoms, and history of allergy have been defined previously [9].

The occupational questionnaire was designed by the authors in collaboration with engineers and technicians from the local Department of Agriculture and the MSA. Some questions have been added to the version used in previous studies [9, 16, 18]. Working status in 2006 was designated as: still working (at the same or another job), retired, and unemployed or having stopped working for personal reasons. Dairy and non-dairy agricultural workers were asked if they handled hay or straw - never, currently (in 2006) or formerly (stopped before 2006) and animal feed (including grain and flour but not hay).

Respiratory function tests

Respiratory function tests were performed according to ATS recommendations [21] with a portable pneumotachograph (SpiroPro Sensormedics). A minimum of three adequate measures of FVC, FEV_1, forced mid-expiratory flow ($FEF_{25-75\%FVC}$), and

forced peak flow (PF) were taken and the best blow was selected. The spirometer was calibrated daily for atmospheric pressure, hygrometry and temperature. Values were expressed as absolute values and as percentages of European Community for Steel and Coal (ECSC) reference values, calculated in relation to gender, age and height [22].

Oximetry data

For each subject, arterial oxygen saturation and pulse rate were evaluated with a finger pulse oximeter Onyx® model 9500 (Nonin Medical Inc). Three measurements were performed at 30-second intervals after subjects had spent at least 30 minutes in a heated room, seated for at least 15 minutes. The highest $Sp0_2$ value and corresponding pulse rate were retained.

Data analysis

A first series of analyses was carried out on the 2006 cross-sectional data. Each respiratory symptom was cross-tabulated by farming (dairy farmers, non-dairy-farmers, controls), age, gender, smoking status (current smokers, ex-smokers, never smokers), altitude (below 400m – 400 to 800m – above 800m), working status. Associations between farming groups (reference controls) and respiratory symptoms were evaluated by multiple logistic regressions adjusted for age and smoking. Respiratory symptoms were compared with the same models in dairy and non-dairy agricultural workers for subjects having handled hay or straw (first: currently and/or formerly; secondly and separately: currently or formerly) and for those never having handled hay or straw. The same factors were compared for the animal feed handling. Secondly, the relationship between lung function in 2006 and SpO_2 and exposure

was analyzed with multiple linear regression models adjusted for age, smoking, gender, height, altitude and, only for SpO_2, for pulse rate and predicted percentage of FEV_1.

Finally, longitudinal analyses of respiratory function were performed. The effect of farming (dairy and non-dairy agricultural workers versus controls) on the annual change in lung function parameters between T1 and T3 (2006 value–1994 value/number of years between the T1 and T3 examinations) was tested by multiple linear regressions adjusted for age, smoking, gender, height, altitude and initial value of the parameter in 1994. Then, multiple linear regression models were used to analyze the relation between annual change in respiratory parameters and hay or straw handling or animal feed handling (coded as categorical value – currently, formerly versus never and as quantitative value – years of exposure between T1 and T3). The level of significance is 0.05 but all p-value less than 0.10 are reported. Statistical analyses were carried out using the SAS 9.1.3 package (SAS Institute Inc., Cary, NC, USA.).

Results

Of the 622 who had participated in 1994, 174 were not available for the 2006 study: 11 dairy farmers, 2 non-dairy agricultural workers and 3 controls died before 2006, 20 dairy farmers, 20 non-dairy agricultural workers and 7 controls refused to participate, and 15 dairy farmers, 56 non-dairy agricultural workers and 40 controls were lost to follow-up. Therefore, 219 dairy farmers (82.6%), 130 (62.5%) non-dairy agricultural workers and 99 (66.4%) controls participated in the 2006 follow-up. Thirty-three of the 448 participants (7.4%) only returned their occupational and medical questionnaires. The subjects lost to follow-up or who refused to participate were: more often male (69.5% versus 60.3%, p=0.03), and more often current smokers in 1994 (34.8% versus 19.2%) than those who participated. They were also younger (mean age at baseline 38.5 versus 42.2 p=0.0007). There was no difference in respiratory symptoms or lung function parameters at baseline between subjects who participated and not participated to the follow up.

