



Contents lists available at ScienceDirect

International Journal of Hygiene and Environmental Health

journal homepage: www.elsevier.com/locate/ijheh



Agricultural exposure and asthma risk in the AGRICAN French cohort

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ARTICLE INFO

Article history:

Received 9 July 2013

Received in revised form 23 August 2013

Accepted 24 August 2013

Keywords:

Epidemiology

Asthma

Risk factors

Farming

Pesticides

ABSTRACT

Epidemiological studies have reported an increased risk of respiratory diseases in agricultural population, but a protective “farm-effect” has also been reported for asthma. In the AGRICAN cohort, self-reported doctor-diagnosed asthma was analyzed according to allergy, in relation with history of life-time exposure to 13 crops and 5 livestock, pesticide exposure and early life on a farm, taking into account sex, age, education and body mass index. Among the 1246 asthmatics (8.0%), 505 were allergic (3.3%) and 719 non-allergic (4.6%). In multivariate analysis, a significant excess was observed, only for allergic asthma, in vine-growing (OR = 1.43, $p = 0.002$), fruit-growing (OR = 1.58, $p = 0.001$), greenhouses (OR = 1.66, $p = 0.02$), grasslands (OR = 1.35, $p = 0.009$), beets (OR = 1.52, $p = 0.003$) and horses (OR = 1.35, $p = 0.04$). Pesticide use and history of pesticide poisoning were significantly associated with allergic asthma in grassland, vineyards and fruit-growing and with non-allergic asthma in beets. Living on a farm in the first year of life tended to be protective for childhood allergic asthma in farms with livestock (OR = 0.72, $p = 0.07$) but deleterious in farms with vineyards, fruit or vegetables (OR = 1.44, $p = 0.07$). In AGRICAN, an increased risk of allergic asthma was observed with crop exposure, pesticide use and early life on a farm, especially in vine-growing, grassland, beets, fruit and vegetable-growing.

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Introduction

Two major epidemiological studies, one among children (“Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema,” 1998) and another among young adults (Burney et al., 1994), have estimated the prevalence of asthma worldwide and demonstrated that it is one of the most common chronic conditions. They suggest that 200–300 million people suffer from asthma worldwide (Masoli et al., 2004). In France, the prevalence of asthma is estimated to be 6.7% in adults and 9.8% in children (Raherison et al., 2007). Moreover, a substantial increase in this prevalence has been observed in most countries in recent decades, suggesting that environmental changes could play a large role, probably in association with genetic predisposition. Epidemiological data consistently indicate a high contribution of occupational exposure, which could explain 18% of the total burden

of asthma in the populations according to a systematic analysis of population-attributable fractions (Torén and Blanc, 2009). A wide range of occupations have been associated with asthma such as painting, hairdressing, cleaning, health care professions and baking (Mapp et al., 2005). The farm environment corresponds to a mixture of various forms of exposure such as dust, mold, animals, crops, pesticides and other chemicals, which have been recognized to promote the occurrence of lung diseases (“Respiratory health hazards in agriculture,” 1998). Nevertheless, the impact of farming on asthma appears controversial. Some studies have shown that being raised on a farm is protective, specifically against atopic asthma (Braun-Fahrlander et al., 1999; Douwes et al., 2007; Leynaert et al., 2001; von Mutius, 2007). Other studies indicated that farming was related to an increase in asthma risk in adults (Kogevinas et al., 1999; Monsó et al., 2000; “Respiratory health hazards in agriculture,” 1998). A French study found that respiratory conditions were more frequent in dairy farmers compared to unexposed controls living in rural areas (Dalphin et al., 1998). Comparable results for asthma were found in farmers involved in livestock, and especially cattle and hogs (Choudat et al., 1994). A large agricultural prospective cohort, the Agricultural Health Study (AHS), demonstrated that farm animals breeders (Hoppin et al.,

