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Sensitization to individual allergens as risk factors for lower FEV_1 in young adults

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Background Atopy may impair ventilatory function, but results are controversial. We assess the association between individual reactivity to allergens and the level of baseline maximal one-second forced expiratory volume (FEV_1), by smoking and respiratory symptoms.

Methods The 1472 participants (response 44.5%) of the five Spanish areas of the European Community Respiratory Health Survey (ECRHS) who performed respiratory function tests, skin prick tests and/or specific IgE against common aeroallergens (e.g. mites, pets, mould, pollens) are included. Bronchial hyperreactivity (BHR) was measured with a methacholine challenge.

Results After adjusting for BHR and smoking, in addition to the other allergens, skin reactivity to *Alternaria* (–208 ml; 95% CI : –451, 35) and IgE antibodies against cat (–124 ml; 95% CI : –269, 21) and Timothy grass (–115 ml, 95% CI : –190, –40) were associated with a decrease in FEV_1 in females. Among males, skin reactivity to olive showed the strongest association (–111 ml; 95% CI : –261, 38). The associations were stronger in females. Smoking modifies the association for *Alternaria* and cat (P for interaction < 0.05). While cat is associated with a decrease in FEV_1 in current smokers (–190 ml), *Alternaria* (–336 ml) was associated among never smokers. The exclusion of subjects with asthma symptoms, or adjustment for respiratory symptoms, led to similar results.

Conclusions We conclude that immunoresponse to individual allergens (particularly outdoor) is associated with the level of FEV_1, and this association occurred independently of asthma, and in smokers and non-smokers, which may be of interest in natural history of chronic obstructive pulmonary disease (COPD).

Keywords Asthma, atopy, COPD, cross-sectional, FEV_1, smoking

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Whether atopy is a host factor that predisposes individuals to chronic airflow obstruction is still unknown, although most of the recent results have been provided by follow-up studies. Follow-up studies are able to separate the temporal order of the events. An association between skin reactivity to common aeroallergens and decline in one-second maximal forced expiratory volume (FEV_1) was found among middle-aged and older males in the US Normative Aging Study whatever the smoking status,[1] but only in smokers in an occupational cohort,[2] and in a cohort of elderly in the UK.[3] These findings agree with the old Dutch hypothesis that 'allergy' was a host factor influencing the development of obstructive lung disease.[4] However, other longitudinal studies of smaller size,[5,6] and cross-sectional studies in the Tucson population (US)[7] did not find such an association. The role of atopy in FEV_1 impairment in the Tucson population was limited to subjects who reported asthma,[7] which led to the proposal of a form of persistent airways obstruction called 'chronic asthmatic bronchitis' different from the classical form found in smokers.[7]

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Most previous studies using skin reactivity included older subjects but skin reactivity is more frequent during youth.[1] In addition, recent epidemiological papers have shown the importance of using data on individual allergens instead of global indicators of atopy.[8] Individual allergens could have a specific role in FEV_1 impairment, and determinants of the individual immunoresponse could also have some specificity.[8] In addition, the measurement error of each allergen is on the side of false negatives when pooling together all allergens in a single indicator,[9] further, the type of error in responses obtained through skin tests was different from that obtained by means of specific IgE.[9] Finally, some of the previous studies[1] only included males. We propose to assess the interrelations between atopy, symptoms and smoking with FEV_1 level using the Spanish data of the European Community Respiratory Health Survey (ECRHS) study. The ECRHS is a cross-sectional study and thus unable to separate the effects on the maximal FEV_1 attained and the rate of decline of FEV_1. Cross-sectional studies can compare the average baseline level of FEV_1 between groups. Therefore, this study assesses the association between the immunoresponse to individual allergens and the level of FEV_1, by smoking and symptoms.

