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Author Contributions Section

All authors made substantial contributions: SJ, BD and JFV conceived and designed the study, analysed, and interpreted the data, and drafted the article; AMR collected the data; SJ, AC, CR, SM and JLV analysed the data; all authors approved the final submitted version.

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Prevalence and risk factors of asthma in dairy farmers: ancillary analysis of AIRBAg

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Ethical approval

The AIRBAg study was approved by the Rennes Ouest V Ethics Committee (11/28–817) and was registered on ClinicalTrials.gov (NCT03654469).

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ABSTRACT

Background: Prolonged occupational agricultural exposure is associated with an increase in asthma diagnosis. This study aimed to identify the prevalence and risk factors for asthma in dairy farmers.

Methods: AIRBAg was a cross-sectional study including 1203 representative dairy farmers. They completed a self-administered questionnaire and underwent a health respiratory check-up. Referral to a pulmonologist was made for any participant with wheezing, dyspnoea, chronic bronchitis, a chronic cough or a FEV_1/FEV_6 ratio<80%. They underwent further examinations such as spirometry with a reversibility test. Controls (non-asthmatic dairy farmers and non-farm employees) were matched to each asthma case for sex and age (±5 years). The odds ratios (OR) between asthma and different risk factors were estimated using conditional multivariate logistic regression models.

Results: Active asthma was diagnosed in 107 (8.9%) farmers. Compared with control dairy farmers, there was a positive association with family history of allergy (OR=8.68; 95% CI [4.26-17.69]), personal history of eczema (OR=3.39; 95% CI [1.61-7.13]), hay manipulation (OR=5.36, 95% CI [1.59-18.01]), and a negative association with farm area (OR=0.92; 95% CI [0.85-0.99]) and handling treated seeds (OR=0.47; 95% CI [0.23-0.95]). Compared with control non-farm employees, there was a positive association between asthma and family history of allergy (OR=95.82, 95% CI [12.55-731.47]).

Conclusions: The prevalence of active asthma in dairy farmers was somewhat higher than the rate observed in the general population but may be controlled by reducing exposure to airborne organic contaminants through occupational adaptions on farms.

Keywords: allergy, asthma, wheezing, bronchial obstruction, chronic respiratory disease

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1. Introduction

Asthma is a heterogeneous disease characterised by chronic airway inflammation, which induces disability, poor quality of life, and requires high health resource use (Eder et al., 2006; Papi et al., 2018). The prevalence of asthma and asthma-like symptoms has been increasing globally over the second half of the 20th century, becoming a major public health problem worldwide (Brogger et al., 2003; James et al., 2010). According to the World Health Survey, the global prevalence of clinical asthma in adults is 4.5% (To et al., 2012). In France, the prevalence is estimated to be 6-7% in adults (Afrite A, 2011; Delmas and Fuhrman, 2010).

Asthma can be triggered by factors such as exercise, exposure to allergens or irritants, or viral respiratory infections (Papi et al., 2018). Environmental factors have been shown to also play a role (Dalphin, 2007) with non-specific irritants such as smoking, pollution or airborne contaminants in professional environments. Interestingly, multiple studies have revealed that in children raised on dairy farms, asthma prevalence is significantly lower than the general population (Braun-Fahrländer et al., 2002; Riedler et al., 2001; Von Ehrenstein et al., 2000; Wlasiuk and Vercelli, 2012). Almost all the protective farm effects for asthma come from consuming unpasteurised milk and contact with straw and cows in childhood (Illi et al., 2012; Pechlivanis and von Mutius, 2020). However, asthma diagnosis increases gradually with prolonged occupational agricultural exposure (Eduard et al., 2009; May et al., 2012; Sigsgaard et al., 2020; Wells et al., 2014), and in adulthood, the risk of asthma in agricultural settings is thought to be linked to recurrent or chronic inflammatory processes (Dalphin, 2007).

In 2019, Jouneau et al. published the AIRBAg study to determine COPD prevalence and characterise the related risk factors in dairy farmers (Jouneau et al., 2019). However, they found an unexpectedly low number of COPD patients (n=16) and no significant occupational risk factors for COPD. Considering the asthma-COPD overlap syndrome (ACOS) (Postma and

Rabe, 2015) it was decided to perform an ancillary study using AIRBAg study data to assess the prevalence of asthma and identify risk factors among dairy farmers.

2. Methods

The design and methods of the AIRBAg cross-sectional study have been previously described (Jouneau et al., 2019).