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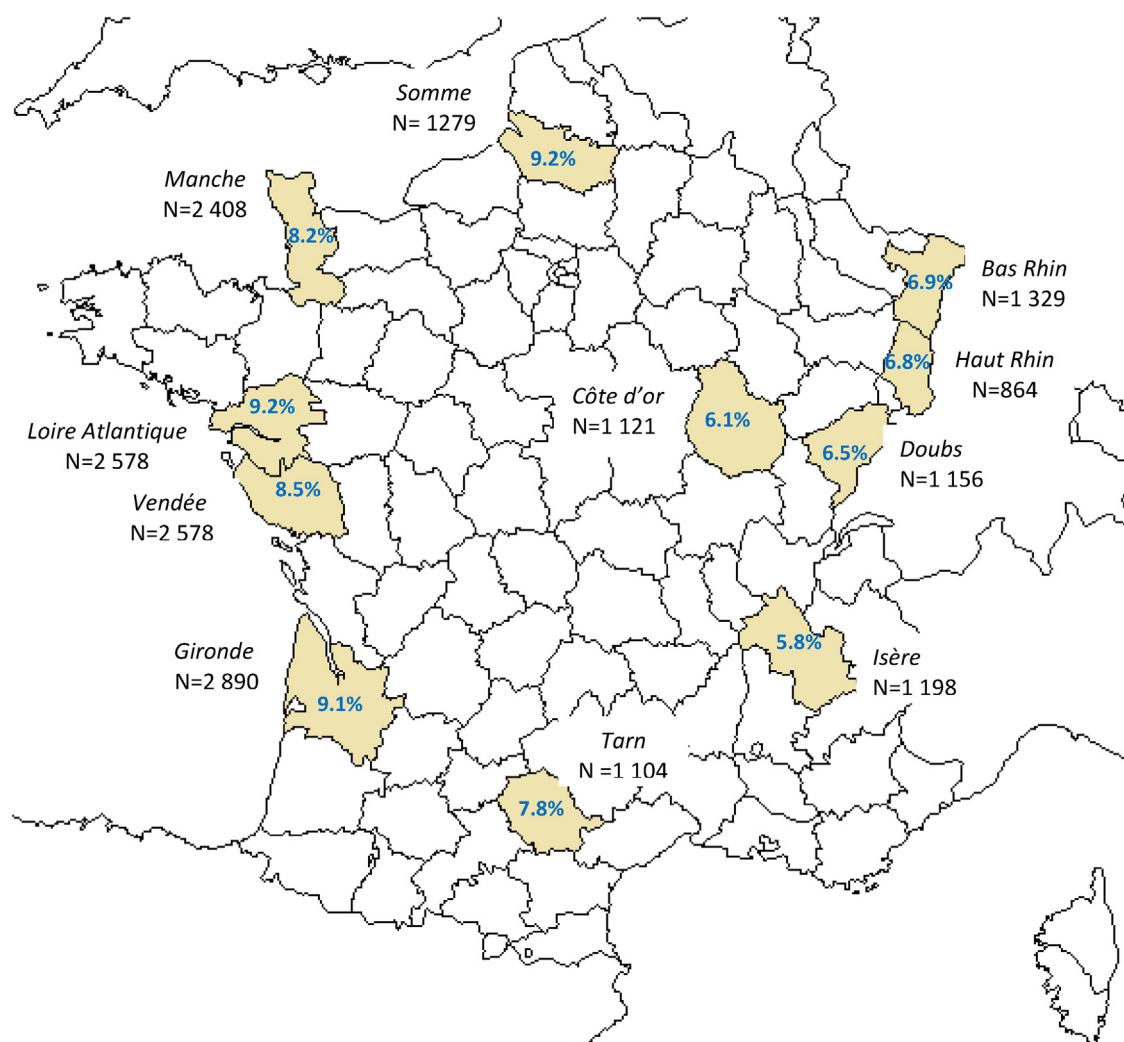


Fig. 1. Number of subjects and prevalence of asthma in the 11 departments of the AGRICAN study (enrolment, 2005–2007).

2003), commercial pesticide applicators and farmers (Hoppin et al., 2006) had a higher risk of wheezing. In the AHS, pesticide use was associated with adult onset asthma in male farmers (Hoppin et al., 2009) and specifically with atopic asthma in farm women (Hoppin et al., 2008). The differences between the studies could be due to differences in the timing (early life or during adulthood) or/and type of farming. The French agricultural setting offers a good opportunity to study the respiratory effects of agricultural exposures as it comprises a wide range of crops and livestock, with a large number of farmers and farm workers (about 5 million professionally active or retired in 2012), and with the greatest use of pesticides in Europe.

We analyzed the role of agricultural exposure, including pesticide use and early life on a farm, on the presence of asthma with and without allergy, at enrolment in a large agricultural prospective cohort: the AGRICAN study.

Methods

Population

The main objective of the AGRICAN cohort was to study the link between agriculture and cancer incidence and mortality in a large French agricultural population. Secondary aims included the study of respiratory conditions and neurological disorders. The

eligible population consisted of all adults, men and women, active or retired, farm-owners and workers, affiliated to the Mutualité Sociale Agricole (MSA), the French Health insurance scheme in agriculture. To be included, individuals had to be 18 years old or over, to have paid at least 12 quarterly contributions to the MSA, and in 2004 to be living in one of the eleven French areas where cancer registries (certified by the National Registry Committee) were set up (Fig. 1). Enrollment was by mail from November 2005 to June 2007. In 2008, 180,060 self-administered questionnaires had been completed and returned (31.7% of eligible individuals). A 10% random sample of these questionnaires was available for preliminary analysis and was used in the current investigation.

Questionnaire

The self-administered questionnaire included: (i) socio-demographic variables (age, sex, education, and marital status), (ii) health outcomes at enrollment (15 diseases including asthma, hay fever and eczema), (iii) occupational data: complete occupational history, history of crops and livestock (the question was: "Have you ever grown this crop/livestock? Yes/No"), details on 2–5 agricultural tasks for each crop/livestock (with years of beginning and end of each task including pesticide use), and history of pesticide poisoning, (iv) other conditions likely to impact health: reproductive life, diet, smoking and alcohol consumption. Moreover, participants

were asked about their place of residence in the first year of life and if on a farm, about the main crops and cattle raised. Concerning asthma, the question was the following: “Has a doctor ever told you that you had asthma?” In case of an affirmative answer, the range of age of diagnosis was collected (before 20, 20–39 yrs, 40–60 yrs, after 60).

Data analysis

A participant was defined as asthmatic if he had answered affirmatively to the question about asthma and/or he had mentioned an age for asthma diagnosis by a doctor and not asthmatic if he responded negatively. Otherwise data were considered missing. We defined as allergic those asthmatics who also mentioned hay fever and/or eczema. Otherwise they were considered as non-allergic (Hoppin et al., 2011).