Methods

Design and sample

The aims and methods of the ECRHS have been described previously.[10] A random sample (n = 16 884) of the general population aged 20–44 years from five areas of Spain were contacted and asked to complete a short (seven questions) screening questionnaire on respiratory symptoms. In a second phase of the study, a 20% random sub-sample of the study population (n = 3310) was contacted. Subjects were asked to complete a long questionnaire, to provide blood samples, to undergo skin tests, a forced spirometric test, and a methacholine challenge test to measure bronchial responsiveness. The 1472 participants (total response rate 44.5%) from the five Spanish areas of the ECRHS, who performed a bronchial spirometry and from whom skin prick tests were obtained, are considered in the present study. The institutional committees on ethical practice approved this study and all subjects gave informed written consent.

Respiratory function and immunological measurements

Subjects underwent baseline spirometry (Biomedin, Padova, Italy), performing at least three acceptable repeatable (within 5% or 100 ml) manoeuvres to measure FEV_1.[8] In 1332 subjects a methacholine bronchial responsiveness challenge (BHR) was carried out.[8] Methacholine (Hoffman La Roche, London, UK) was administered in a standard reproducible way by dosimeter (Mefar, Bovezzi, Italy). Hyperreactivity, n = 217 (16.3%), was defined as any subject with a $\geqslant$20% fall in FEV_1 with respect to the highest post-diluent FEV_1 during the methacholine challenge with an accumulated dose of 5.117 μmol or extrapolated to 8 μmol of methacholine.

Atopy was assessed by means of serum specific IgE and skin sensitivity tests. A participant was considered to have measurable specific serum IgE when he/she had a specific IgE >0.35 kU/l by the CAP method (Pharmacia, Uppsala, Sweden) to any of the following allergens: cat, *Cladosporium, Dermatophagoides pteronyssinus, Parietaria* or Timothy grass. Total IgE was measured by the CAP system.

Skin sensitivity was assessed with standard extracts from the same batch. Individual antigen-coated lancets (Phazets, Kabi-Pharmacia, Uppsala, Sweden) and two control lancets (histamine and uncoated) were applied to the volar surface of the forearm. After 15 min the outline of the wheal was drawn on adhesive tape, which was transferred to data collection sheets. The largest diameter and that perpendicular to it were measured. A participant was considered to have a positive specific skin test when he/she produced a wheal of $\geqslant$3 mm to any of the following allergens*: Alternaria alternata,* birch, cat, *Cladosporium, Dermatophagoides pteronyssinus (DerP1),* olive, *Parietaria,* ragweed, or Timothy grass in the presence of a positive histamine control and a negative uncoated control.[11] Note that denominators for serum and skin analyses are not the same because a few participants gave serum samples but refused to have skin prick testing, and vice versa.

Statistical analysis

The association between pulmonary function and specific allergens was calculated using multiple linear regression, adjusting for age, study area and height. The best goodness-of-fit was obtained after controlling for height squared in males and height in females. Age and height were centred by their mean value to provide a meaningful intercept for each pulmonary function parameter. Area was included because of differences in the participation rates between cities and possible differences arising from differing technicians and interviewers between centres. The analysis was stratified by sex due to the important sex variations in the interactions between atopy, smoking and symptoms in lung function.[12] Interaction between smoking and allergens was assessed by testing the significance of interaction terms in the linear regression models and by stratifying the analysis by smoking, excluding ex-smokers. To assess the effect modification of asthma symptoms, two strategies were followed: the inclusion of symptoms in the multivariate model, and the exclusion of subjects with asthma symptoms. A second analysis focused on the association of atopy with having an FEV_1 below the lower limit of reference (abnormal FEV_1) was also carried out in order to obtain results with a clearer clinical interpretation. Abnormal FEV_1 values were defined as being below the lower limit of reference calculated as: predicted value –1.645*RSD, where RSD is the residual standard deviation, based on the reference values provided by Roca *et al.*[13] The association of abnormal lung function with allergens was assessed by the odds ratio (OR) using standard methods of logistic regression analysis. Subjects without abnormal FEV_1 values, according to previous definition, were considered as the control group.