2.1 Study population

Of the 3831 Brittany dairy farmers registered in the farmers' health insurance scheme ("Mutualité sociale agricole" - MSA), 2089 were randomly selected. Only farmers who had exclusively dairy farmed for more than ten years were included. Farmers with no dairy farming activity for more than five years, a major activity in pig, poultry, or arable farming, a legal guardian, a history of a respiratory infection in the two months prior to screening, ongoing oral corticosteroids or immunosuppressive treatments, or pregnant women were excluded.

The Rennes Ouest V Ethics Committee (11/28–817) approved the AIRBAg study (ClinicalTrials.gov registration number: NCT03654469).

2.2 Data collection

Potential participants were randomly selected and solicited by post to participate in the study. Once included, the participants provided informed consent and completed a standardised self-administered questionnaire containing two sections. The first collected health-related data about respiratory symptoms including wheezing during hay manipulation, chronic cough, chronic bronchitis and the modified Medical Research Council (mMRC) score. The second collected information about occupational and farm characteristics including farm size, cattle and milking cow numbers, crops grown and daily activities.

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Subsequently, farmers were asked to attend a health visit with a local occupational physician. For each participant, the occupational physicians reviewed the questionnaire and performed pulmonary auscultation, electronic mini-spirometry (EMS) and standard spirometry.

2.3 Definition of bronchial obstruction risk and asthma

Following the occupational health check-up, any farmer with wheezing, dyspnoea (mMRC $\geq$1), chronic bronchitis, a chronic cough, FEV_1/FEV_6 ratio (forced expiratory volume in one second/forced expiratory volume in six seconds) < 80% using EMS, or a combination of these features, was classified as at-risk of bronchial obstruction. Those farmers at risk of bronchial obstruction were then referred to the nearest pulmonologist where they underwent further examinations, including spirometry with a reversibility test. Any participant with post-bronchodilator FEV_1/FVC ratio <70% was diagnosed with COPD (GINA, 2022; Vollmer et al., 2009) and excluded from this study. The remaining farmers were not considered to have bronchial obstruction.

A pulmonologist (S.J.) contacted all farmers who reported wheezing, a history of asthma, taking inhaled treatment, taking antihistamine medication, or a combination of these features, irrespective of whether or not asthma was diagnosed during the pulmonologist appointment. These farmers were asked to complete an additional standardised questionnaire based on international questionnaires validated by the ECRHS (European Community Respiratory Health Survey) (Biino et al., 2000), EGEA (Epidemiological Study of the Genetic and Environmental Factors of Asthma, Bronchial Hyperresponsiveness and Atopy)(Siroux et al., 2012) and the asthma control test (ACT) questionnaires(Thomas et al., 2009) over the telephone.

Active asthma was defined as those taking asthma medication and/or experiencing any asthma symptoms (Dodd and Mazurek, 2016; Mirabelli et al., 2014; Phipatanakul et al., 2021). The

pulmonologist diagnosed active asthma based on clinical history, allergic features, suggestive symptoms, and inhaled treatment use, even if spirometry had been negative for asthma.

2.4 Control populations

Each asthma case was matched for sex and age (± 5 years) with three dairy farmers and one to two non-farm employees. The control farmers were randomly selected from respiratory disease-free dairy farmers who participated in the AIRBAg study (nested control population). The respiratory disease-free non-farm controls were recruited from other businesses affiliated with the MSA in the same geographical area in which AIRBAg was conducted. The inclusion criterion for the non-farm controls was a principal activity in a tertiary industry in addition to the matching variables. The exclusion criteria were identical to those for the farmers, plus no farming activity. The non-farm control examination included a medical health check-up, EMS, and standard spirometry, all performed on the same day by a pulmonologist (S.J.).

