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Host determinants for the development of allergy in apprentices exposed to laboratory animals

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Host determinants for the development of allergy in apprentices exposed to laboratory animals. D. Gautrin, H. Ghezzo, C. Infante-Rivard, J-L. Malo. ©ERS Journals Ltd 2002.

ABSTRACT: The aim of this study was to evaluate whether determinants of work-related symptoms, skin sensitization and diseases differ between atopic and nonatopic subjects starting a career with exposure to laboratory animals (LA).

A cohort of 417 apprentices in animal-health technology was prospectively followed during 32 or 44 months. The effect on the study outcomes of variables derived from questionnaire, skin reactivity, and lung function assessments at baseline were compared in atopic (n=212) and nonatopic (n=183) subjects.

Eighty-five incident cases of sensitization to a LA-derived allergen were identified, 67 among atopic and 18 among nonatopic subjects. Baseline rhinitis symptoms in contact with pets and skin sensitization to pets were associated with the development of work-related rhinoconjunctivitis (RC) symptoms in atopic subjects, whereas perannual rhinitis symptoms and having a PC_{20} (provocative concentration causing a 20% fall in forced expiratory volume in one second) $\leqslant 32$ mg·mL^{-1} were associated in nonatopic subjects. Baseline rhinitis symptoms on contact with pets and a PC_{20} value $\leqslant 32$ mg·mL^{-1} were significant determinants for developing sensitization to a specific allergen in atopic subjects only. Finally, baseline rhinitis symptoms in contact with pets and perannual rhinitis symptoms were associated with the development of occupational RC in atopic subjects, whereas in nonatopic subjects this was associated with having a PC_{20} value $\leqslant 32$ mg·mL^{-1}.

In conclusion, the determinants for the development of specific skin sensitization, symptoms and disease are different between atopic and nonatopic apprentices starting occupational exposure to laboratory-animal-derived allergens.

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Exposure to laboratory animal-derived allergens carries a significant risk for immunoglobulin (Ig)-E-mediated sensitization and development of oculonasal and respiratory symptoms as well as occupational rhinoconjunctivitis (RC) and asthma (OA) [1]. In a prospective assessment of 342 laboratory-animal workers, CULLINAN *et al.* [2] found that 46 (13%) developed skin reactivity to rat urine over a 3.5-yr period. In a prospective study of 417 apprentices starting exposure to laboratory animals and seen for a 32- to 44-month period, 85 (20%) incident cases of sensitization to at least one laboratory-animal-derived allergen were identified [3]. Interestingly, one third of these cases had probable OA as they also developed significant changes in bronchial hyperresponsiveness [4].

As for most high molecular weight occupational allergens, almost all cross-sectional studies on animal workers to date [1] have shown atopy to be a risk factor for sensitization to animal-derived allergens. In a prospective assessment, the present authors found that atopy was a risk factor for skin sensitization although the relative risk (RR) was relatively low (RR=2.2, 95% confidence interval (CI)=1.2–3.9). The only other factor associated with the development of skin sensitization to animal-derived allergens was the presence of respiratory symptoms in the pollen season (RR=5.2, 95% CI=1.7–16.1) [3]. Although atopic subjects are at greater risk for sensitization, it is known that only one third of subjects will progress to symptomatic state, at least in the first 5 yrs of follow-up after sensitization [5]. The positive predictive value of atopy is therefore relatively low and considering that ~50% of young adults are currently atopic subjects [6], therefore excluding them from entering a career in which they will be exposed to laboratory animals cannot be recommended. A non-negligible proportion of nonatopic subjects exposed to laboratory animals might also develop skin sensitization. In a pooled survey of 649 workers from four countries who were exposed to laboratory animals, 18/401 (4.5%) nonatopic subjects had skin reactivity to rat urine [7]. Among the 85 incident cases of sensitization to a laboratory-animal-derived allergen identified in the present authors' previous study, 18 (21%) had entirely negative skin tests to common allergens [3].

Risk factors for outcomes of allergy might well

differ according to atopic status. The present study, therefore, aimed to examine the determinants for the development of skin sensitization to a common allergen (mites) and laboratory animal-derived allergens, as well as the development of work-related oculonasal and respiratory symptoms, occupational RC and probable OA, by examining atopic and nonatopic subjects separately.