The main characteristics and comparison of the three exposure groups for the 12-year follow-up participants are reported in table 1. Dairy farmers were more often never smokers than controls and non-dairy agricultural workers were more often current smokers than controls. However at baseline dairy farmers were older (mean age 45.8) more often never smokers (75.3%) than non-dairy agricultural workers (mean age 38.4, never smokers 52.3%) and controls (mean age 37.9, never smokers 57.8%). In 2006, 166 subjects (37.5%) had already stopped working and 280 were still working, however lung function parameters at baseline did not differ between the two groups.

Respiratory symptoms in 2006

Six dairy farmers with hypersensitivity pneumonitis were excluded from the following analyses. Respiratory diseases (asthma, chronic bronchitis, emphysema, pulmonary infections) were more frequent in dairy farmers (Odds ratio (OR) 2.85 interval confidence (IC) 95% [1.20-6.80]) than in controls. The prevalence of respiratory symptoms in the three exposure groups is presented in table 2. After adjustment for age and smoking, usual morning phlegm was more frequent both in dairy farmers – 4.27 OR IC95% [1.41-12.95] – and in non-dairy agricultural workers – OR 3.59 IC95% [1.16-11.10] – than in controls. In the same model, usual morning phlegm was also more frequent in current smokers and in former smokers than in never smokers (OR respectively 4.88 IC95% [2.10-11.34] and 2.29 IC 95% [1.15-4.57]).

Farmers handling or having handled hay or straw seemed to be at an increased risk of wheezing and personal history of allergy. The age and smoking adjusted OR was 3.49 IC95% [1.43-8.54] for wheezing at any moment in their life, and 1.55 IC95% [1.16-2.07] for personal history of allergy. They also reported waking up more during the night due to coughing (adjusted OR 2.73 IC95% [1.02-7.31]).

Farmers handling or having handled animal feed seemed to present increased risks of wheezing at any moment in their life (adjusted OR 2.40 IC95% [1.14-5.04]). They also reported waking up more during the night due to coughing (adjusted OR 2.95 IC95% [1.17-7.39]) and more usual morning cough (adjusted OR 2.75 IC95% [1.03-7.29]).

Subjects who had stopped handling hay or straw or animal feed have higher risks of respiratory symptoms (table 3).

Lung function in 2006

In 2006, dairy farmers had lower PF (mean 101.7% versus 109.0%, p=0.007), FEV_1/FVC (100.1% versus 102.6%, p=0.07) and $FEF_{25-75\%FVC}$ (81.3% versus 87.7% p=0.08) than controls. Current smokers had lower FEV_1 (p=0.05) and FEV_1/FVC (p=0.05) than never smokers. Dairy farmers also had lower $Sp0_2$ than controls (96.06% versus 96.68%, p=0.02 after adjustment for age, smoking, height, gender, altitude, pulse rate and FEV_1).

Lung function decline during follow-up

Lung function parameter decline during follow-up in the three exposure groups is presented in table 4. Dairy farmers had greater declines in FEV_1 and FEV_1/FVC than controls (respectively p=0.04 and p=0.007). After adjustment for smoking, age, height, gender and altitude (table 5), dairy farmers still had a greater decline in FEV_1/FVC (p=0.01) than controls. Non-dairy agricultural workers also showed an increased decline in FEV1/FVC and in $FEF_{25-75\%FVC}$ but these differences did not reach the level of significance. Current handling of animal feed was associated with an increased decline in FEV_1 (p=0.05, table 5). Moreover decline in FEV_1 increased with years spent handling animal feed during the survey period – T1 to T3 (p=0.03, table 5). Current smoking was also associated with an accelerated decline in FEV_1 (p=0.02), FEV_1/FVC (p=0.02) and $FEF_{25-75\%FVC}$ (p=0.0003).