2.5 Statistical analyses

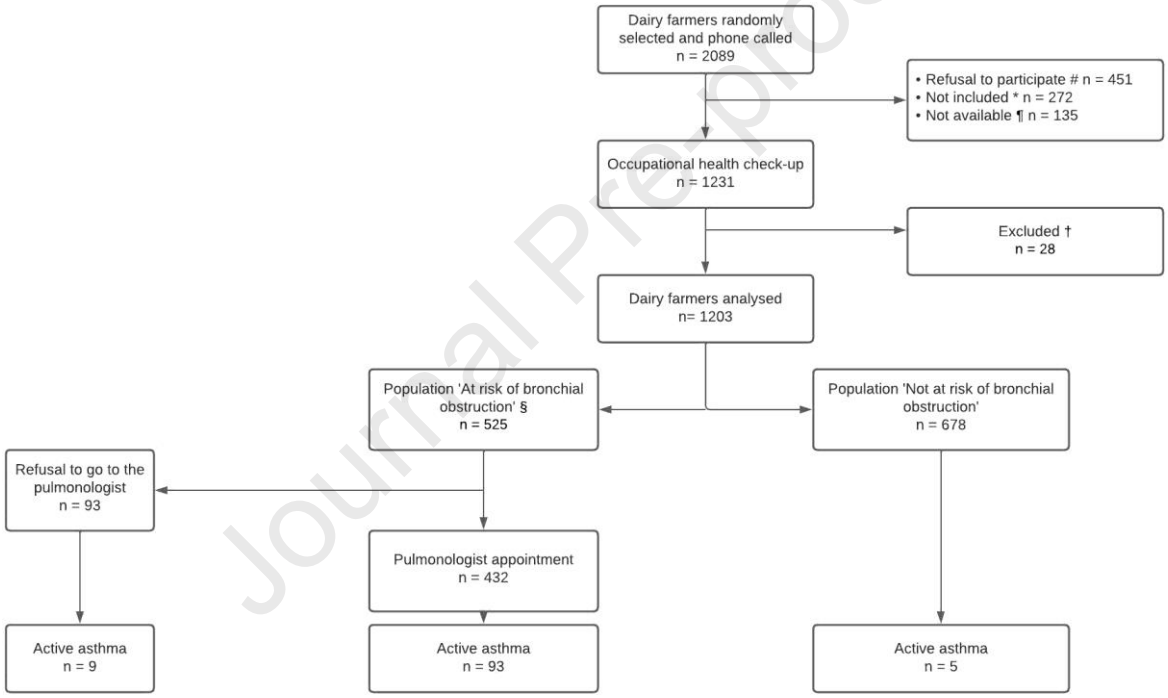
Data from each population was reported using descriptive analysis. The association between asthma (presence/absence) and different risk factors was estimated using conditional logistic regression models, matching for age and sex. Health-related risk factors used for the analyses were family history of allergy, BMI, history of eczema, rhinitis, or smoking. Farm-related risk factors included milking cows (per 10 heads), farm area (per 10 ha), hay manipulation, use of chemical products, handling treated seeds and protective mask use. Covariates found to be significant ($p<0.20$) in univariate analyses were included in multivariate logistic regression models. Initially, logistic modelling using control farmers was performed, followed by non-farm controls. LogXact-11 software (Cambridge, USA) was used for all analyses. Results are presented as odds ratios (OR) with their 95% confidence intervals (CI).

3. Results

3.1 Characteristics of the AIRBAg population

Of the 1231 farmers that underwent an occupational health check-up, 28 were excluded, leaving 1203 dairy farmers in the analysis population of the AIRBAg study. Of these, 525 (43.6%) were at risk of bronchial obstruction and 432 of them went to the pulmonologist appointment. Asthma was diagnosed in 136 (11.3%) patients, of which, 107 (8.9%) had active asthma and 29 had a history of asthma (2.4%). The present study focused on the 107 active asthmatics (Figure 1).

Figure 1: Flow chart of subjects included in the AIRBAg study and asthma cases



not interested / no time; * inclusion criteria not met; ¶ Not contactable; † excluded: poultry farmer (n=5), pig farmer (n=5), arable farmer (n=1), treatment with antibiotics or corticosteroids within 2 months (n=7), immunosuppressive treatment (n=4), no signed consent (n=1), incomplete questionnaire (n=5); § presence of at least one of the following: chronic cough, chronic bronchitis, wheezing, dyspnoea mMRC ≥1, FEV_1/FEV_6 <80%.

3.2 Asthma cases and control populations

The general characteristics of asthma cases and controls are reported in Table 1.

Table 1: General characteristics of the three populations studied: active asthma cases, control farmers, and non-farm controls.