Material and methods

Study subjects

Baseline characteristics of the 417 apprentices in animal-health technology recruited in five different specialized schools between 1993–1995 have been reported previously [6]. Subjects in these schools were eligible to participate in a prospective study for the duration of their vocational programme provided that they had not been exposed to the aeroallergens relevant to this study in the course of an apprenticeship or job for a total of $\geqslant 3$ months before entering the program, as assessed in a preliminary visit. Among the 417 subjects initially recruited, 395 attended at least one follow-up visit and had interpretable skin tests results. The study protocol was approved by the Ethical Committee of Sacré-Coeur Hospital, Montreal, Canada. The subjects gave written consent to their participation when recruited in this cohort study.

Study design

The subjects in animal-health technology were reassessed at 8, 20, 32 and 44 months after starting the programme. The majority of students attended the 20- (n=345) and 32-month (n=355) visits. There were 136 students at the 8-month assessment because the others had not been exposed to laboratory animals since starting in the programme; these students were seen at the 20- and 32-month assessments. Finally, 98 subjects attended the longest programme and were seen up to the 44-month assessment.

Study methods

At the time of entry into the apprenticeship programme and at each follow-up visit, each student answered a respiratory questionnaire derived from the standardized questionnaire of the International Union Against Tuberculosis and Lung Diseases (IUATLD) [8]. Information was obtained on physician-diagnosed asthma, personal allergic conditions and familial asthma. Symptoms suggestive of asthma included wheezing, chest tightness, shortness of breath, or cough under usual conditions or under such conditions as exercise or exposure to cold air, strong odours, smoke, or dusts. Respiratory symptoms and RC on contact with pets and pollens were also documented.

Skin tests were done with the prick method [9] using 11 common inhalants: mixed trees, mixed grass, and ragweed pollens; Alternaria, Aspergillus, and Hormodendrum; feathers; *Dermatophagoides farinae* and *D. pteronyssinus*; and cat and dog dander (Omega, Montreal, Canada). For mite-derived allergens and cat dander, standardized extracts were used. Histamine phosphate (1/200 $g \cdot mL^{-1}$) was used as a positive control, and diluent (glycerine, 50%), as a negative control. The largest weal diameter was assessed 10–15 min after introduction of the antigen. A positive reaction was defined as a weal $\geqslant 3$ mm in the absence of reaction to the diluent and in the presence of a positive reaction to histamine phosphate. Contrary to a previous publication by the present authors in which atopy was defined as at least two positive reactions to the common inhalants [3], in the present study atopy was defined as one positive reaction in order to have no occurrence in nonatopic subjects at baseline in the case of skin reactions to mites.

In addition, skin-prick tests were performed with extracts of aeroallergens potentially present in the students' working areas, specifically urinary proteins from rat, mouse, and rabbit (Pharmacia Allergon AB, Angelholm, Sweden), as well as rabbit dander (Omega). All extracts were obtained before the beginning of the study in sufficient amounts to perform the total estimated number of skin tests to the end of the project. The skin-prick tests were performed by the same nurse throughout the study.

Skin sensitization to a specific agent was considered positive if sensitization developed at one or the other of the follow-up visits and remained positive at a later visit when three assessments were performed. The same criteria were applied for incident symptoms.

Spirometry with the assessment of forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) was carried out using a Collins apparatus (Survey/1 Plus Collins, Braintree, MA, USA) according to published standards [10]. Methacholine inhalation tests were performed using a Wright's nebulizer (Roxon Meditech Ltd, Montreal, Quebec, Canada) (output=0.14 $mL \cdot min^{-1}$) at tidal volume breathing for 2 min according to guidelines slightly modified from those of the European Respiratory Society [11]. The procedure for performing the methacholine test was modified as described elsewhere to take into account the absence of an on-site physician [12]. The provocative concentration causing a 20% fall in FEV_1 (PC_{20}) was interpolated from individual dose-response curves drawn on a semi-logarithmic scale using non-cumulative doses. Reference values for FEV_1 and FEV_1/FVC were taken from KNUDSON *et al.* [13]. Bronchial hyperresponsiveness was set at $\leqslant 16$ $mg \cdot mL^{-1}$ [14].

Exposure assessment

The number of hours spent in contact with rodents was considered as a potential determinant for the development of the outcomes. Three categories ($\leqslant 16$, $17–\leqslant 52$, >52 h) that best delineated the frequency distribution were set previously [3].