Results

Table 1 shows the characteristics of the study subjects, who had a low prevalence of asthma symptoms, a moderate prevalence of BHR and atopy, and a high prevalence of smoking. Among females, skin reactivity to *Alternaria,* olive and *Parietaria*, and IgE antibodies to cat, *Parietaria* and Timothy grass were related with a lower FEV_1, whereas in males an association was only seen for skin reactivity to olive (Table 2).

Table 1 Description of participants by sex

	Females (n = 718)	Males (n = 754)
	Mean (SD)	Mean (SD)
FEV_1 (ml)	3099.7 (471.1)	4172.1 (703.3)
Age (years)	32.1 (7.2)	31.6 (7.5)
Height (cm)	159.2 (6.0)	172.5 (6.7)
	N (%)	N (%)
Abnormal FEV_1[a]	38 (5.3%)	43 (5.7%)
Education		
Secondary	207 (28.8%)	266 (35.3%)
High	205 (28.5%)	245 (32.4%)
Any Prick >2 mm	109 (15.2%)	200 (26.5%)
Any specific IgE >0.35 IU/ml[b]	119 (18.7%)	213 (31.7%)
BHR <1 mg methacholine[c]	112 (18.5%)	105 (15.7%)
Symptoms of asthma[d]	50 (6.9%)	63 (8.3%)
Smoking		
Current	331 (46.1%)	438 (58.1%)
1–9 cig/day	89 (12.3%)	81 (10.7%)
10–19 cig/day	109 (15.2%)	102 (13.5%)
≥20 cig/day	133 (18.5%)	255 (33.8%)
Past	94 (13.1%)	106 (14.1%)

[a] Predicted FEV_1 based on Roca equations—1.645*Residual Standard Deviation.

[b] Specific IgE was performed in 637 females and 672 males.

[c] Bronchial hyperreactivity, only performed in 604 females and 668 males.

[d] Reporting a nocturnal attack of shortness of breath, an attack of asthma during last year or taking medication for asthma during last year.

After adjusting for bronchial reactivity and smoking, in addition to the other allergens, only skin reactivity to *Alternaria* and IgE antibodies against cat and Timothy grass were associated with a lower FEV_1 in females (Table 3). Among males, the association with olive was slightly reduced. There was no statistically significant interaction between the association of specific immunoresponse and FEV_1 and sex, although a qualitative interaction with *Alternaria* seemed to occur (P for interaction = 0.12). Smoking modified the association for *Alternaria* and cat (P for interaction < 0.05). While cat is associated with a decrease in FEV_1 in current smokers, *Alternaria* was found to be so among never smokers. Education was associated with FEV_1 in some of the models. There was no interaction between specific immunoresponse and BHR.

Among females, wheezing, shortness of breath after exercise, asthma, and chronic bronchitis (defined as cough and phlegm >3 months) were related to a lower FEV_1 (Table 4). Among these symptoms, only wheezing was still related with FEV_1 after adjusting for BHR. Among males, in addition to shortness of breath after exercise, asthma, and chronic bronchitis, habitual cough and habitual phlegm were also associated with a lower FEV_1. After adjusting for BHR, shortness of breath after exercise and chronic bronchitis maintained their associations with a decrease in FEV_1. The differences in FEV_1 associated with individual allergens observed in Table 3 were almost identical to those observed in Table 4, after adjusting for symptoms. The same occurred in the analysis for smokers and never smokers (data not shown). In addition, the exclusion of subjects with asthma symptoms, weakened slightly the association of

Table 2 Differences in FEV_1 for subjects with specific skin reactivity or presence of IgE antibodies in comparison with those without