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	Active asthma cases *n*=107		**Control farmers *n*=321**		**Non-farm controls *n*=199**	
Qualitative variable	*n*	%	*n*	%	*n*	%
Quantitative variable	m	sd	m	sd	m	sd
Age (years)	49.9	± 7.38	50	± 6.3	49.7	± 7.4
Gender						
Male	80	74.8	240	74.8	147	73.9
Female	27	25.2	81	25.2	52	26.1
BMI (kg/m^2)	26.1	± 4.1	25.6	± 3.5	24.9	± 4.2
Smoking status						
Never	80	74.8	225	70.1	97	48.7
Former	16	14.9	58	18.1	62	31.2
Current	11	10.3	38	11.8	40	20.1
Respiratory symptoms						
Chronic cough	24	22.4	31	9.7	8	4.0
Chronic bronchitis	20	18.7	25	7.8	4	2.0
Wheezing (hay)	49	45.8	10	3.1	-	-
Wheezing (other situation)	61	57.0	8	2.5	11	5.5
mMRC ≥ 1	34	31.8	28	8.7	17	8.5
Respiratory tests						
EMS FEV_1/FEV_6	0.77	± 0.06	0.80	± 0.10	0.80	± 0.06
Spirometry FEV_1 (L)	3.28	± 0.89	3.62	± 0.82	3.75	± 0.91
FEV_1 (%)	96.50	± 16.80	108.50	± 14.90	110.20	± 16.90
FEV_1/FVC*	0.76	±0.07	0.81	± 0.05	0.78	± 0.07
Farm characteristics						
Area (Ha)	75.9	± 40.4	84.9	± 44.8	-	-
Dairy farming activities (years)	44.2	± 11.4	44.1	± 11.4	-	-
Milking cows (number)	49.1	± 22.9	52.1	± 25.1	-	-

sd=standard deviation; m=mean. BMI=Body Mass Index; mMRC=modified Medical Research Council; EMS= Electronic Mini Spirometer, FEV1=forced expiratory volume in one second; FEV6=forced expiratory volume in six seconds; FVC=forced vital capacity. * pre-bronchodilator values.

Most active asthma cases were men (74.8%), non-smokers (74.8%), with a mean age of 49.9 ± 7.4 years. Among them, 44 (41.1%), developed asthma in childhood. Their mean ACT score was 23.5 ± 2.9 and none of them had pre-bronchodilator obstruction on standard spirometry.

Their mean FEV_1/FVC (forced vital capacity) ratio was 0.76 ± 0.07 and their mean FEV_1/FEV_6 ratio was 0.77 ± 0.06. They had lived a median of 44.2 ± 11.4 years on their farm.

The asthma population had more respiratory symptoms than the controls: 48.5% wheezed when manipulating hay, 57.0% wheezed during other activities and 31.8% suffered from dyspnoea. The FEV_1 values were lower (96.5 ± 16.8% predicted) in the asthmatic farmers than the control farmers (108.5 ± 14.9% predicted) or the non-farm controls (110.2 ± 16.9% predicted).

3.3 Risk factor analyses

Table 2 shows the association between asthma and medical history or farming practices, using respiratory disease-free control farmers.

Table 2: Univariate and multivariate analyses between active asthma cases (n=107) and control farmers (n=321)

	Univariate analysis[#]		**Multivariate analysis**	
	OR	CI	OR	CI
Family history of allergy	**5.89**	**3.32 – 10.88**	**8.68**	**4.26 – 17.69**
History of eczema	**4.21**	**2.18 – 8.31**	**3.39**	**1.61 – 7.13**
Milking cows (per 10 heads)	0.98	0.94 – 1.01	0.99	0.93 – 1.04
Farm area (per 10 ha)	0.95	0.89 – 1.00	**0.92**	**0.85 – 0.99**
Hay manipulation	2.53	0.92 – 7.83	**5.36**	**1.59 – 18.01**
Use of chemical products	1.63	0.82 – 3.41	1.80	0.71 – 4.60
Handling treated seeds	0.64	0.36 – 1.15	**0.47**	**0.23 – 0.95**
Protective mask use	1.52	0.91 – 2.58	1.63	0.87 – 3.06

#: covariate associated with the outcome in the bivariate analysis ($p<0.20$) and introduced into the multivariate analysis.

OR: Odds ratio, CI: Confidence interval

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Univariate analysis showed a significant positive association with family history of allergy (OR=5.89; 95%CI 3.32 – 10.88; $p<10^{-9}$) and personal history of eczema (OR=4.21; 95%CI 2.18 – 8.31; $p<10^{-5}$). Multivariate analysis found a significant positive association with family history of allergy (OR=8.68, 95%CI 4.26– 17.69; $p<10^{-8}$), personal history of eczema (OR=3.39; 95%CI 1.61–7.1; p<0.01), hay manipulation (OR=5.36; 95%CI 1.59–18.01, p<0.01), and a significant negative association with the farm area (OR=0.92, 95%CI 0.85– 0.99; p=0.04) and handling treated seeds (OR=0.47; 95%CI 0.23– 0.95; p=0.04).

