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Ange-Marie Robert, Thomas Gouyet, Chantal Belleguic, Cécile
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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.

Journal Pre-proof

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

2

3 Stéphane Jouneau^{a,b*}, Anthony Chapron^{b,c,d*§}, Cécile Ropars^a, Solenne Marette^e, Ange-Marie
4 Robert^f, Thomas Gouyet^e, Chantal Belleguic^a, Cécile Rochefort-Morel^a, Stéphanie Guillot^g,
5 Carole Mailloux^h, Benoît Desrues^{a,i}, Jean-François Viel^{b,j}

6

7 ***Both authors contributed equally.**

8 ^a Univ Rennes, CHU Rennes, Department of Respiratory Medicine, F-35033 Rennes, France.

9 ^b Univ Rennes, CHU Rennes, Inserm, EHESP, Irset (Institut de recherche en santé,
10 environnement et travail) - UMR_S 1085, F-35000 Rennes, France

11 ^c Univ Rennes, CHU Rennes, Department of General Practice, F-35000 Rennes, France.

12 ^d INSERM, CIC-1414, Primary Care Research Team, F-35000 Rennes, France.

13 ^e Univ Rennes, CHU Rennes, Department of Occupational Pathology, University Hospital, F-
14 35033 Rennes, France.

15 ^f Univ Rennes, CHU Rennes, Department of Clinical Research, F-35033 Rennes, France.

16 ^g Univ Rennes, CHU Rennes, Department of Pulmonary Function Tests, F-35033 Rennes,
17 France.

18 ^h Mutualité Sociale Agricole des Portes de Bretagne, F-35170 Bruz, France.

19 ⁱ INSERM, U1242-COSS, CLCC Eugène Marquis, Rennes 1 University, F-35000 Rennes,
20 France.

21 ^j Univ Rennes, CHU Rennes, Department of Epidemiology and Public Health, F-35033 Rennes,
22 France.

23

24 [§] **Corresponding author:** Anthony Chapron, Department of General Practice, Rennes 1
25 University, 2 avenue Leon Bernard, 35043 Rennes, France.

26 E-mail: anthony.chapron@univ-rennes1.fr

27

28 **Running title:** Screening of dairy farmers for asthma

29

30 **AIRBAg research group:**

31 Jean Barakat, Anne-Laure Barel, Henri-Pierre Baron, Rachel Bassen, Florence Behaghel-
32 Baruteau, Cyril Bernier, Séverine Beyer, Romain Boissel, Vanessa Brault, Graziella Brinchault,
33 Dominique Bureau, Odile Castel, Anne-France Cazuguel, Anthony Chapron, Catherine
34 Decelle-Trochet, Benoît Desrues, Marcel Delaunay, Isabelle Delaunay-Lelièvre, Bruno Eveno,
35 Krisztina Fekete, Lisa Fourmont, Thomas Gouyet, Amandine Guervin, Stéphanie Guillot,
36 Tiphaine Guy, Guillaume Héry, Pauline Hardouin, Anne Hespel, Nathalie Jeffray, Stéphane
37 Jouneau, Yves Koskas, Virginie de Lauzun, Antoine Lebossé, Sandrine Lecot, Carole Mailloux,
38 Solenne Marette, David Marquette, Virginie Martin, Ahmed Merzoug, Hugues Morel, Jean
39 Morer, Patrick Morisseau, Aurélie Oksenhendler, Elisabeth Orhant, Dominique Peron,
40 Mauricette Piguel-Royer, Marie Pinault, Jean-Paul Pousset, Jean-Claude Presle, Patrick

41 Raillard, Bernard Regnault, Ange-Marie Robert, Antoine Séguineau, Anne Sevin, Fanny
42 Thépault, Christian Verger, Jean-François Viel.

43

44 **Ethical approval**

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

47

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52 and Novartis Pharma.

53

54

55 **ABSTRACT**

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

59 **Methods:** AIRBAg was a cross-sectional study including 1203 representative dairy farmers.
60 They completed a self-administered questionnaire and underwent a health respiratory check-
61 up. Referral to a pulmonologist was made for any participant with wheezing, dyspnoea, chronic
62 bronchitis, a chronic cough or a FEV₁/FEV₆ ratio < 80%. They underwent further examinations
63 such as spirometry with a reversibility test. Controls (non-asthmatic dairy farmers and non-farm
64 employees) were matched to each asthma case for sex and age (± 5 years). The odds ratios (OR)
65 between asthma and different risk factors were estimated using conditional multivariate logistic
66 regression models.