Statistical analysis

The cohort of students was divided into two groups according to atopic status at baseline. The outcomes studied were: 1) skin sensitization to mites; 2) skin sensitization to specific laboratory animal-derived allergens; 3) nasoocular symptoms; 4) work-related respiratory symptoms; 5) occupational RC defined as the association of the development of skin sensitization to at least one specific programme-derived allergen and at least one nasoocular symptom; and 6) probable OA defined as the association of the development of skin sensitization to at least one specific programme-derived allergen and significant changes (3.2-fold difference or more) in PC_{20}. The independent variables in the analyses assessed at baseline included: atopy and immediate skin reaction to pets, history of hay fever, asthma, exercise-induced respiratory symptoms, cold air-induced respiratory symptoms, perannual rhinitis, rhinitis on contact with pets, respiratory symptoms in the pollen season, and familial history of asthma as well as PC_{20} (dichotomized into $\leqslant 32$ *versus* >32 mg·mL^{-1} and $\leqslant 16$ *versus* >16 mg·mL^{-1}). Univariate analyses were used separately for each group to evaluate odds ratios (OR) and 95% CI for the effect of several host factors on each outcome. Multivariate logistic regression analyses were performed for each group and each outcome with the independent variables meeting the 0.10 level of significance in the univariate analyses. In the individual logistic regression analyses to estimate the OR for the incidence of a given outcome, only the subjects free of this condition at baseline were included. Statistical analyses were performed using the SPSS software package. The level of statistical significance was set at $p<0.05$ (two-sided).

Results

Of the 395 eligible subjects, 212 (54%) were atopic and 183, nonatopic. Table 1 shows the prevalence of the study outcomes at baseline as well as the number of incident cases during follow-up. The incidence of skin positivity to mites, work-related RC, respiratory symptoms, specific immunological sensitization and occupational RC was higher in atopic subjects than in nonatopic apprentices. The incidence of probable OA was also greater in atopic than in nonatopic subjects.

Table 2. – Respiratory symptoms suggestive of asthma at baseline (prevalent) and during follow-up (incidence) according to incidence of probable occupational asthma and atopic status

	Probable occupational asthma		
	Present		Absent
	Atopic	Nonatopic	
Subjects (n)	24	6	367
Symptoms suggestive of asthma[#]			
At baseline	9 (37.5)	0	59 (16.1)
Incident[¶]	8/15 (53.3)	1/6 (16.7)	51/308 (16.6)
Exercise-induced symptoms			
At baseline	11 (45.8)	0	70 (19.1)
Incident[¶]	6/13 (46.2)	1/6 (16.7)	50/297 (16.8)
Symptoms on exposure to cold air			
At baseline	5 (20.8)	0	53 (14.4)
Incident[¶]	9/19 (47.4)	1/6 (16.7)	28/314 (8.9)

Data are presented as n (%); [#]: at least two of the following symptoms: wheezing, chest tightness, dyspnoea, awakening at night with cough; [¶]: the denominator is the number of subjects without symptoms at baseline.

Among the 131 subjects with skin reactivity to mites at baseline, 14% had reported a physician-diagnosed asthma and 64.8% nonseasonal rhinitis; in contrast, among subjects without skin reactivity to mites at baseline, the proportions were respectively 6.3% and 30.4%. Table 2 illustrates that only one nonatopic subject with probable OA also developed respiratory symptoms suggestive of asthma and symptoms induced by exercise and cold air, while >50% atopic subjects with OA also developed symptoms suggestive of asthma. The incidence of symptoms suggestive of asthma, as well as of symptoms induced by exercise and cold air was more than two-fold in apprentices who developed probable OA than in the other members of the cohort.