Table 3 shows the associations using non-farm controls.

Table 3: Univariate and multivariate analyses between active asthma cases (n=107) and non-farm controls (n=199)

	Univariate analysis#		**Multivariate analysis**	
	OR	CI	OR	CI
Family history of allergy	**121.09**	**16.80 - 872.96**	**95.82**	**12.55 - 731.47**
BMI	**1.06**	**1.01 - 1.13**	1.08	0.96 - 1.20
History of rhinitis	**2.64**	**1.61 - 4.31**	1.19	0.47 - 3.01
History of eczema	**2.59**	**1.39 - 4.84**	3.88	0.95 - 15.71
Smoking status				
Former	**0.33**	**0.17 - 0.61**	0.69	0.26 - 1.80
Current	**0.33**	**0.16 - 0.71**	0.27	0.07 - 1.01
Surgical history	**0.47**	**0.28 - 0.80**	0.42	0.15 - 1.17

covariate associated with the outcome in a univariate analysis (p<0.20) and introduced into the multivariate analysis

OR: Odds ratio, CI: Confidence interval, BMI: body mass index

Univariate analysis showed a positive association with family history of allergy (OR=121.09, 95%CI 16.80–872.96, $p<10^{-9}$), BMI (OR=1.06, 95% CI 1.01– 1.13]; p=0.03), history of chronic

rhinitis (OR=2.64; 95% CI 1.6– 4.31]; $p<10^{-4}$), history of eczema (OR=2.59; 95%CI 1.38–4.84], $p<0.01$), and a significant negative association according to smoking status (former smoker: OR=0.33, 95%CI 0.17–0.61; current smoker: OR=0.33, 95% CI 0.16– 0.71; $p<10^{-4}$) and surgical history (OR=0.47; 95%CI 0.28, –0.80; $p<0.01$).

Multivariate analysis found a positive association only with family history of allergy (OR=95.82, 95%CI 12.55– 731.47, $p<10^{-5}$).

4. Discussion

This study indicates a high prevalence of asthma in dairy farmers in France. Multivariate analyses showed that a family history of allergy, personal history of eczema and hay handling were positively associated with asthma among dairy farmers. Also, asthmatic farmers run significantly smaller farms and handled less treated seeds than control farmers.

We found a prevalence of active asthma of 8.9% among dairy farmers when COPD had been ruled out with spirometry evaluation. This prevalence rate is somewhat higher than observed in adults of the general population in France (6-7%) (Delmas and Fuhrman, 2010; To et al., 2012). This contradicts other studies which revealed asthma prevalence in farmers to be between 2.7% and 7.7%, lower than the estimated national rate (Eduard et al., 2004; Heinonen et al., 1987; Jenkins et al., 2005; Mazurek et al., 2015; Radon et al., 2002). However, most of these studies do not focus on dairy farming, making a direct comparison difficult. Furthermore, some studies are based on data from around 30 years ago, during which time farming practices have changed dramatically and this may impact prevalence.

Having a personal or family history of allergy was associated with asthma occurrence (regardless of the control group). This is in line with the fact that atopy is present in 50-60% of adults with asthma (Papi et al., 2018), and that allergy occurs more frequently in dairy farmers compared to non-farmers (Veil-Picard et al., 2019). This result apparently varies from the

concept that extensive exposure to environmental endotoxins and fungal spores prevents asthma and atopy in children. (Ege et al., 2011; Kauffmann et al., 2002) However, one must bear in mind that this study population consists of adults who had dairy farmed for more than ten years. Asthma was also shown to be strongly associated with hay handling, in agreement with Thaon et al. who reported that hay or straw handling increased the risk of wheezing in dairy and non-dairy farmers (Thaon et al., 2011). Dust liberated by spreading straw bedding has been found to significantly and strongly increase pro-inflammatory TNF-α, IL-1β, IL-6, and IL-8 cytokine expression at both mRNA and protein levels in human monocyte-derived macrophages (Pfister et al., 2017). Therefore, these biologically active thoracic particles from occupational dust may play a role in the development of *de novo* asthma during adulthood in dairy farmers.