67 **Results:** Active asthma was diagnosed in 107 (8.9%) farmers. Compared with control dairy
68 farmers, there was a positive association with family history of allergy (OR=8.68; 95% CI
69 [4.26-17.69]), personal history of eczema (OR=3.39; 95% CI [1.61-7.13]), hay manipulation
70 (OR=5.36, 95% CI [1.59-18.01]), and a negative association with farm area (OR=0.92; 95% CI
71 [0.85-0.99]) and handling treated seeds (OR=0.47; 95% CI [0.23-0.95]). Compared with control
72 non-farm employees, there was a positive association between asthma and family history of
73 allergy (OR=95.82, 95% CI [12.55-731.47]).

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

77

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

79

80 **1. Introduction**

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

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

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

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

106

107 **2. Methods**

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

110 ***2.1 Study population***

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

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

119 ***2.2 Data collection***

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

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

130 ***2.3 Definition of bronchial obstruction risk and asthma***

131 Following the occupational health check-up, any farmer with wheezing, dyspnoea (mMRC ≥ 1),
132 chronic bronchitis, a chronic cough, FEV₁/FEV₆ ratio (forced expiratory volume in one
133 second/forced expiratory volume in six seconds) < 80% using EMS, or a combination of these
134 features, was classified as at-risk of bronchial obstruction. Those farmers at risk of bronchial
135 obstruction were then referred to the nearest pulmonologist where they underwent further
136 examinations, including spirometry with a reversibility test. Any participant with post-
137 bronchodilator FEV₁/FVC ratio < 70% was diagnosed with COPD (GINA, 2022; Vollmer et al.,
138 2009) and excluded from this study. The remaining farmers were not considered to have
139 bronchial obstruction.

140 A pulmonologist (S.J.) contacted all farmers who reported wheezing, a history of asthma, taking
141 inhaled treatment, taking antihistamine medication, or a combination of these features,
142 irrespective of whether or not asthma was diagnosed during the pulmonologist appointment.
143 These farmers were asked to complete an additional standardised questionnaire based on
144 international questionnaires validated by the ECRHS (European Community Respiratory
145 Health Survey) (Biino et al., 2000), EGEA (Epidemiological Study of the Genetic and
146 Environmental Factors of Asthma, Bronchial Hyperresponsiveness and Atopy)(Siroux et al.,
147 2012) and the asthma control test (ACT) questionnaires(Thomas et al., 2009) over the
148 telephone.