General characteristics of the sample with no missing data were described and compared with the total 10% sample. Descriptions were performed for all asthmatics and separately for allergic and non-allergic asthmatics. Multivariate logistic regressions tested the association between asthma (separately for allergic and non-allergic asthma) and crop or livestock exposure, pesticide use (including duration assessed with the dates of beginning and end of pesticide use), and pesticide poisoning. The multivariate analysis were finally run separately for childhood (before age 20) and adult onset asthma, combining exposure into 3 classes: (i) livestock (cattle, sheep/goats; swine, horses, poultry), (ii) vineyards/fruit/vegetables (including greenhouses) and (iii) open field crops (grassland, corn, wheat/barley, peas, beet, sunflower, rape, tobacco, potatoes). Analysis was adjusted on age, sex and educational level, together with Body Mass Index in non-allergic asthma. All statistical analyses were done using SAS version 9.1 (SAS Institute, Inc., Cary, NC, USA).

Results

Population characteristics

The sample included 18,429 participants, among whom 15,494 completed questions on asthma (84.1%). Non-responders to the asthma questions were older (means 68.6 vs 62.9 yrs, $p < 10^{-3}$), more frequently males (55.5 vs 51.1%, $p < 10^{-3}$), more frequently smokers (11.0 vs 9%) and less educated (secondary level or higher: 52.4 vs 38.1% $p < 10^{-3}$) than responders.

Responders were 8598 men (55.5%) and 6896 women (44.5%) aged 62.9 (sd 15.9) yrs on average at enrolment (Table 1). Most lived as couples (71.6%). Half had a primary or lower educational level (47.6%), 41.7% had completed high school and 10.7% had a higher educational level. Most had never smoked (61.4%), whereas 28.8% were ex-smokers and only 9.8% current smokers. Fewer than half had a low or normal weight (42.8%), 41.6% were overweight and 15.6% obese.

Characteristics of asthmatics according to allergy

A total of 1246 participants were classified as asthmatics in our sample (8.0%): 505 reported allergy (3.3%) while 719 were non-allergic (4.6%). Twenty-two asthmatics (0.1%) reported no information on eczema and hay fever and could not be classified according to allergy. The prevalence of allergic asthma tended to be higher in women than in men (3.6% vs 3.0%, $p = 0.07$), while the prevalence was more comparable in the two genders for non-allergic asthma (4.5% vs 4.8%, $p = 0.4$). Prevalence of asthma was higher in the youngest participants (<50 yrs) for allergic asthma (4.4%, $p < 0.01$) and in oldest participants (≥ 80 yrs) for non-allergic

asthma (6.2%, $p < 0.01$). The prevalence of asthma did not significantly differ between participants living single or as couples ($p = 0.29$) nor according to tobacco smoking ($p = 0.57$), but it differed according to educational level ($p = 0.04$): allergic asthma was more frequent in higher educated participants (4.6%, $p = 0.01$) while non-allergic asthma was more frequent in low-educated ones (5.7%, $p < 0.01$). Obese participants tended to have higher prevalence of asthma (9.0%) due to a higher prevalence of non-allergic asthma (5.3%, $p = 0.02$). The proportion of asthmatics with a diagnosis before the age of 20 years was larger in allergic (37.8%) than in non-allergic (27.9%) participants.

Description of exposure

Crop and farm animal exposure

Data on crops grown during life were completed by more than two thirds of individuals, except for fruits (58.4%). The proportion of missing data on the type of crops was comparable in asthmatic and non-asthmatics (13.0% vs 13.2%, $p = 0.9$) and inversely correlated with the frequency of crop exposure. The most frequently reported crops were grassland (53.3%), wheat/barley (44.0%), vineyards (33.0%) and corn (31.0%), ahead of beets, fruit and potatoes which each concerned about 20% of the participants. Other crops (peas, sunflower, tobacco, vegetables and greenhouses) concerned 10% of participants or less.

Data on livestock were completed by 69.1%–85.4% of individuals according to the animals raised. The proportion of missing data on livestock was comparable in asthmatics and non-asthmatics (12.0% vs 12.9%, $p = 0.4$) and lower in the most frequent livestock. Frequency of livestock raised during life ranked as follows: cattle (59.2%), poultry (31.1%), hogs (25.2%), horses (19.7%) and sheep/goats (12.5%).

Pesticide exposure

Among the 11,280 participants who completed questions on asthma and pesticides, a history of pesticide use was reported by 5004 individuals (44.4% in all participants, 63.7% in men and 14.1% in women). The proportion of participants having used pesticides on a given crop was 17.0% on wheat/barley, 14.0% on corn, 12.8% on grasslands, 10.7% on vineyards and less than 5% on other crops. Among those exposed to a specific crop, the proportion of participants who used pesticides on the crop ranged from 27.2% in fruit-growing to 67.4% in sunflower. A history of pesticide poisoning was reported by 845 individuals (6.1%) among the 13,900 who completed the information (89.7%).

Farm residence in early childhood

About two thirds of the participants reported they had lived on a farm during their first year of life (67.6%), and more precisely on a farm with cattle (47.7%), grasslands (40.9%), poultry (19.9%), hogs (17.4%), open fields (35.2%) and vineyards (16.6%).