Table 3 shows the proportions of atopic and nonatopic subjects developing specific sensitization to rodents, occupational rhinoconjunctivitis and probable OA according to number of hours of exposure to rodents. Among atopic subjects, a high proportion

Table 1. – Skin reactivity to common and specific allergens, work-related symptoms, and occupational diseases at baseline (prevalent) and during follow-up (incidence) according to atopic status

	Atopic n=212			Nonatopic n=183		
	At baseline	Incident[#]	Absent[#]	At baseline	Incident[#]	Absent[#]
Skin reactivity to mites	131 (61.8)	15/81 (18.5)	66/81 (81.5)	0 (0)	17/183 (9.3)	166/183 (90.7)
Work-related rhinoconjunctivitis	30 (14.2)	82/182 (45.1)	100/182 (54.9)	1 (0.6)	33/182 (18.0)	149/182 (81.4)
Work-related respiratory symptoms	0 (0)	24/212 (11.3)	188/212 (88.7)	0 (0)	3/183 (1.6)	180/183 (98.4)
Specific sensitization	14 (6.6)	67/198 (33.8)	131/198 (66.2)	1 (0.6)	18/182 (9.8)	164/182 (89.6)
Occupational rhinoconjunctivitis	9 (4.2)	51/203 (25.1)	152/203 (74.9)	0 (0)	11/183 (6.0)	172/183 (94.0)
Probable occupational asthma	-	24/67[¶] (35.8)		-	6/18[¶] (33.3)	

Data are presented as occurrence of outcome n (%); [#]: the denominator is the number of subjects at risk (*i.e.*, without the outcome at baseline); [¶]: the denominator is the number of cases of specific immunological sensitization.

Table 3. – Skin reactivity to specific allergens, work-related rhinoconjunctivitis, and occupational diseases according to atopic status and hours of exposure to rodents

Outcome (hrs of exposure)	Atopic	Nonatopic
Specific immunological sensitization		
⩽16	35/78 (44.9)	3/52 (5.8)
17 to ⩽52	20/86 (23.3)	4/78 (5.1)
>52	12/34 (35.3)	11/52 (21.2)
Work-related rhinoconjunctivitis		
⩽16	26/61 (42.6)	4/52 (7.7)
17 to ⩽52	30/77 (39.0)	11/77 (14.3)
>52	20/34 (58.8)	17/52 (32.7)
Occupational rhinoconjunctivitis		
⩽16	21/73 (28.8)	1/52 (2.0)
17 to ⩽52	16/86 (18.6)	2/78 (2.6)
>52	8/34 (23.5)	7/52 (13.5)
Probable occupational asthma		
⩽16	12/78 (15.4)	2/52 (3.8)
17 to ⩽52	9/86 (10.5)	1/78 (1.3)
>52	3/34 (8.8)	3/52 (5.8)

Data are presented as susjects with outcome (n (%)).

developed specific sensitization and occupational rhinitis at the lowest duration of exposure and no increase was seen with higher duration; on the other hand, among nonatopics, the incidence of the same outcomes clearly augmented with the number of hours of exposure. Although the number of new case of probable OA was small, it was noted that atopic subjects appeared more likely to develop probable OA than nonatopics at the two lowest categories of exposure, but that the proportions were similar in atopic (8.8%) and nonatopic (5.8%) individuals at the highest exposure category.

Table 4 gives the results of the nonadjusted logistic regression analyses. Having a mother with asthma was a significant factor associated with the development of skin reactivity to mites in atopic subjects whereas smoking was the only significantly associated factor in nonatopic subjects. For the development of specific sensitization to a work-related antigen, several factors were found to be contributive but in atopic subjects only. Perannual rhinitis, respiratory symptoms on contact with pets, and a PC20 value $\leqslant 8$ and $\leqslant 32$ mg·mL^{-1} were associated with work-related RC for both atopic and nonatopic subjects. Whereas several factors were significant predictors of work-related respiratory symptoms, occupational rhinoconjunctivits and probable OA in atopic subjects, having a PC20 $\leqslant 32$ mg·mL^{-1} was the only significant predictor of occupational RC in both atopic and nonatopic individuals.

Tables 5 and 6 show the results of the multivariate analysis. It can be seen that having a mother with asthma in atopic subjects and smoking in nonatopic subjects were significantly associated with the incidence of skin reactivity to mites, a nonwork-related environmental allergen. As regards work-related RC symptoms, the predictive factors in atopic subjects (rhinitis on contact with pets, immediate skin reactivity to pets) and in nonatopic subjects (perannual rhinitis, respiratory symptoms on contact with pets, and a PC20 $\leqslant 32$ mg·mL^{-1}) were different. In the case of work-related respiratory symptoms, significant determinants (rhinitis on contact with pets, immediate skin reactivity to pets, a PC20 $\leqslant 32$ mg·mL^{-1}) were found only in atopic subjects. Table 6 shows that rhinitis on contact with pets, and having a PC20 $\leqslant 32$ mg·mL^{-1} were associated with specific immunological sensitization in atopic subjects. No factor was a significant determinant in nonatopic subjects. Perannual rhinitis and immediate skin reactivity to pets were significantly associated with occupational RC in atopic subjects, whereas a PC20 $\leqslant 32$ mg·mL^{-1} was significantly associated with occupational RC for both atopic and nonatopic subjects. Finally, skin reactivity to pets was significantly associated with probable OA in atopic subjects.

