Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY

Allergy

ORIGINAL ARTICLE EPIDEMIOLOGY AND GENETICS

The risk of respiratory symptoms on allergen exposure increases with increasing specific IgE levels

M. Olivieri[1], J. Heinrich[2,3], V. Schlünssen[4], J. M. Antó[5,6,7,8], B. Forsberg[9], C. Janson[10], B. Leynaert[11,12], D. Norback[13], T. Sigsgaard[4], C. Svanes[14,15], C. Tischer[2,5,7,8], S. Villani[16], D. Jarvis[17,18] & G. Verlato[19] for the European Community Respiratory Health Survey II *Verona and Pavia, Italy Neuherberg, Germany, Aarhus, Denmark, Barcelona, Spain, Umea and Uppsala, Sweden, Paris, France, Bergen, Norway, and London, U.K*

[1]Unit of Occupational Medicine, University Hospital of Verona, Verona, Italy; [2]Helmholtz Zentrum München – German Research Center for Environmental Health, Institute of Epidemiology I, Neuherberg; [3]Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine, University Hospital Munich, Ludwig Maximilians University Munich, Munich, Germany; [4]Department of Public Health, Section of Environment, Occupation and Health, Danish Ramazzini Centre, Aarhus University, Aarhus, Denmark; [5]Centre for Research in Environmental Epidemiology (CREAL); [6]IMIM (Hospital del Mar Medical Research Institute); [7]Universitat Pompeu Fabra (UPF); [8]CIBER Epidemiología y Salud Pública (CIBERESP), Barcelona, Spain; [9]Department of Public Health and Clinical Medicine, Division of Occupational and Environmental Medicine, Umea University, Umea; [10]Department of Medical Sciences/Respiratory, Allergy and Sleep Research, Uppsala University, Uppsala, Sweden; [11]Inserm, UMR 1152, Pathophysiology and Epidemiology of Respiratory Diseases; [12]University Paris Diderot Paris 7, UMR 1152, Paris, France; [13]Department of Medical Science/Occupational and Environmental Medicine, Uppsala University, Uppsala, Sweden; [14]Centre for International Health, University of Bergen; [15]Department of Occupational Medicine, Haukeland University Hospital, Bergen, Norway; [16]Unit of Biostatistics and Clinical Epidemiology, Department of Public Health, Experimental and Forensic Medicine, University of Pavia, Pavia, Italy; [17]Respiratory Epidemiology and Public Health Group, Imperial College London; [18]MRC-PHE Centre for Environment and Health, Imperial College, London, United Kingdom; [19]Unit of Epidemiology and Medical Statistics, Department of Diagnostics and Public Health, University of Verona, Verona, Italy

To cite this article: Olivieri M, Heinrich J, Schlünssen V, Antó JM, Forsberg B, Janson C, Leynaert B, Norback D, Sigsgaard T, Svanes C, Tischer C, Villani S, Jarvis D, Verlato G, for the European Community Respiratory Health Survey II *Verona and Pavia, Italy, Neuherberg, Germany, Aarhus, Denmark, Barcelona, Spain, Umea and Uppsala, Sweden, Paris, France, Bergen, Norway, and London, U.K.* The risk of respiratory symptoms on allergen exposure increases with increasing specific IgE levels. *Allergy* 2016; DOI 10.1111/all.12841.

Keywords
allergen exposure; allergic respiratory symptoms; specific IgE levels; united airways disease.

Correspondence
Giuseppe Verlato, PhD, Sezione di Epidemiologia & Statistica Medica, Università di Verona - c/o Istituti Biologici II, Strada Le Grazie 8 - 37134 Verona, Italy.
Tel.: +39 045 8027628
E-mail: giuseppe.verlato@univr.it

Accepted for publication 9 January 2016

DOI:10.1111/all.12841

Edited by: Wytske Fokkens

Abstract

Background: The relation between IgE sensitization and allergic respiratory symptoms has usually been evaluated by dichotomizing specific IgE levels. The aim of this study was to evaluate the association between specific IgE levels and risk of symptoms on allergen-related exposure, with special reference to allergen-related asthma–rhinitis comorbidity.

Methods: We considered 6391 subjects enrolled within the European Community Respiratory Health Survey 2, having information on cat/grass/*D. pteronyssinus* IgE levels and symptoms on exposure to animals/pollen/dust. The risk of oculonasal/asthmalike/both symptoms was evaluated by a multinomial logistic model.

Results: A clear positive association was observed between specific IgE levels to cat/grass/mite and the risk of symptoms on each allergen-related exposure (test for trend with $P < 0.001$). This trend was particularly pronounced when considering the coexistence of asthmalike and oculonasal symptoms. Compared to non-sensitized subjects, subjects with specific IgE to cat >= 3.5 kU/l presented relative risk ratios of 11.4 (95% CI 6.7–19.2), 18.8 (8.2–42.8), and 55.3 (30.5–100.2) when considering, respectively, only oculonasal symptoms, only asthmalike symptoms, or both. A similar pattern was observed when considering specific IgE to grass/mite and symptoms on exposure to pollen/dust. Also the proportion of people using inhaled medicines or visiting a general practitioner for breathing problems

Abbreviations
ECRHS, European Community Respiratory Health Survey; IgE, immunoglobulin E.

in the previous year increased with increasing sum of specific IgE to cat/grass/mite.