Discussion:

An increased risk in respiratory symptoms related to chronic bronchitis (usual morning phlegm and to a lesser degree usual morning cough) was found in dairy farmers and non-dairy agricultural workers. Dairy farmers also presented an increased decline in FEV_1/FVC and lower $Sp0_2$ than controls. Animal feed handling and hay or straw handling were associated with increased risks of respiratory symptoms and with an increased decline in FEV1 – for animal feeding only. Finally, we found a healthy worker effect indicated by the stronger effect of animal feed, hay and straw handling observed in former than in the current handlers.

This longitudinal study has limitations. We have no measurements of exposure associated with hay, straw or animal feed handling. These parameters were evaluated by self-report questionnaires previously used in dairy farmer studies conducted in the same province [16, 18, 23], one of which included measurements of hay and fodder contamination by microorganisms [23]. We observed high levels of hay contamination by microorganisms, especially in relation to low modernity of farms [23-25] and to bad climatic conditions during hay-making season. In particular, we highlighted a large variability in results in that the concentration of microorganisms differed considerably between farms as well as within the same farm, depending on the time of day and where measures were taken with respect to work patterns and the time of year [26]. The conditions inherent to this type of longitudinal study, with a 12-year follow-up, made it extremely difficult to reach an accurate estimate of the level of professional exposure. In our study, animal feed handling and hay and straw handling were strongly related: only 24.4% had discordant exposures to animal feed and to hay or straw. Similarly in a cross-sectional study recently published on farmers lung function and including personal

measurements of exposures to dust, microorganisms and gas, many agents were strongly correlated [27]. In our study, these correlations of exposures limit the possibility to conclude about the specific role of each exposure on respiratory impairment.

A second limitation concerns the differences in participation rates between the three groups. These differences were not related to increased mortality or more refusals to participate in the non-dairy agricultural workers or in controls than in dairy farmers. They can be explained by an excess of loss to follow-up in non-dairy agricultural workers and controls in that dairy farmers in our area are less likely to move than non-dairy agricultural workers and administrative employees, particularly to find a new job. Subjects lost to follow-up were younger than those who participated. However it is important to note that there was no difference in respiratory symptoms or lung function parameters at baseline between subjects who participated or did not participate in the follow up. Moreover, the difference observed at T3 in age, and smoking rates between dairy farmers and non-dairy agricultural workers and controls, can be related to similar differences observed at baseline. The same differences in smoking rates have been observed in all studies conducted in the same province. However the inclusion of fewer smokers in the dairy farmer group than in the control group would only have lead to a lack of power as smoking is related to an increased risk of lung function impairment. On the other hand, the inclusion of more older farmers than controls would have induced a selection bias but all multiple analyses were adjusted for age.

Finally as we did not perform postbronchodilator spirometries we cannot affirm that the decrease in FEV_1/FVC observed in dairy farmers is related to COPD even if it is the most probably hypothesis since dairy farmers also presented an excess risk of

morning phlegm.

An excess of respiratory symptoms related to chronic bronchitis has been already found in dairy farmers from the same province [15, 16] as well as in other agricultural settings: poultry workers [4, 5], pig farmers [2, 3], flower cultivators [28], grain silo workers [17] and sawmill or wood workers [29]. On the other hand, the accelerated decline in FEV_1/FVC ratio we observed over a long follow-up period has rarely been reported and then, was not reproducible within other agricultural sectors, [14]. Lung function parameters and mean annual changes were correlated with smoking and age. This shows the relevance of our measures and therefore of our results. The decrease in $Sp0_2$ in dairy farmers might not be clinically relevant, even if at this level of the haemoglobin dissociation curve, a small variation in Sp02 corresponds to a greater variation in PaO_2. However this consistent finding [16, 18], probably indicates an alveolar involvement related to occupational exposure.