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

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

153 **2.4 Control populations**

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

163 **2.5 Statistical analyses**

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

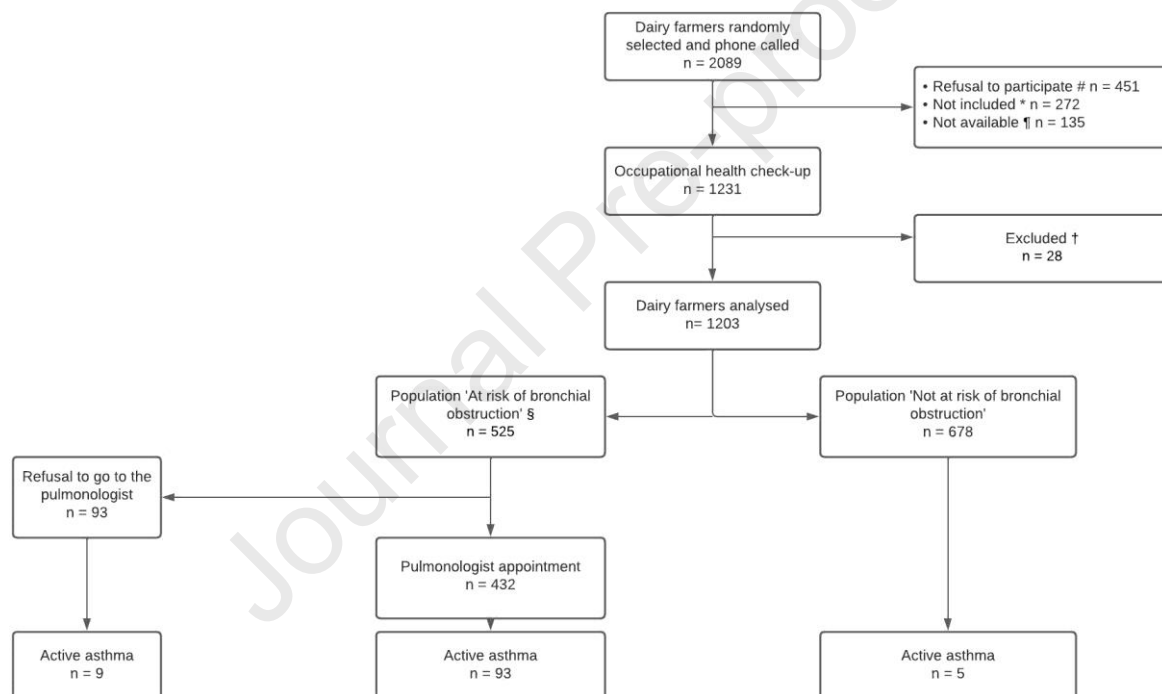
174

175 **3. Results**

176 3.1 Characteristics of the AIRBAg population

177 Of the 1231 farmers that underwent an occupational health check-up, 28 were excluded, leaving
 178 1203 dairy farmers in the analysis population of the AIRBAg study. Of these, 525 (43.6%) were
 179 at risk of bronchial obstruction and 432 of them went to the pulmonologist appointment.
 180 Asthma was diagnosed in 136 (11.3%) patients, of which, 107 (8.9%) had active asthma and
 181 29 had a history of asthma (2.4%). The present study focused on the 107 active asthmatics
 182 (Figure 1).

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



184

185 # not interested / no time; * inclusion criteria not met; † Not contactable; ‡ excluded: poultry farmer (n=5), pig farmer (n=5),
 186 arable farmer (n=1), treatment with antibiotics or corticosteroids within 2 months (n=7), immunosuppressive treatment (n=4),
 187 no signed consent (n=1), incomplete questionnaire (n=5); § presence of at least one of the following: chronic cough, chronic
 188 bronchitis, wheezing, dyspnoea mMRC ≥ 1 , FEV₁/FEV₆ <80%.

189

190 3.2 Asthma cases and control populations

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

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

	Active asthma cases <i>n</i> =107		Control farmers <i>n</i> =321		Non-farm controls <i>n</i> =199	
Qualitative variable	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
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/m²)	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	-	-

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

197

198 Most active asthma cases were men (74.8%), non-smokers (74.8%), with a mean age of 49.9 ±
 199 7.4 years. Among them, 44 (41.1%), developed asthma in childhood. Their mean ACT score
 200 was 23.5 ± 2.9 and none of them had pre-bronchodilator obstruction on standard spirometry.

201 Their mean FEV₁/FVC (forced vital capacity) ratio was 0.76 ± 0.07 and their mean FEV₁/FEV₆
 202 ratio was 0.77 ± 0.06 . They had lived a median of 44.2 ± 11.4 years on their farm.

203 The asthma population had more respiratory symptoms than the controls: 48.5% wheezed when
 204 manipulating hay, 57.0% wheezed during other activities and 31.8% suffered from dyspnoea.

205 The FEV₁ values were lower ($96.5 \pm 16.8\%$ predicted) in the asthmatic farmers than the control
 206 farmers ($108.5 \pm 14.9\%$ predicted) or the non-farm controls ($110.2 \pm 16.9\%$ predicted).

207 *3.3 Risk factor analyses*

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

210 **Table 2:** Univariate and multivariate analyses between active asthma cases (n=107) and
 211 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

212

213

214 Univariate analysis showed a significant positive association with family history of allergy
 215 (OR=5.89; 95%CI 3.32 – 10.88; $p<10^{-9}$) and personal history of eczema (OR=4.21; 95%CI 2.18
 216 – 8.31; $p<10^{-5}$). Multivariate analysis found a significant positive association with family
 217 history of allergy (OR=8.68, 95%CI 4.26– 17.69; $p<10^{-8}$), personal history of eczema
 218 (OR=3.39; 95%CI 1.61–7.1; $p<0.01$), hay manipulation (OR=5.36; 95%CI 1.59–18.01,
 219 $p<0.01$), and a significant negative association with the farm area (OR=0.92, 95%CI 0.85– 0.99;
 220 $p=0.04$) and handling treated seeds (OR=0.47; 95%CI 0.23– 0.95; $p=0.04$).