Multivariate analysis

Allergic asthma and crop/animal exposure

Adjusting on age, sex and educational level, increases in risk of allergic asthma were significant in participants exposed to grassland (OR = 1.35, 1.08–1.68), vineyards (OR = 1.43, 1.15–1.77), beet (OR = 1.52, 1.16–2.00), fruit (OR = 1.58, 1.20–2.09), greenhouses (OR = 1.66, 1.10–2.51) and in horse-breeders (OR = 1.35, 1.02–1.80, Table 2). Some non-significant excess were also observed with other crops but sunflower. No association was found with cattle and hogs. Risks of allergic asthma were slightly increased when analysis was restricted to participants diagnosed after 20 yrs old, in most

Table 1
Characteristics of the population and prevalence of allergic and non-allergic asthma AGRICAN 10% sample at enrolment, 2005–2007.

	10% Cohort		Sample		Asthmatics [*]								
	N = 18,429		N = 15,494		All N = 1246			Allergic N = 505			Non-allergic N = 719		
	n	%	n	%	n	%	p	n	%	p	n	%	P
Gender (N = 18,429)							0.54			0.07			0.40
Males	10,098	54.8	8598	55.5	681	7.9		260	3.0		411	4.8	
Females	8331	45.2	6896	44.5	565	8.2		245	3.6		308	4.5	
Age at enrolment (N = 18,429)							0.11			<0.01			<0.01
<50 yrs	3892	21.1	3576	23.1	297	8.3		155	4.4		137	3.8	
[50–59 yrs]	2914	15.8	2558	16.5	194	7.6		91	3.6		98	3.9	
[60–69 yrs]	3638	19.7	3003	19.4	216	7.2		89	3.0		124	4.2	
[70–79 yrs]	5016	27.2	4017	25.9	326	8.1		105	2.6		215	5.4	
>= 80 yrs	2969	16.1	2340	15.1	213	9.1		65	2.8		145	6.2	
Marital Status (N = 17,815)							0.29			0.65			0.32
Single	5203	29.2	4275	28.4	358	8.4		145	3.4		207	4.9	
Couples	12612	70.8	10805	71.6	849	7.9		352	3.3		483	4.5	
Educational Level (N = 17,141)							0.04			0.01			<0.01
Lower than elementary	3547	20.7	2920	19.9	265	9.1		92	3.2		165	5.7	
Elementary	4972	29.0	4053	27.7	310	7.6		109	2.7		198	4.9	
High School	6952	40.6	6108	41.7	454	7.4		200	3.3		246	4.0	
Higher	1670	9.7	1562	10.7	131	8.4		72	4.6		59	3.8	
Tobacco smoking (N = 16,860)							0.57			0.73			0.64
Never smokers	10,540	62.5	8924	61.4	696	7.8		279	3.1		404	4.6	
Ex smokers	4721	28.0	4196	28.8	345	8.2		141	3.4		196	4.7	
Smokers	1599	9.5	1423	9.8	106	7.4		48	3.4		58	4.1	
Body Mass Index (N = 15,958)							0.06			0.38			0.02
Normal or low	6858	43.0	5928	42.8	439	7.4		202	3.4		232	3.9	
Overweight	6663	41.7	5771	41.6	442	7.7		174	3.0		261	4.5	
Obesity	2437	15.3	2161	15.6	194	9.0		76	3.5		114	5.3	
Farm in early childhood (N = 16,717)							0.07			0.09			0.3
No	11,486	68.7	9788	67.6	752	65.2		300	64.1		438	65.9	
Yes	5231	31.3	4691	32.4	401	34.8		168	35.9		227	34.1	

^{*} Information on the allergic status was missing in 22 asthmatics (1.8%).

crops but in vineyards, while no significant association was seen in subjects diagnosed before 20 years old (Table 3).

Non allergic asthma and crop/livestock exposure

Slight non-significant increases in risk of non-allergic asthma were also observed in vineyards (OR = 1.17, 0.96–1.44), beet (OR = 1.24, 0.97–1.58), vegetables (OR = 1.28, 0.93–1.74), potatoes (OR = 1.17, 0.93–1.48), and in poultry (OR = 1.21, 0.97–1.50) when

taking into account age, sex, educational level and BMI. A non-significantly reduced risk was observed for cattle (Table 3).

Asthma and history of pesticide use or poisoning

A significant association with allergic asthma was noted in participants involved in pesticide use on vineyards (OR = 1.35, 1.02–1.80), fruit-growing (OR = 1.56, 1.01–2.40) and grasslands (OR = 1.35, 1.03–1.76) (Table 4). Duration of pesticide use was not associated with asthma risk (data not shown). Risks of allergic

Table 2
Association between allergic and non-allergic asthma and lifelong exposure to crops and livestock. AGRICAN, 2005–2007.