Discussion

In a prospective cohort of apprentices starting exposure to laboratory animals, the present authors previously identified several factors associated with the development of IgE-mediated sensitization to laboratory-animal allergens. These were atopy and respiratory symptoms in the pollen season [3]. The determinants for probable OA were baseline skin reactivity to pets, bronchial responsiveness (PC20 $\leqslant$ 32 mg·mL^{-1}) and FEV1 [4]. In this cohort of laboratory workers, 18 of the 85 incident cases of sensitization and six of the 30 incident cases of probable OA were nonatopic. Although atopy is clearly a major risk factor, work-related specific sensitization and probable OA do occur in nonatopic subjects as well. It is therefore of interest to know whether the secondary risk factors differ in atopic and nonatopic subjects. In a previous paper [3], by the present authors, the interaction between atopy and the other factors was not studied in the analysis because of the small number of cases. Therefore, in the study presented here parallel analyses were performed in atopic and nonatopic subjects. Such separate analyses have rarely been carried out. HEEDERIK *et al.* [7] examined the effect of ranked levels of exposure in 650 atopic and nonatopic subjects exposed to laboratory animals. These authors found that atopic workers in three levels of antigen exposure had a constant three-fold increased sensitization risk compared with non-exposed workers, while nonatopic workers showed an increased sensitization risk with higher exposure category. These findings were confirmed in the present authors study for the development of specific sensitization and occupational rhinoconjunctivitis

In the present study, for most analyses, except for work-related respiratory symptoms in nonatopic subjects (n=3), the number of incident outcomes was sufficient to allow firm conclusions. Indeed, when the incidence is <10, the results from a logistic regression analysis may be spurious or imprecise as discussed elsewhere [15].

In atopic subjects, certain factors such as rhinitis on contact with pets and immediate skin reactivity to pets as well as having a PC20 $\leqslant 32$ mg·mL^{-1} were associated with more than one outcome. The ORs for work-related

Table 4. – Odds ratios (OR) and 95% confidence intervals (CI) for skin reactivity to common and specific allergens, work-related symptoms, and occupational diseases in relation to host factors

Outcome and factor	Atopic	Nonatopic
Skin reactivity to mites		
Mother with asthma	3.9 (0.9–16.0)	
Smoking		4.8 (1.7–13.8)
Work-related rhinoconjunctivitis		
Rhinitis on contact with pets	4.2 (2.3–7.7)	
Perannual rhinitis	4.0 (2.1–7.4)	2.4 (1.0–5.4)
Respiratory symptoms on contact with pets	2.6 (0.8–8.1)	7.6 (1.2–47.5)
Immediate skin reaction to pets	4.6 (2.3–9.1)	
$PC_{20}<32$ mg·mL^{-1}	1.8 (1.0–3.3)	2.9 (1.3–6.3)
$PC_{20}<8$ mg·mL^{-1}	1.9 (0.9–4.0)	3.8 (1.3–10.8)
Work-related respiratory symptoms		
Hay fever	6.1 (2.3–15.9)	
Rhinitis on contact with pets	33.4 (4.4–252.1)	
Perannual rhinitis	16.9 (2.2–127.3)	
Respiratory symptoms on contact with pets	8.7 (3.2–23.6)	
Immediate skin reaction to pets	13.5 (4.4–41.4)	
$PC_{20}<32$ mg·mL^{-1}	8.0 (2.6–24.4)	
$PC_{20}<8$ mg·mL^{-1}	4.3 (1.8–10.3)	
Specific immunological sensitization		
Hay fever	4.0 (1.5–10.7)	
Rhinitis on contact with pets	4.0 (2.1–7.7)	
Perannual rhinitis	4.6 (2.2–9.5)	
Respiratory symptoms on contact with pets	5.1 (1.7–15.5)	
Immediate skin reaction to pets	3.4 (1.7–6.6)	
$PC_{20}<32$ mg·mL^{-1}	4.0 (2.0–7.7)	
$PC_{20}<8$ mg·mL^{-1}	2.9 (1.4–6.2)	
Occupational rhinoconjunctivitis		
Rhinitis on contact with pets	3.9 (2.0–7.6)	
Perannual rhinitis	4.9 (2.2–11.1)	
Respiratory symptoms on contact with pets	2.4 (0.9–6.8)	
Immediate skin reaction to pets	5.6 (2.9–11.1)	
$PC_{20}<32$ mg·mL^{-1}	3.6 (1.8–7.1)	4.1 (1.1–15.2)
$PC_{20}<8$ mg·mL^{-1}	2.6 (1.2–5.4)	
Probable occupational asthma		
Respiratory symptoms on contact with pets	3.2 (1.1–9.7)	
Immediate skin reaction to pets	4.1 (1.6–10.2)	