221 Table 3 shows the associations using non-farm controls.

222 **Table 3:** Univariate and multivariate analyses between active asthma cases (n=107) and non-
 223 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

224

225 Univariate analysis showed a positive association with family history of allergy (OR=121.09,
 226 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

227 rhinitis (OR=2.64; 95% CI 1.6– 4.31]; $p<10^{-4}$), history of eczema (OR=2.59; 95%CI 1.38–
228 4.84], $p<0.01$), and a significant negative association according to smoking status (former
229 smoker: OR=0.33, 95%CI 0.17–0.61; current smoker: OR=0.33, 95% CI 0.16– 0.71; $p<10^{-4}$)
230 and surgical history (OR=0.47; 95%CI 0.28, –0.80; $p<0.01$).

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

233

234 **4. Discussion**

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

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

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

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

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

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

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

277 clinical practice, asthma diagnosis is based on a history of respiratory symptoms, a clinical
278 examination (often normal) and lung function testing (GINA, 2022). The diagnostic procedure
279 followed in this study matched the guidelines available at the time. Therefore, asymptomatic
280 patients with a history of episodic flare-ups of asthma-like symptoms and who respond well to
281 inhaled treatments (short-acting bronchodilator or corticosteroid) or antihistamine treatment,
282 can be diagnosed with asthma despite negative spirometry (Lim et al., 2014). The 2022 Global
283 Initiative for Asthma guidelines state that diagnosis is based on the history of characteristic
284 symptom patterns and evidence of variable expiratory airflow limitation using bronchodilator
285 reversibility testing or other tests (GINA, 2022). Incorporating the requirement for evidence of
286 variable expiratory airflow limitation into the diagnosis of active asthma in this study may have
287 slightly altered our results but not significantly as a majority had airflow limitation on testing.
288 It should however be noted that not confirming variable airflow limitation at diagnosis can lead
289 to overdiagnosis or underdiagnosis of asthma producing significant consequences for patients
290 and healthcare systems (Aaron et al., 2018). The occupational health check-up was refused by
291 21.6% (451/2089) of the farmers, and of those considered "at risk of bronchial obstruction",
292 17.7% (93/525) did not visit the pulmonologist (as described in Figure 1). It is possible that
293 some of these farmers had asthma but decided not to undergo examination for fear of an
294 unwanted diagnosis or because they felt it was "normal" for dairy farmers to experience these
295 types of symptoms. However, to partly address this issue, we conducted telephone interviews
296 with the 93 suspected cases (in addition to the health check-up and the spirometry performed
297 by the occupational physician) and established a robust diagnosis, as would have been done in
298 an outpatient setting.

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

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

305 **5. Conclusion**

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

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319

320 Data sharing

321 Data supporting the findings of this study are available from the corresponding author on
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323

324 Conflict of interest

325 Prof Jouneau declares a conflict of interest with the Brittany Association for Respiratory Failure
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330 Author contributions

331 All authors made substantial contributions: SJ, BD and JFV conceived and designed the study,
332 and drafted the article; AMR collected the data; SJ, BD, AC, CR, SM and JFV analysed and
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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

Journal Pre-proof

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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Author's name: Stéphane Jouneau^{a,b*}, Anthony Chapron^{b,c,d**\$}, Cécile Ropars^a, Solenne Marette^e, Ange-Marie Robert^f, Thomas Gouyet^e, Chantal Belleguic^a, Cécile Rochefort-Morel^a, Stéphanie Guillot^g, Carole Mailloux^h, Benoît Desrues^{a,i}, Jean-François Viel^{b,j}

Affiliation:

***Both authors contributed equally.**

^a Univ Rennes, CHU Rennes, Department of Respiratory Medicine, F-35033 Rennes, France.

^b Univ Rennes, CHU Rennes, Inserm, EHESP, Irset (Institut de recherche en santé, environnement et travail) - UMR_S 1085, F-35000 Rennes, France

^c Univ Rennes, CHU Rennes, Department of General Practice, F-35000 Rennes, France.

^d INSERM, CIC-1414, Primary Care Research Team, F-35000 Rennes, France.

^e Univ Rennes, CHU Rennes, Department of Occupational Pathology, University Hospital, F-35033 Rennes, France.

^f Univ Rennes, CHU Rennes, Department of Clinical Research, F-35033 Rennes, France.

^g Univ Rennes, CHU Rennes, Department of Pulmonary Function Tests, F-35033 Rennes, France.

^h Mutualité Sociale Agricole des Portes de Bretagne, F-35170 Bruz, France.

ⁱ INSERM, U1242-COSS, CLCC Eugène Marquis, Rennes 1 University, F-35000 Rennes, France.

^j Univ Rennes, CHU Rennes, Department of Epidemiology and Public Health, F-35033 Rennes, France.

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