Our study originally found associations of hay, straw and animal feed (grains and flour) exposures with significant increased risks of asthma and wheezing. In Hoppin et al. study, handling ground animal feed and stored hay was related with an increased risk of wheeze [30]. In addition, animal feed handling, and in particular the number of years of exposure to animal feed, was also associated with an increased decline in FEV1. In Eduard et al. study [27] chronic bronchitis was significantly associated with exposure to all agents except glucans and hydrogen sulfide. In the same study there was an inverse association of FEV1 with organic dust, bacteria, endotoxins, glucans, ammonia, and hydrogen sulphide. Another study carried out in the same area (Eastern Franche-Comté and Switzerland) showed that working in the barn, particularly animal feed handling, was associated with high peaks of air contamination for mold and actinomycetes as well as for poaceae pollens [31].

Conversely, the concentration of airborne bacteria was not significantly influenced by animal feed handling. Therefore, it is likely that the exposure to molds and actinomycetes contributes to the deleterious effect of exposure to hay and to animal feed on respiratory status in our study. Moreover animal feed and straw and hay handling can also induce exposure to organic dust, bacteria, mites, endotoxins, muramic acid, and even-numbered carbon chain length 3-Hydroxy fatty acids. [1, 32] Working on a farm is associated with exposure to numerous inflammatory substances which could contribute to the bronchial involvement observed in our study.[32] The risk for asthma and wheezing generated by this type of exposure might also be linked to a high concentration of pollen.

A final result worth noting was the stronger effect of former exposure to hay, straw or animal feed on respiratory symptoms than the effect of current exposure (table 3). This can probably be explained by the selection effect induced by respiratory diseases [33]. Farmers or agricultural workers who developed respiratory diseases are likely to have stopped dusty tasks. Similarly, Chenard *et al.* found that predicted FEV_1/FVC ratio and $FEF_{25-75\%FVC}$ at baseline were lower in subjects who stopped swine farming compared to those who continued [34]. In Eduard *et al. study* farmers who had left farming had more chronic bronchitis, lower FEV_1 and FVC, and farmers who had changed farm production because of dust-related respiratory problems have an increased prevalence of chronic bronchitis and asthma [27].

Conclusion: Our study shows an excess of usual morning phlegm and an accelerated decline in FEV_1/FVC in dairy farmers. Handling hay, straw and animal feed is probably responsible for the excess of respiratory symptoms in dairy farmers and animal feed handling is associated with an accelerated decline in FEV_1. However our

data are insufficient to affirm a causality relation and the exposure measurement needs to be refined.

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Table 1: Main characteristics of the participants in 2006 in the 3 exposure groups.

	TOTAL	Dairy farmers	Non-dairy agricultural workers *	Controls	p
	n= 448	n=219 (50.0%)	n=130 (28.5%)	n=99 (21.6%)	
Age mean (SD)	54.8 (11.4)	58.0 (11.1)	52.0 (11.2)	51.2 (10.0)	<0.0001
Gender :					
Male	270 (60.3%)	123 (56.2%)	99 (76.2%)	48 (48.5%)	<0.0001
Female	178 (39.7%)	96 (43.8%)	31 (23.8%)	51 (51.5%)	
Smoking status in 2006					
Never n (%)	273 (61.0%)	159 (72.6%)	62 (47.7%)	52 (52.5%)	
Currently n (%)	49 (10.9%)	15 (6.8%)	22 (16.9%)	12 (12.1%)	<0.0001
Formerly n (%)	126 (28.1%)	45 (20.6%)	46 (35.4%)	35 (35.4%)	
Mean pack-years† (SD)	25.5 (20.8)	28.3 (25.8)	23.9 (16.0)	24.1 (20.0)	<0.0001
Altitude					
Plain (<400m), n (%)	218 (48.7%)	118 (53.9%)	49 (37.7%)	51 (51.6%)	
Tableland (400 to 800 m), n (%)	134 (29.9%)	50 (22.8%)	60 (46.2%)	24 (24.4%)	0.0001
Mountain (≥800 m)	96 (21.4%)	51 (23.4%)	21 (16.1%)	24 (24.4%)	
Working status in 2006					
Working (the same or another job)	280 (62.5%)	118 (53.9%)	90 (69.2%)	72 (72.7%)	<0.0001
Retired	151 (33.3%)	97‡ (44.3%)	35 (26.9%)	19 (20.0%)	
Unemployed or had stopped working for other reasons	17 (4.2%)	4§ (1.8%)	5¶ (3.9%)	8¶ (8.1%)	
Hay or straw handling					
Never	93 (27.3%)	39 (18.2%)	54 (42.5%)	-	
Formerly	128 (37.5%)	80 (37.4%)	48 (37.8%)	-	
Currently	120 (35.2%)	95 (44.4%)	25 (19.7%)	-	
Animal feed handling (grains)					
Never	109 (32.1%)	43 (20.1%)	66 (52.4%)	-	
Formerly	141 (41.5%)	101 (47.2%)	40 (31.7%)	-	
Currently	90 (26.5%)	70 (32.7%)	20 (15.9%)	-	