Data are presented as OR (95% CI). Nonadjusted analyses. PC_{20}: provocative concentration causing a 20% fall in forced expiratory volume in one second.

respiratory symptoms and their CIs, are larger for most risk factors in comparison with the ORs for the other outcomes (*i.e.*, work-related rhinoconjunctivitis, occupational rhinitis or probable OA) (table 4). This may be a spurious effect, indeed most subjects with work-related respiratory symptoms also have positive skin reaction to pets (20/24) and all, except one, have symptoms of rhinitis in contact with pets (table 5). However, when rhinitis in contact with pets is taken into account in the multiple logisitic regression analysis, the OR for work-related respiratory symptoms due to skin reaction to pets (OR=6.1) is comparable to the other ORs shown in table 4.

Rhinitis symptoms on contact with pets and immediate skin reactivity to pets might have been suspected to be reasonable predictors of the likelihood of developing one or the other of the selected outcomes in atopic subjects. In particular, the relationship between the latter risk factor and the development of specific immunological sensitization to laboratory animals could be attributable to cross-immunological reactivity between these mammalian species, as discussed previously [5, 16], major allergens belonging to the "same super-family of proteins" [17]. However, increased bronchial responsiveness could not have been so readily suspected. As previously discussed, it would therefore seem interesting to consider following-up subjects exposed to laboratory animals by using both skin-prick testing and bronchial responsiveness assessment [3] although positive predictive values are low, at least for a follow-up of 3–4 yrs as in the current study (in the order of 30–50%).

The most interesting finding of the present study is the fact that not only do a substantial number of nonatopic subjects develop specific sensitization (18/85, 21.2%) and probable OA (6/30, 20%), but the associated factors differ in atopic and in nonatopic subjects. For instance, perannual rhinitis and having a $PC_{20} \leqslant 32$ mg·mL^{-1} were significantly associated with the development of work-related RC symptoms in nonatopic subjects, but not in atopic individuals. It is reasonable to assume that having perannual rhinitis symptoms may place someone more at risk to develop work-related RC, and also, that having a $PC_{20} \leqslant 32$ mg·mL^{-1} is a reflection of upper and/or lower

Table 5. – Odds ratios (OR) and 95% confidence intervals (CI) for skin reactivity to common allergens, and work-related symptoms in relation to host factors. In multivariate logistic regression analyses adjusting each factor to the others

Outcome	Factor	Atopic			Nonatopic		
		Number of subjects with factor/outcome[#]		OR (95% CI)	Number of subjects with factor/outcome		OR (95% CI)
		Present	Absent		Present	Absent	
Skin reactivity to mites							
Mother with asthma	Present	4	5	4.88 (1.11–21.33)			
	Absent	10	61				
Smoking	Present				6	19	4.51 (1.47–3.83)
	Absent				10	143	
Work-related rhinoconjunctivitis							
Rhinitis on contact with pets	Present	44	24	3.44 (1.77–6.69)			
	Absent	34	81				
Perannual rhinitis	Present				11	23	2.60 (1.04–6.35)
	Absent				21	121	
Respiratory symptoms on contact with pets	Present				3	2	6.26 (0.93–42.09)
	Absent				29	142	
Immediate skin reaction to pets	Present	33	16	2.97 (1.43–6.21)			
	Absent	45	88				
PC_{20}<32 mg·mL^{-1}	Present				15	34	3.21 (1.40–7.34)
	Absent				17	110	
Work-related respiratory symptoms							
Rhinitis on contact with pets	Present	23	75	18.18 (2.32–142.5)			
	Absent	1	115				
Immediate skin reaction to pets	Present	20	50	6.11 (1.86–20.03)			
	Absent	4	139				
PC_{20}<32 mg·mL^{-1}	Present	20	73	3.94 (1.18–13.15)			
	Absent	4	117				