	Allergic asthma (N = 505) [*]					Non-allergic asthma (N = 719) [†]				
	N exposed	%	Adjusted OR	95% CI	p	N exposed	%	Adjusted OR	95% CI	P
Crops										
Grassland	171	44.6	1.35	[1.08–1.68]	0.009	256	56.9	1.01	[0.82–1.24]	0.92
Vineyards	141	38.3	1.43	[1.15–1.77]	0.002	160	37.3	1.17	[0.96–1.44]	0.13
Corn	116	32.5	1.27	[0.99–1.62]	0.054	150	35.6	1.12	[0.90–1.39]	0.33
Wheat/Barley	161	43.5	1.20	[0.95–1.50]	0.12	205	47.2	0.98	[0.80–1.20]	0.83
Peas	28	8.6	1.40	[0.94–2.10]	0.10	27	7.0	0.98	[0.65–1.46]	0.90
Beet	77	22.3	1.52	[1.16–2.00]	0.003	97	24.3	1.24	[0.97–1.58]	0.09
Sunflower	23	6.9	0.92	[0.59–1.43]	0.72	36	9.3	1.10	[0.77–1.57]	0.61
Rape	43	12.8	1.36	[0.97–1.90]	0.08	44	11.4	1.01	[0.73–1.40]	0.97
Tobacco	37	10.1	1.30	[0.92–1.85]	0.14	33	7.7	0.85	[0.59–1.22]	0.38
Fruit-growing	77	27.4	1.58	[1.20–2.09]	0.001	77	24.1	1.05	[0.80–1.37]	0.75
Potatoes	86	24.3	1.23	[0.94–1.60]	0.13	122	29.0	1.17	[0.93–1.48]	0.18
Vegetables	38	11.5	1.34	[0.95–1.90]	0.10	48	12.2	1.28	[0.93–1.74]	0.13
Greenhouses	26	7.8	1.66	[1.10–2.51]	0.02	15	3.9	–	–	–
Livestock										
Cattle	231	55.7	1.01	[0.82–1.25]	0.92	288	58.4	0.86	[0.71–1.05]	0.14
Sheep/Goats	41	12.2	1.15	[0.82–1.62]	0.41	57	14.0	1.12	[0.83–1.49]	0.46
Swine	78	22.2	1.02	[0.78–1.35]	0.86	123	28.8	1.15	[0.92–1.45]	0.23
Horses	71	20.3	1.35	[1.02–1.80]	0.04	86	21.7	1.05	[0.81–1.37]	0.71
Poultry	114	31.8	1.26	[0.99–1.61]	0.06	149	35.3	1.21	[0.97–1.50]	0.10

^{*} OR adjusted on age, sex and educational level.

[†] OR adjusted on age, sex, educational level and BMI.

Table 3

Association between allergic asthma and lifelong exposure to crops and livestock, according to age at asthma diagnosis. AGRICAN, 2005–2007.

	Diagnosis before 20 yrs (N = 150)*					Diagnosis after 20 yrs (N = 247)*				
	N exposed	%	Adjusted OR	95% CI	p	N exposed	%	Adjusted OR	95% CI	P
Crops										
Grassland	47	40.2	0.93	[0.62–1.39]	0.71	117	59.7	1.42	[1.04–1.94]	0.02
Vineyards	38	32.5	1.35	[0.91–2.01]	0.14	72	38.3	1.32	[0.98–1.78]	0.07
Corn	27	23.5	0.72	[0.46–1.15]	0.17	61	33.7	1.40	[1.00–1.96]	0.05
Wheat/Barley	38	33.0	0.84	[0.55–1.28]	0.41	89	47.1	1.33	[0.97–1.82]	0.08
Peas	8	7.3	0.96	[0.46–2.00]	0.90	13	7.9	1.42	[0.79–2.54]	0.24
Beet	13	11.9	1.07	[0.59–1.96]	0.82	53	29.9	1.99	[1.41–2.81]	0.001
Sunflower	8	7.1	0.84	[0.40–1.76]	0.65	10	6.1	0.87	[0.45–1.68]	0.68
Rape	11	10.0	0.86	[0.45–1.64]	0.65	27	15.8	1.90	[1.23–2.94]	0.004
Tobacco	10	8.4	1.34	[0.69–2.58]	0.39	16	8.8	1.00	[0.59–1.69]	1.00
Fruit-growing	10	12.0	0.79	[0.40–1.55]	0.49	46	30.9	1.67	[1.16–2.41]	0.005
Potatoes	13	11.5	0.86	[0.47–1.57]	0.13	58	32.2	1.48	[1.05–2.07]	0.03
Vegetables	13	11.5	1.55	[0.86–2.79]	0.14	22	13.1	1.43	[0.91–2.26]	0.12
Greenhouses	9	8.0	1.50	[0.74–2.98]	0.26	13	7.8	1.79	[1.01–3.19]	0.04
Livestock										
Cattle	56	45.2	0.98	[0.67–1.43]	0.92	127	59.9	1.02	[0.76–1.37]	0.88
Sheep/Goats	12	11.2	1.39	[0.75–2.57]	0.30	20	11.7	0.98	[0.61–1.58]	0.93
Swine	16	14.6	1.04	[0.60–1.83]	0.87	47	26.3	1.05	[0.73–1.50]	0.80
Horses	21	18.9	2.17	[1.30–3.61]	0.003	38	21.7	1.16	[0.79–1.72]	0.45
Poultry	27	24.1	1.47	[0.93–2.33]	0.10	61	33.7	1.10	[0.78–1.54]	0.60

* OR adjusted on age, sex and educational level.

asthma were increased in participants reporting a history of pesticide poisoning (OR = 1.97, 1.43–2.73). For non-allergic asthma the only significant association was observed in participants involved in pesticide use on beets (OR = 1.47, 1.03–2.10).