The negative association with handling of treated seed may be explained by farmers perceiving this activity was linked to their symptoms. Consequently, they adopted avoidance behaviours such as delegating some tasks to a third person with no respiratory symptoms, rather than seeking medical help to diagnose and treat the condition (it is well known that the agricultural population is slow or reluctant to seek medical care). In the same line, asthma cases tended to reduce their activity by reducing the number of dairy cows or decreasing their farm size.

The AIRBAg study has several main strengths including the cross-sectional study design with robust methodology. A large number of randomly selected dairy farmers were included thus creating a representative sample. The same pulmonologist (S.J.) carefully determined each asthma case and assessed each suspected case thus reducing observer bias. To limit confounding by occupational and demographic factors, matched control populations were used with a case/control ratio up to 1:3 which increased statistical power.

The main limitation of the present study is that the AIRBAg study was initially designed to screen for agricultural COPD. Consequently, the questionnaire did not include a validated asthma screening tool (such as the Asthma Screening questionnaire) (Shin et al., 2010). In

clinical practice, asthma diagnosis is based on a history of respiratory symptoms, a clinical examination (often normal) and lung function testing (GINA, 2022). The diagnostic procedure followed in this study matched the guidelines available at the time. Therefore, asymptomatic patients with a history of episodic flare-ups of asthma-like symptoms and who respond well to inhaled treatments (short-acting bronchodilator or corticosteroid) or antihistamine treatment, can be diagnosed with asthma despite negative spirometry (Lim et al., 2014). The 2022 Global Initiative for Asthma guidelines state that diagnosis is based on the history of characteristic symptom patterns and evidence of variable expiratory airflow limitation using bronchodilator reversibility testing or other tests (GINA, 2022). Incorporating the requirement for evidence of variable expiratory airflow limitation into the diagnosis of active asthma in this study may have slightly altered our results but not significantly as a majority had airflow limitation on testing. It should however be noted that not confirming variable airflow limitation at diagnosis can lead to overdiagnosis or underdiagnosis of asthma producing significant consequences for patients and healthcare systems (Aaron et al., 2018). The occupational health check-up was refused by 21.6% (451/2089) of the farmers, and of those considered "at risk of bronchial obstruction", 17.7% (93/525) did not visit the pulmonologist (as described in Figure 1). It is possible that some of these farmers had asthma but decided not to undergo examination for fear of an unwanted diagnosis or because they felt it was “normal” for dairy farmers to experience these types of symptoms. However, to partly address this issue, we conducted telephone interviews with the 93 suspected cases (in addition to the health check-up and the spirometry performed by the occupational physician) and established a robust diagnosis, as would have been done in an outpatient setting.

Overall, this study revealed some non-modifiable asthma risk factors by (medical history). However, others may be accessible to occupational adaptations including controlling exposure to airborne organic contaminants (hay handling) and choosing farm set-ups that are less

associated with asthma, such as smaller farms. Furthermore, multifaceted interventions combining patient education programs with reduced exposure could significantly improve asthma control (Schuers et al., 2019).

5. Conclusion

The prevalence of active asthma in dairy farmers was somewhat higher than the rate observed in the general population in France and the key risk factors were having a family history of allergy, personal history of eczema and hay handling among dairy farmers. Asthma prevalence among dairy farmers may be controlled by reducing exposure to airborne organic contaminants through occupational adaptions on farms-.

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Data sharing

Data supporting the findings of this study are available from the corresponding author on request.

Conflict of interest

Prof Jouneau declares a conflict of interest with the Brittany Association for Respiratory Failure (AIRB): fees, funding or reimbursement for national and international conferences, boards, expert or opinion groups and research projects over the past 5 years.

All the other authors declare that there is no conflict of interest regarding the publication of this article.

Author contributions

All authors made substantial contributions: SJ, BD and JFV conceived and designed the study, and drafted the article; AMR collected the data; SJ, BD, AC, CR, SM and JFV analysed and interpreted the data; all authors approved the final submitted version.

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Highlights

- There is a high prevalence of asthma in dairy farmers in France
- Family history of allergy is positively associated with asthma
- Personal history of eczema is positively associated with asthma
- Hay handling is positively associated with asthma
- Asthmatic farmers run smaller farms and handle less treated seeds

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Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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Prof Jouneau declares a conflict of interest with the Brittany Association for Respiratory Failure (AIRB): fees, funding or reimbursement for national and international conferences, boards, expert or opinion groups and research projects over the past 5 years.
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