SD = Standard deviation. Chi-square tests for qualitative variables; Student's t test for quantitative variables.

* Including 40 farmers (23 poultry workers, 2 pig farmers, 2 fish farmers, 2 agricultural labourers, 1 beekeeper, 9 flower cultivators), 11 people with regular cows contacts (3 herdsmen, 7 cow inseminators, two cattle- truck drivers and a slaughter worker), 2 subjects in regular contact with grain (1 grain silo worker and 1 miller), 42 forestry or sawmill workers, 24 cheesemakers and 9 who frequently went to the dairy farms (6 milk quality control technicians or collectors and 3 agricultural machine mechanics).

†Mean pack-years for current smokers and ex-smokers

‡Two retired farmers had stopped work before retirement age due to respiratory diseases (asthma or farmer's lung disease).

§Only one farmer stopped working due to asthma. ¶None stopped working due to respiratory diseases.

Table 2: Prevalence of respiratory symptoms in 2006 in the 3 exposure groups and adjusted odds ratio for dairy farmers and non-dairy agricultural workers (reference non exposed controls) *

	Dairy farmers		Non-dairy agricultural workers		Controls		Adjusted odds ratio† [confidence intervals at 95%] (reference controls)	
	n=219 *		n=130		n=99		Dairy farmers	Non-dairy agricultural workers
Respiratory antecedents (including asthma)	33	(15.5%)	14	(10.8%)	7	(7.1%)	2.42 [1.002 – 5.83]	1.55 [0.60 – 4.00]
Personal history of allergy ‡	92	(44.0%)	61	(47.3%)	42	(43.3%)	1.21 [0.73 – 2.02]	1.19 [0.70 – 2.03]
Familial history of allergy ‡	64	(34.0%)	32	(30.8%)	40	(46.5%)	0.73 [0.42 – 1.26]	0.53 [0.29 – 0.97]
Asthma (self-reported), at any time in their life	16	(7.5%)	6	(4.6%)	5	(5.1%)	1.60 [0.56 – 4.56]	0.92 [0.27 – 3.11]
Asthma (doctor), at any time in their life	15	(7.0%)	5	(3.9%)	5	(5.1%)	1.54 [0.53 – 4.45]	0.76 [0.21 – 2.71]
Asthma attack, in the previous year §	4	(1.9%)	2	(1.5%)	0	(0.0%)	-	-
Attack of shortness of breath at rest, in the previous year §	4	(1.9%)	4	(3.1%)	1	(1.0%)	1.59 [0.17 – 15.25]	3.20 [0.35 – 29.32]
Woken by shortness of breath, in the previous year §	7	(3.3%)	2	(1.5%)	1	(1.0%)	3.81 [0.43 – 33.36]	1.35 [0.12 – 15.27]
Woken by cough, in the previous year §	25	(11.8%)	12	(9.2%)	15	(15.5%)	0.83 [0.40 – 1.73]	0.54 [0.24 – 1.21]
Wheezing at any time in their life	35	(16.5%)	18	(13.9%)	12	(12.1%)	1.63 [0.78 – 3.42]	1.10 [0.50 – 2.43]
Wheezing, in the previous year §	18	(8.5%)	10	(7.7%)	6	(6.1%)	1.25 [0.45– 3.43]	1.16 [0.40 – 3.36]
Wheezing apart from a cold, in the previous year §	12	(5.6%)	5	(3.9%)	4	(4.0%)	0.97 [0.28 – 3.35]	0.76 [0.20 – 3.04]
Wheezing with breathlessness, in the previous year §	7	(3.3%)	5	(3.9%)	5	(5.1%)	0.54 [0.15 – 1.86]	0.70 [0.19 – 2.53]
Usual morning cough	23	(10.8%)	12	(9.2%)	5	(5.1%)	2.46 [0.83 – 7.32]	1.65 [0.53 – 5.16]
Usual morning phlegm	29	(13.6%)	18	(13.8%)	4	(4.0%)	4.27 [1.41 – 12.95]	3.59 [1.16 – 11.10]
Chronic bronchitis	8	(3.8%)	3	(2.3%)	1	(1.0%)	4.66 [0.53 – 40.78]	2.00 [0.20 – 20.06]
Dyspnoea	43	(22.8%)	17	(14.2%)	12	(12.8%)	1.26 [0.61 – 2.58]	1.01 [0.46 – 2.25]