Role of living on a farm during first year of life in asthma diagnosed in childhood

Participants living on a farm with vineyards, fruit or vegetables during their first year of life had a higher non-significant risk of allergic asthma diagnosed before 20 yrs of age (OR = 1.44, 0.97–2.15) (Fig. 2). This risk increased to OR = 1.77, 1.02–3.06 when not exposed to any other crop or livestock in the first year of life. On the other hand, a non-significant decreased in risk of allergic asthma was observed in participants growing up on farms with open field (OR = 0.84, 0.59–1.19) or livestock (OR = 0.72, 0.51–1.03). No association was observed between non-allergic asthma and living during the first year of life on a farm growing vineyards/fruit/vegetables, open field or livestock (Fig. 2).

Role of crop exposure in asthma diagnosed in adults

Participants exposed to vineyards/fruit/vegetables had a higher risk of allergic asthma diagnosed after 20 yrs of age, significant if they had not been living on a farm growing these crops during

their first year of life (OR = 1.60, 1.14–2.25) (Fig. 3). For open field and livestock exposure, there were also increased risks of allergic asthma, more pronounced in participants exposed during first year of life, but not significant.

Concerning non-allergic asthma, the risk was non-significantly raised in participants exposed to vineyards. In participants life-long exposed to livestock an increase in the risk of non-allergic asthma was observed if they had been living on a farm during their first year of life, while a decrease was observed otherwise.

Discussion

In a large French agricultural prospective cohort, we observed a higher prevalence of allergic asthma in participants occupationally exposed to various crops and livestock, and also in those having used pesticides or reporting pesticide poisoning. The associations were more pronounced in fruit-growing, vineyards, greenhouses and grassland farming. Moreover, living on a farm in early childhood tended to be protective for allergic asthma in farms with livestock but deleterious in farms with vineyards, fruits or vegetables.

These results, based on a large number of doctor-diagnosed asthmatics, enabled us to analyze separately the role of various agricultural activities in asthma. Our definition of asthma was based on

Table 4

Association between allergic and non-allergic asthma and pesticide use on crops or pesticide poisoning AGRICAN, 2005–2007.

	Allergic asthma N = 473					Non allergic asthma N = 575				
	N	% exposed	Adj. OR*	95% CI	p	N	% exposed	Adj. OR**	95% CI	P
Pesticide use on crops										
Grassland	72	15.2	1.35	1.03–1.76	0.03	63	14.8	1.15	0.91–1.47	0.24
Vineyards	61	12.9	1.35	1.02–1.80	0.04	53	12.1	0.89	0.67–1.18	0.41
Corn	55	11.7	0.82	0.61–1.15	0.21	50	11.8	1.01	0.79–1.30	0.94
Wheat/Barley	79	16.7	1.05	0.80–1.38	0.72	73	17.2	1.12	0.89–1.41	0.33
Peas	12	2.5	0.96	0.53–1.73	0.89	11	2.6	0.97	0.57–1.65	0.91
Beet	22	4.7	1.26	0.85–2.08	0.21	20	4.7	1.47	1.03–2.10	0.04
Sunflower	12	2.5	0.66	0.37–1.19	0.17	11	2.6	1.33	0.91–1.97	0.14
Rape	20	4.2	0.87	0.55–1.39	0.57	19	4.5	1.16	0.80–1.67	0.44
Tobacco	11	2.3	1.03	0.56–1.90	0.92	10	2.3	0.64	0.34–1.21	0.17
Fruit-growing	23	4.9	1.56	1.01–2.40	0.04	16	3.8	1.09	0.71–1.67	0.69
Potatoes	23	4.9	1.23	0.80–1.89	0.35	17	4.0	1.33	0.94–1.88	0.11
History of pesticide poisoning	44	5.8	1.97	1.43–2.73	<10–3	37	5.4	1.24	0.88–1.76	0.22

* OR adjusted on age, sex and educational level.