	Differences in FEV_1 (ml)[a]			
	Females (n = 718)		Males (n = 754)	
	n	Difference (95% CI)[b]	n	Difference (95% CI)[b]
Prick >2 mm				
Alternaria	9	–261 (–500, –22)	15	145 (–136, 429)
Birch	11	–110 (–327, 107)	14	152 (–138, 442)
Cat	22	–62 (–217, 93)	38	–122 (–298, 54)
DerP1	62	–24 (–108, 60)	142	42 (–58, 142)
Olive	43	–136 (–254, –18)	46	–144 (–305, 16)
Parietaria	8	–232 (–485, 20)	12	64 (–242, 370)
Timothy grass	42	–93 (–207, 20)	76	13 (–116, 142)
Any[c]	112	–64 (–138, 10)	203	47 (–41, 135)
Specific IgE >0.35 IU/ml				
Cat	30	–161 (–296, –25)	33	–46 (–238, 146)
Cladosporium	22	–73 (–227, 81)	10	120 (–223, 463)
DerP1	72	–19 (–109, 71)	150	55 (–45, 155)
Parietaria	28	–127 (–264, 10)	38	37 (–145, 219)
Timothy grass	59	–123 (–221, –25)	101	–34 (–145, 219)
Total IgE (IU/ml)				
10–100	375	–21 (–109, 67)	370	–16 (–132, 100)
>100	123	–79 (–148, –10)	206	–33 (–158, 92)

[a] For total and specific IgE the numbers were 663 females and 699 males.

[b] Adjusted for age and height.

[c] Any prick positive to *Alternaria*, birch, cat, *Cladosporium*, olive, *Parietaria*, *Plantago*, *Dermatophagoides pteronissinum*, ragweed, rye grass, Timothy grass. Prevalence of specific allergens not individualized in the Table was <1%.

Table 3 Factors related with an adjusted difference in FEV_1 by sex and by smoking

	Difference in FEV_1 (95% CI) (ml)[a]			
	Females (n = 592)	Males (n = 663)	Current smokers (n = 605)	Never smokers (n = 376)
Prick *Alternaria* >2 mm	–208 (–451, 35)	–	–[b]	–336 (–724, 52)
IgE cat >0.35 IU/ml	–124 (–269, 21)	–	–190 (–349, –31)	–[b]
Prick olive >2 mm	–	–111 (–261, 38)	–	–
IgE Timothy grass >0.35 IU/ml	–115 (–190, –40)	–	–[b]	–129 (–252, –6)
Education (Secondary/High)	–	63 (16, 110)	67 (24, 110)	–
Bronchial reactivity (<1 mg of methacholine)	–265 (–337, –193)	–227 (–335, –119)	–270 (–354, –185)	–225 (–343, –107)
Smoking 10–19 cig/day	–69 (–139, –1)	–177 (–265, –89)	–153 (–354, –185)	
Smoking >19 cig/day	–128(–247, –9)	–233 (–117, –348)	–212 (–229, –76)	

[a] Adjusted for age in years, height in cm, and variable in the Table. For smokers and never smokers also adjusted for sex. Reference group: non-reactive to individual allergens, primary education, non-bronchial hyperreactive and non-smokers.

[b] *P* for interaction with smoking; for *Alternaria* = 0.04, for cat = 0.02, and for Timothy grass = 0.23.

– Not included in the model due to $P > 0.2$.

Table 4 Respiratory symptoms associated with differences in FEV_1, and association between individual immunoresponse and change in FEV_1 adjusted for symptoms

	Difference in FEV_1 (ml)			
	Females (n = 718)		Males (n = 754)	
	n	Difference (95% CI)[a]	n	Difference (95% CI)[a]
Wheezing apart from colds	75	–135 (–227, –43)	106	–49 (–125, 27)
Shortness of breath after exercise	142	–97 (–164, –30)	154	–145 (–217, 53)
Symptoms of asthma[b]	50	–50 (–152, 52)	63	–133 (–265, –1)
Asthma ever	24	–127 (–272, 18)	33	–227 (–409, –45)
Usual cough	116	–11 (–83, 61)	121	–125 (–231, –19)
Usual phlegm	77	27 (–40, 93)	134	–140 (–240, –40)
Cough and phlegm >3 months	26	–127 (–272, 18)	48	–227 (–410, –45)
		Adjusted difference (SE)[c]		**Adjusted difference (SE)[c]**
Prick *Alternaria* >2 mm		–223 (–468, 22)		–
IgE cat >0.35 IU/ml		–110 (–257, 47)		–
Prick olive >2 mm		–		–126 (–227, 25)
IgE Timothy grass >0.35 IU/ml		–114 (–222, –6)		–
Wheezing apart from colds		–109 (–223, 14)		–
Shortness of breath after exercise		–		–80 (–172, –12)
Cough and phlegm >3 months		–		–222 (–381, –63)

[a] Adjusted for age, height and smoking. Individual models for each symptom.