* Six farmers with hypersensitivity pneumonitis have been excluded

† Odds ratio adjusted for age and smoking (reference never having smoked). ‡History of allergy covered nasal allergies including hay fever, eczema or any kind of skin allergy, or allergy to insect stings or bites §At any time in the year before examination

Table 3: Influence of farming exposure on respiratory symptoms in farmers *

(adjusted odds ratio†)

	Hay or straw handling		Animal food handling	
	Current (n=118) versus never (n=92)	Former (n=125) versus never (n=92)	Current (n=90) versus never (n=109)	Former (n=135) versus never (n=109)
Personal history of allergy	1.51 [0.84 – 2.71]	2.31 [1.29 – 4.14]	1.26 [0.70 – 2.25]	1.79 [1.03 – 3.09]
Asthma (self-reported), at any time in their life	1.20 [0.21 –6.82]	8.37 [1.78 – 39.25]	0.50 [0.09 – 2.84]	5.69 [1.53 – 17.04]
Asthma (doctor), at any time in their life	0.93 [0.15 – 5.81]	7.51 [1.59 – 35.41]	0.26 [0.03 – 2.39]	4.56 [1.36 – 15.33]
Woken by cough, in the previous year‡	1.88 [0.61 – 5.78]	3.57 [1.26 –10.10]	2.47 [0.84 – 7.23]	3.31 [1.24 – 8.86]
Wheezing at any time in their life	2.21 [0.81 – 6.01]	4.99 [1.93 – 12.88]	1.25 [0.48 – 3.20]	3.58 [1.60 – 8.00]
Wheezing, in the previous year‡	1.26 [0.31 – 5.01]	3.31 [1.06 – 10.36]	1.61 [0.38 – 6.85]	3.55 [1.13 – 11.15]
Wheezing apart from a cold, in the previous year‡	1.10 [0.14 – 8.40]	4.67 [0.99 – 21.95]	2.99 [0.45 – 19.80]	3.65 [0.77 – 17.35]
Usual morning cough	1.34 [0.44 – 4.09]	2.11 [0.78 – 5.68]	2.21 [0.64 – 7.49	3.04 [1.09 – 8.50]
Usual morning phlegm	1.91 [0.76 – 4.88]	2.26 [0.94 – 5.45]	1.14 [0.48 – 2.74]	1.21 [0.57 – 2.59]
Chronic bronchitis §	-	-	2.63 [0.23 – 30.44]	7.39 [0.85 – 64.16]

* Six farmers with hypersensitivity pneumonitis have been excluded

† odds ratio adjusted for age and smoking status in 2006 (reference never smoking)

‡ at any time in the year before examination

§ no cases of chronic bronchitis in subjects never having handled hay or straw

Table 4: Mean annual changes in respiratory function parameters between 1994 and 2006