** OR adjusted on age, sex and educational level and Body mass index.

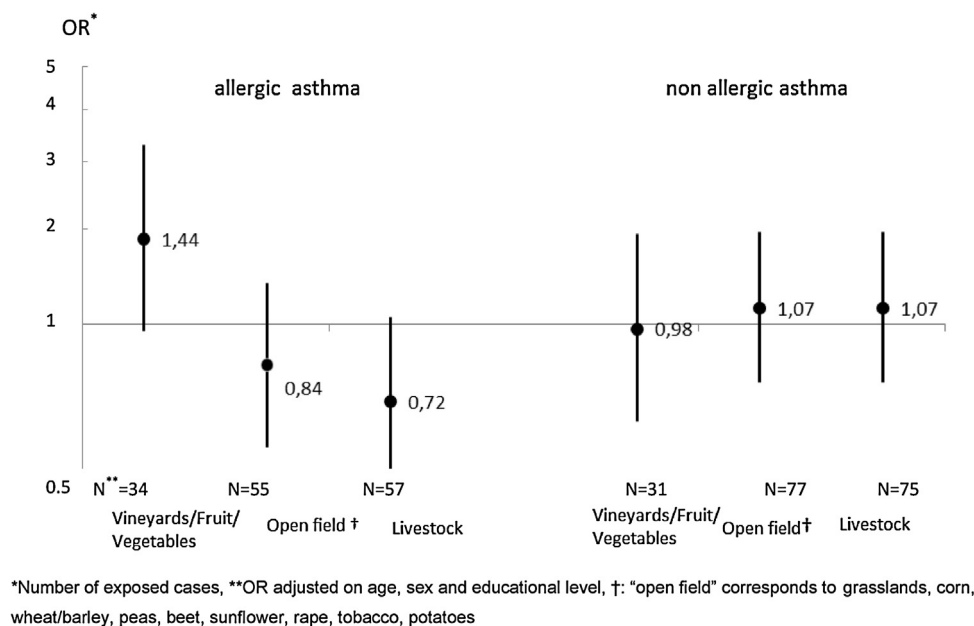


Fig. 2. Risk of allergic ($N=150$) and non-allergic ($N=165$) childhood asthma according to living on a farm during first year of life devoted to vineyards/fruit/vegetables (including greenhouses), open field or livestock, AGRICAN 10% sample at enrolment, 2005–2007.

questionnaires, which have been shown to be reliable and reproducible regarding doctor-diagnosed asthma (Burney et al., 1989; Jenkins et al., 1996) and have been used in other large studies, also in agriculture like the Agricultural Health Study. On the basis of the questionnaire, we could differentiate allergic and non-allergic asthma which are thought to have different etiologies. We were unable to perform the skin prick test in order to assess atopy, and even though personal allergy as measured by questionnaires and hay fever and/or eczema remain the best way to collect information in epidemiological studies, they have been recognized not to capture all aspects of allergy-atopy spectrum (Hoppin et al., 2011).

It seemed rational to consider the various types of farming separately since environmental factors, which may differ from one crop

or farm animal to another, can impact the development of allergy. Missing data were limited concerning asthma, allergy and the most frequent crops and livestock. Our analysis, which was based on data collected at baseline, was cross-sectional. Nevertheless, participants reported asthma and exposure life-long so that the analysis was based both on current and past activities.

The healthy worker effect is a concern in studies on occupational asthma. Individuals who experienced asthma in relation with farm environment at young ages may indeed have chosen work outside agriculture or sensitive individuals may leave work once hired. However, participants were included in the cohort even if they had left the healthcare system after 36 months of work, a strategy which should have limited the bias. Anyway, this effect would

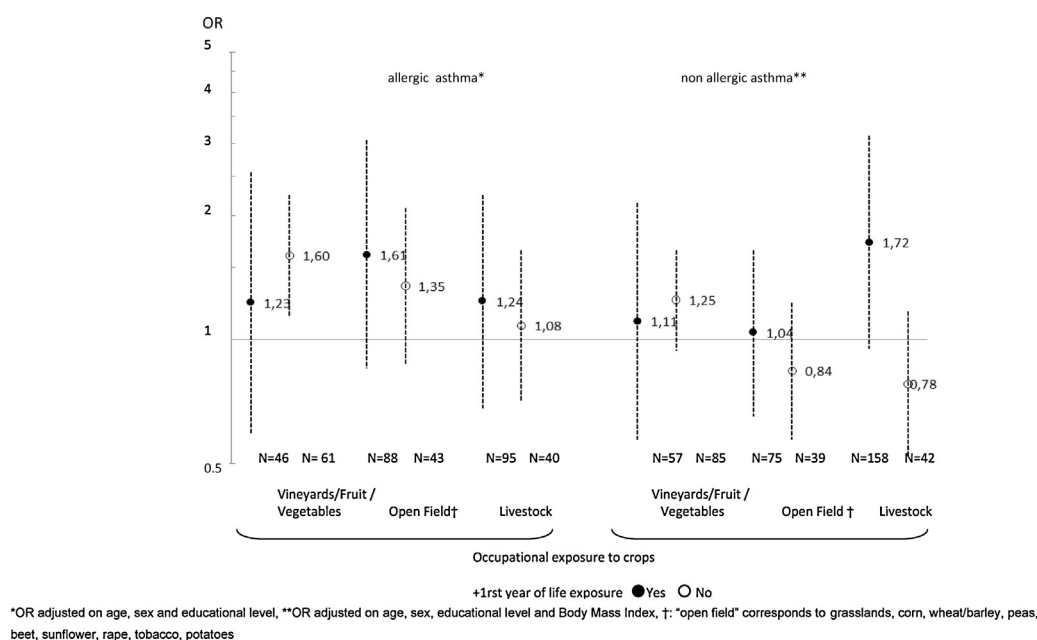


Fig. 3. Risk of allergic ($N=247$) and non-allergic ($N=427$) adult onset asthma according to life-long vineyards/fruit/vegetables, open field or livestock farming and according to exposure on a farm during first year of life.

have led to underestimating the impact of farming exposure but cannot explain the positive associations we found.

In our study, the role of early-life on a farm in the first year of life depended on the farm activity. Contact with farm animals in early childhood was found protective against allergic asthma, consistently with other studies. A recent meta-analysis including 39 studies found that the prevalence of asthma and wheezing was 25% lower among participants exposed to farming environments, but it also pointed to a substantial heterogeneity across studies (Genuneit, 2012). In our view, the discrepancies could be due to differences in farming activities. Indeed, contrary to the results on livestock, we found an increase in risk of allergic asthma in participants raised on farms with vineyards, fruit or vegetables.