[#]: The number of cases with the outcome present or absent is given, as is the number of cases with the factor present or absent. PC_{20}: provocative concentration causing a 20% fall in forced expiratory volume in one second.

airways responsiveness. In atopic subjects, these factors are individually associated with the incidence of work-related RC symptoms, but are overshadowed by the presence of atopy, and symptomatology on contact with pets in a multivariate analysis.

The present authors found that smoking was

Table 6. – Odds ratios (OR) and 95% confidence intervals (CI) for skin reactivity to specific allergens, and occupational diseases in relation to host factors. In multivariate logistic regression analyses adjusting each factor to the others

Outcome	Factor	Atopic			Nonatopic		
		Number of subjects with factor/outcome[#]		OR (95% CI)	Number of subjects with factor/outcome		OR (95% CI)
		Present	Absent		Present	Absent	
Specific immunological sensitization							
Rhinitis on contact with pets	Present	40	37	3.71 (1.83–7.52)			
	Absent	19	77				
PC_{20}<32 mg·mL^{-1}	Present	37	34	2.95 (1.46–5.95)			
	Absent	22	80				
Occupational rhinoconjunctivitis							
Perannual rhinitis	Present	39	81	2.90 (1.21–6.95)			
	Absent	8	75				
Immediate skin reaction to pets	Present	28	34	3.20 (1.50–6.85)			
	Absent	19	121				
PC_{20}<32 mg·mL^{-1}	Present	31	55	2.13 (1.00–4.56)	6	45	4.10 (1.11–15.20)
	Absent	16	101		4	123	
Probable occupational asthma							
Immediate skin reaction to pets	Present	16	42	4.05 (1.60–10.21)			
	Absent	8	85				

[#]: The number of cases with the outcome present or absent is given, as is the number of cases with the factor present or absent. PC_{20}: provocative concentration causing a 20% fall in forced expiratory volume in one second.

associated with the development of skin reactivity to mites in nonatopic individuals. Although smoking has been associated in some studies with the development of airway hyperresponsiveness, its association with the development of IgE-mediated sensitization to common allergens has not been documented. Increase in total IgE levels is associated with both smoking and atopy, but separately [18, 19]. Atopic markers such as increased specific IgE levels and immediate skin reactivity to common inhalants seem to be even less common in smokers [20]. Smoking has however been found to be a determinant of IgE-mediated sensitization to such occupational agents as psyllium [21] and platinum salts [22]. However, smoking was not found to be associated with the development of specific skin reaction to laboratory animals in previously published studies by CULLINAN *et al.* [2] and HEEDERIK *et al.* [7]. The results of the present study, obtained in nonatopic subjects and with a small number of cases, are in accordance with these findings. However, the results of this study do not provide a clear statement on the role of cigarette smoking in the development of the outcomes studied here. The absence of an association between smoking sensitization and work-related allergens could be due to the young age of the subjects (mean age 19.5±2.9 yrs). Including such subjects allowed the present study, however, to observe the effects of work-related exposure independently of the effects of smoking.

The incidence of skin sensitization to mites was higher in atopic than in nonatopic subjects which was expected. However, the incidence of sensitization to this common allergen was lower than for most work-related outcomes.

The prospective design of this study performed in a cohort of apprentices, enabled the present authors to assess the subjects′ baseline atopic and airway responsiveness status, and medical history before any/or not more than 3-months exposure to the occupational allergens took place. This approach allows reduction in the bias that may otherwise be present when a cohort is assembled after some years of exposure [23]. In addition, it allows the natural history of the development of specific sensitization and OA to be studied, which is difficult in the case of common asthma as discussed elsewhere and as presented when the study was initiated [6].

In conclusion, as determinants of sensitization, symptoms and diseases differ in atopic and nonatopic subjects, it might be suggested to use such discrete analyses in population surveys.

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