[b] Reporting a nocturnal attack of shortness of breath, an attack of asthma during last year or taking medication for asthma during last year.

[c] Multivariate model including bronchial responsiveness, age, height, education, smoking, and variables in the Table. The number of subjects in the models were 619 females and 692 males.

– Not included in the model due to $P > 0.2$.

Timothy grass (adjusted difference in FEV_1 = –85 ml; 95% CI : –193, 23), but not the association for cat (–156 ml; 95% CI : –302, –11) or *Alternaria* (–235 ml; 95% CI : –470, –1).

Having IgE antibodies to Timothy grass and skin reactivity to *Alternaria* appeared as important risk factors of abnormal FEV_1 in females, even after the exclusion of subjects with asthma symptoms (Table 5), and IgE to cat in smokers of both sexes. Important to note is the association of chronic bronchitis with abnormal FEV_1, despite adjusting for number of cigarettes.

Discussion

Specific immunoresponse to Timothy grass, *Alternaria alternata*, and cat were all associated with a lower baseline FEV_1, after adjusting for BHR, respiratory symptoms, and smoking. The associations were stronger in women. Smoking modified the association for cat and *Alternaria*. The association with cat was stronger in smokers, while the association of *Alternaria* was stronger in non-smokers. Finally, the association with total IgE disappeared after adjusting for BHR.

Table 5 Factors associated (odds ratio and 95% CI) with abnormal lung function (based on Roca equations) in non-asthmatics[a]

	Females (19/492)[b]	Males (41/679)	Current smokers (33/843)
Cough and phlegm >3 months	–	4.52 (1.82, 11.0)	2.46 (1.35, 4.48)
Smoking (10 cig/day)	–	1.97 (0.96, 3.63)	1.48 (0.92, 2.36)
BHR[c] <1 mg methacholine	5.41 (2.05, 14.1)	–	2.48 (1.16, 5.31)
IgE Timothy grass >0.35 IU/ml	3.12 (0.96, 10.3)	–	–
Prick *Alternaria* >2 mm	5.36 (0.67, 45)	–	–
IgE cat >0.35 ml IU/ml	–	–	3.09 (0.99, 9.68)

[a] Exclusion of subjects reporting a nocturnal attack of shortness of breath, an attack of asthma during last year or taking medication for asthma during last year.

[a] Number of cases and controls.

[c] Bronchial hyperreactivity.

– Not included in the model due to $P > 0.2$.

We found an association with decreased lung function for outdoor allergens and cat, but not for *DerP1*, although *DerP1* is the most frequent immunoresponse in Spain.[14] A previous report in children with asthma in the US had suggested a stronger relation with FEV_1 for indoor allergens, including *DerpP1*, than outdoor allergens.[15] Variations in the level of allergen in the environment could explain the discrepancy between studies,[16] although differences in study populations (i.e. age and selection of subjects with asthma symptoms) could also explain the discrepancies. In the Normative Aging Study,[1] an association was found with all the allergens, including house dust. We found an association with *Alternaria* even though it is not among the commonest allergens in our area.[14] *Alternaria* has been shown to be a major allergen of asthma in some areas,[17] although there is no previous evidence of its role on FEV_1 impairment. Total IgE has been related to decline in FEV_1 in some studies[6,18,19] but the crude effect of total IgE that we observed in females disappeared after adjusting for specific IgE and BHR. Similarly, in a previous longitudinal study, the association with total IgE disappeared after adjusting for BHR.[3] Total IgE is probably a marker of phenomena other than allergy.