	Dairy farmers	Non-dairy agricultural workers	Controls
Time between the two surveys, years (SD)	12.7 (0.29)	12.4 (0.40)	12.5 (0.41)
Respiratory function. mean (SD)			
Available data. n	157*	105	72
Δ FVC $mL.yr^{-1}$ (SD	- 10.7 (29.6)	- 12.6 (37.1)	-11.0 (42.7)
Δ FEV_1 $mL.yr^{-1}$ (SD)	- 16.4 (30.0) ‡	- 14.0 (27.9)	-8.2 (23.0)
Δ $FEV_1/FVC\%.yr^{-1}$ (SD)	- 0.21 (0.64) **	- 0.11 (0.41)	0.005 (0.57)
Δ PF $mL.s^{-1}.yr^{-1}$ (SD)	33.2(112.1) †	65.4 (125.4)	64.0 (118.9)
Δ $FEF_{25-75\%FVC}$ $mL.s^{-1}.yr^{-1}$ (SD)	- 41.5 (57.4) §	- 41.4 (60.0) ¶	-20.7 (58.2)

* 6 Farmers with hypersensitivity pneumonitis excluded (only 4 have valid respiratory function tests)

Significance level of the comparison with controls: † p= 0.07, ‡ p=0.04, § p=0.02, ¶ p=0.01, **p=0.007,

Δ: change in spirometric parameters. Δ = (2006 value –1994 value)/ (number of years between the T1 and T3 examinations)

SD: standard deviation

Table 5: Influence of farming and farming exposure on mean annual change in respiratory function parameters: multiple regressions models adjusted for age, gender, altitude and parameter value in 1994

	Δ FVC $mL.yr^{-1}$	Δ FEV1 $mL.yr^{-1}$	Δ $FEV_1/FVC\%.yr^{-1}$	Δ PF $mL.s^{-1}.yr^{-1}$	Δ $FEF_{25-75\%FVC}$ $mL.s^{-1}.yr^{-1}$
	Coef (SD) p value	Coef (SD) p value	Coef (SD) p value	Coef (SD) p value	Coef (SD) p value
Model 1 : Farming *					
Dairy farmers	6.67 (4.65) †	- 3.20 (3.86) †	-0.21 (0.08) (p= 0.01)	- 26.25 (14.52) (p= 0.07)	- 14.22 (8.02) (p= 0.08)
Non-dairy agricultural workers	2.22 (5.00) †	- 2.51 (4.15) †	- 0.10 (0.09) †	- 4.64 (15.60) †	- 12.77 (8.64) †
Model 2: Hay or straw handling ‡					
Formerly	- 10.33 (4.71) (p=0.03)	- 3.45 (4. 24) †	0.12 (0.08) †	- 15.87 (15.80) †	10.17 (8.40) †
Currently	- 8.78 (5.19) (p=0.09)	- 7.96 (4.68) (p=0.09)	0.01 (0.09) †	- 12.26 (17.51) †	1.88 (9.24) †
Model 3: Animal feed handling ‡					
Formerly	2.80 (4.59) †	3.30 (4.65) †	0.03 (0.08) †	- 19.60 (15.33) †	7.94 (8.18) †
Currently	- 7.78 (5.22) †	- 9.12 (4.65) (p=0.05)	- 0.07 (0.10) †	- 14.01 (17.43) †	- 2.59 (9.27) †
Model 4: Animal feed handling ‡					
Years spent handling between T1 and T3	- 0.38 (0.36) †	- 0.71 (0.32) (p=0.03)	- 0.009 (0.006) †	- 1.08 (1.20) †	- 0.61 (0.64) †

* multiple linear regressions performed in the whole cohort with adjustment for smoking status (current smokers, ex-smokers versus never smokers), age (year),

height (cm), gender, altitude (mountain, tableland versus plain), and analysis of the initial value of the lung function parameter

† p value ≥ 0.10

‡ multiple linear regressions performed in dairy farmers and other agricultural workers with adjustment for smoking status (current smokers, ex-smokers versus never smokers), age (year), height (cm), gender, altitude (mountain, tableland versus plain), and analysis of the initial value of the lung function parameter

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