We found an excess of asthma in participants exposed to several crops but not in livestock breeders, as observed elsewhere including France (Choudat et al., 1994; Dalphin et al., 1998; Hoppin et al., 2002a; Preller et al., 1996; Radon et al., 2001; Sprince et al., 2000). However, in those studies, the breeding conditions were often those of animal confinement, which was not the only animal husbandry practice in our participants. Results from the Agricultural Health Study demonstrated that participants respond differently to livestock exposure according to the type of animals raised, the agricultural practices, the activities performed and their individual characteristics (Hoppin et al., 2002b).

Our data suggest that pesticide exposure could play a role in allergic asthma, in line with the finding of the AHS, which showed stronger associations with pesticides for atopic than for non-atopic asthma (Hoppin et al., 2009, 2008). Few individual pesticides have been studied in epidemiological studies on respiratory health. Paraquat, a herbicide, has been associated with wheezing and decreased lung function (Dalvie et al., 1999). Organophosphates, carbamates and organochlorine insecticides have been associated with asthma in population-based studies (Hernández et al., 2011). At this stage of the cohort AGRICAN, we could not assess exposure to individual pesticides but we did find a risk of allergic asthma in participants exposed to fruit, greenhouse plants and vineyards, which extensively use pesticides and especially fungicides. In existing population-based studies, data on fungicides and respiratory health are scarce. However, a risk of atopic asthma was identified for all the fungicides included in the AHS questionnaire in women (captan, chlorothalonil, maneb, metalaxyl) (Hoppin et al., 2008) and it was higher for captan, maneb/mancozeb and metalaxyl in men (no increase for benomyl and chlorothalonil) (Hoppin et al., 2009). Due to the low prevalence of fungicide exposure in the AHS (less than 5% in women and 20% in men), the associations reached significance only for metalaxyl in women (OR=2.61, 1.35–5.04) and captan in men (OR=1.83, 1.15–2.94). In another epidemiological study exploring whether pesticides increase asthmatic symptoms in occupationally exposed subjects, a slight increase in asthma diagnosis and medication was found when exposure was assessed through dithiocarbamate metabolite in urine, while no association was observed when considering pesticide exposed workers versus non exposed (Boers et al., 2008).

Epidemiological studies have demonstrated that respiratory diseases are also associated with a variety of other agents in agriculture including grains, hay and animals. However, in the crops found associated with asthma (vineyards, fruits and greenhouse plants), these factors could not have played a major role. We cannot completely rule out the role of other factors possibly related to lung diseases such as dust, gasoline exhaust and solvents.

In line with the AHS results on high pesticide events, we found an increase in asthma in participants with a history of pesticide poisoning (Hoppin et al., 2009). This result might be explained by delayed effects of acute exposure or by the fact that poisonings occur more frequently in the most exposed workers.

Several mechanisms may underlie the development or maintenance of asthma following pesticide exposure (direct airway damage, interactions with irritant receptors, modulation of inflammatory response, etc.). Some experimental data suggest that organophosphates induce airway hyper-reactivity at doses below those causing acetylcholinesterase inhibitions (Lein and Fryer, 2005). Other studies suggested that low levels of dithiocarbamates, an important fungicide group, could exert immunomodulatory effects (Corsini et al., 2013). Further studies at the molecular level are needed to clarify the role of pesticides in allergic and non-allergic asthma (Hernández et al., 2011).

In the AGRICAN study, we found that the risk of allergic asthma was associated with several farming activities, including crops on which fungicides are widely used, while no significant excess in risk was seen for non-allergic asthma and in livestock breeders. We also demonstrated that the association between living on a farm during early childhood and asthma occurrence differed according to the type of farming. Our findings reinforce the need to study separately allergic and non-allergic asthma, and the assumption that the various types of farming have a different impact on childhood and occupational asthma. They also point to the need for physicians and researchers to be aware of respiratory hazards in the farming population, despite their low prevalence of smoking. Even if the precise mechanisms remain unclear, practical measures to reduce the impact of potentially harmful risk factors like pesticides should be carefully considered.

Acknowledgements

We are indebted to S Deant, M Niez and V Tribouillard for processing data from the enrolment questionnaire and AS Lacauve, C Meyer and E Niez for technical assistance. MA Presles and J Estru (MSA Loire Atlantique-Vendée), Y Cosset (Caisse Centrale MSA), M Delanoë (MSA Midi Pyrénées Nord), G Gastinger (MSA Alsace), AV Guizard (Registre Général des Tumeurs du Calvados), C Hermouet (Caisse Centrale MSA), B Ladépêche (MSA Gironde), JJ Laplante (MSA Franche Comté), D Lenoir (MSA Bourgogne), A Morel (MSA Côtes Normandes), S Papazian (MSA Picardie) E Rigaud (Caisse Centrale MSA), O Surot (MSA Alpes du Nord), M Velten (Registre des Cancers du Bas Rhin) are members of the Steering Committee of the AGRICAN cohort. The enrolment phase of the cohort was funded by the *Mutualité Sociale Agricole, Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail, Fondation de France, Conseil Régional de Basse Normandie and Ligue Contre le Cancer*.

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