For allergens assayed both by means of specific IgE and Prick test, we found a stronger association with IgE antibodies, although in previous work[20] skin test reactivity was the specific immunoresponse marker that correlated best with level of lung function. A possible explanation is that prevalence of positive specific IgE was larger than prevalence of positive skin reactivity. Alternatively, differences in the intensity of the immunoresponse could explain this discrepancy. However, due to the small number of subjects who responded to the individual allergens in our study, we have classified the response to each individual allergen in a dichotomous way and are thus unable to assess a dose-response relation with intensity of the immune response. Gottlieb *et al.*[1] have demonstrated a relation to an arithmetic average of all the skin wheals but this strategy is not possible in our study due to the heterogeneity in the association of the individual allergens with FEV_1, which did not allow the pooling of all the skin wheals.

When stratifying by sex, the role of individual allergens in FEV_1 is stronger in females. A possible explanation could be the difference in the reference groups, as has been shown when analysing the different role of smoking in FEV_1 for sex.[12] In fact, when we analysed together males and females in the same model and tested for interactions we did not find any significant interaction by sex. A problem in our study is the high non-response rate, which is not related to age or sex, but more females with symptoms tended to participate than those without. This selection bias could have modified the reference groups of comparison and limited the male/female comparisons. However, a possible greater susceptibility of females than males has to be further investigated, and could be linked to the greater susceptibility of adult females to asthma.[21]

Longitudinal studies have shown a relation between BHR and decline in FEV_1.[22] We also found an association between BHR and level of FEV_1, but our cross-sectional study did not allow us to distinguish the temporal sequence relating pulmonary function and BHR. The interrelationship between smoking and atopy led to two different views in relation to the natural history of COPD. While the Dutch theory proposed that atopy and BHR might promote the role of smoking in the decline of FEV_1,[23] the Tucson group maintained that atopics form a different group than true smokers, with a different pathophysiology driven by an allergic inflammation.[24] Our findings suggest an independent role of atopy in FEV_1 impairment, and also an interaction between atopy and smoking in FEV_1 impairment, in agreement with other studies.[1] Mechanisms of an independent role of atopy are unknown, and some hypotheses related to mast cell degranulation and emphysema are discussed by Gottlieb *et al.*[1] Interactions of smoking with individual allergens are even more difficult to explain. Whether cat and *Alternaria* are markers of some non-measured exposures, or whether there is an actual biological explanation for this specific association is beyond the present study. It could be that the role of atopy was stronger in the young and early adulthood, as seems to be the case for BHR.[25] However, in our age range we did not find any interaction of the association between specific atopy and FEV_1 with age. Alternatively, if the effect of atopy is cumulative throughout life, the association between atopy and FEV_1 impairment should increase with age, which could explain why the US study with an elderly population[1] found a stronger association than the present study.

The relation between symptoms and FEV_1 has been explored in depth.[26] The major controversy is the independent role of mucus secretion in FEV_1.[27] We found an independent association of mucus hypersecretion with FEV_1 in males and in smokers, which was not explained by intensity of smoking. A

second point in relation to symptoms was the old proposal that the effect of atopy on FEV_1 is limited to subjects with symptoms of asthma.[7] However, as previous studies have reported,[1,3] we found an association for specific atopy, after adjusting for respiratory symptoms, including mucus hypersecretion, as well as after excluding subjects with symptoms of asthma, which disagrees with the proposal that atopy only plays a role in lung function in asthmatics.[24]

Overall, the two main contributions of the paper are the stronger effects in women, and the specific analysis by allergen that permits a better understanding of the role of atopy. However, our observations come from a cross-sectional setting (which precludes disentangling the effects of atopy on FEV_1 baseline level and decline, and the temporal order of events). We conclude that specific immunoresponse is associated with the level of FEV_1, and this occurred independently of asthma, asthma-like symptoms, other respiratory symptoms, and BHR. The fact that we observed the association in specific immunoresponse among both smokers and non-smokers provides new data on the role of atopy in the natural history of COPD.

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