Conclusion: Specific IgE level is the most important predictor of allergen-related symptoms. The risk of both oculonasal/asthmalike symptoms increases with specific IgE levels, suggesting that specific IgE contributes to the 'united airways disease'.

The relationship between IgE sensitization and allergic respiratory symptoms has usually been evaluated considering specific IgE levels as a dichotomous variable (sensitized *vs* not sensitized) on the basis of different cutoffs (1, 2). This simplistic dichotomous approach had been largely prevalent also in the field of food allergies (3). However, in the last years the evaluation of clinical reactivity to food as a function of specific IgE levels allowed not only to acknowledge the existence of a dose–response relation (4), but also to avoid unnecessary and potentially dangerous tests, such as double-blind, placebo-controlled food challenge, in patients with the highest specific IgE levels (5).

On the other hand, the dose–response approach has seldom been adopted to investigate the relation between specific IgE levels and the risk of allergic symptoms in respiratory diseases. In children increasing levels of specific IgE have been associated with increasing risk of current wheeze in the general population (6), and with an increase in asthma exacerbation in children with the disease (7–9). In adults results are less consistent. The National Health and Nutrition Examination Survey (NHANES) 2005–2006 found that the risk of current allergies increased with increasing specific IgE to plants, pets, and molds in people aged 6 years and over (10). In the same study, the risk of asthma ED visits increased as a function of specific IgE levels, in particular IgE to mites (9). At variance, asthma morbidity was not affected by log-transformed IgE levels to indoor allergens in asthmatics, recruited in an American inner-city clinic (11).

Inhaled allergens can elicit not only asthmalike symptoms but also oculonasal symptoms by an IgE-mediated allergic response, and asthma and rhinitis often coexist in the same subjects as manifestations of a single inflammatory process (12, 13). Several factors are known to contribute to this nosographic entity, named 'united airways disease' (14, 15). The coexistence of asthma and rhinitis is particularly evident in the more severe forms (16), but to our knowledge the role of specific IgE levels has never been evaluated as a risk factor for this respiratory comorbidity in a large random sample of the general population.

The objective of this study was to evaluate the relation between specific IgE to mite, cat, or grass and symptoms on exposure to dust, domestic animals, or pollen, using the random sample of the European Community Respiratory Health Survey (ECRHS) 2 database. In particular, it was verified whether a dose–effect relation exists between specific IgE levels and risk of respiratory allergen-related symptoms, grouped in oculonasal, asthmalike, or both, and consequent healthcare utilization.

Methods

Study design

ECRHS is an international multicenter study of asthma and allergy. The first survey (ECRHS I) (17) was carried out in 1991–1993 on random community-based samples of adults aged 20–44 years. Each participant was sent a brief questionnaire (stage 1) and, from those who responded, a 20% random sample was invited to undergo a more detailed clinical examination (stage 2). An additional sample, consisting of subjects who reported asthmalike symptoms in the last 12 months, or who were using asthma medication in stage 1 ('symptomatic sample'), was not considered in the present analysis. ECRHS II (18) was a follow-up study of participants in stage 2 of ECRHS I, performed between 1999 and 2002 (the full protocol can be found at www.ecrhs.org). Ethical approval was obtained for each center from the appropriate institutional or regional ethics committee, and written consent was obtained from each participant.

This study considered 6391 subjects from 25 European centers, who had information both on specific IgE level and symptoms related to at least one allergen.

Measurements

In the frame of ECRHS II, subjects underwent assessment of specific IgE to cat, timothy grass, and house dust mite. Subjects were also asked whether they presented cough, wheeze, a feeling of tightness in the chest, shortness of breath, runny or stuffy nose, or sneezing, itchy or watering eyes on exposure to *'animals such cats, dogs or horses*', '*trees, grass or flowers, or when there is a lot of pollen*', or '*a dusty part of the house, or near pillows or duvets*'. Allergen-related symptoms were either considered altogether (any symptom) or grouped as follows: (1) asthmalike symptoms (wheeze, chest tightness, shortness of breath); (2) oculonasal symptoms; and (3) both asthmalike and oculonasal symptoms. Indexes of healthcare utilization in the last 12 months were also considered, that is, using inhaled medicines to help breathing and having been seen by a general practitioner because of breathing problems or shortness of breath.

Assessment of serum IgE

Total serum IgE and IgE levels specific to cat, timothy grass, *Dermatophagoides pteronyssinus*, and *Cladosporium* were measured centrally at King's College London for ECRHS II, using the Pharmacia. CAP system (Uppsala, Sweden). Specific IgE values of 0.35 kIU/l or more were considered positive (19).

The lower and upper detection limits of specific IgE were, respectively, 0.35 and 100 kIU/l. Values, too low to be measured, were coded as <0.35 kIU/l, while the other values were grouped as follows: 0.35–0.69, 0.70–3.49, 3.50–17.4, 17.5–49.9, >=50 kU/l. Total IgE was set to 1 if <2 kU/l or 2050 if >2000 kU/l.

Statistical analysis

The relation between any allergen-related symptoms and the corresponding IgE level was investigated by a two-level logistic regression model with level-one units (subjects) nested into level-two units (ECRHS centers) (20). For each allergen-specific IgE, the model had allergen-related symptoms as the dependent variable, a random intercept term at level two, and specific IgE levels as fixed effect. The following potential confounders were taken into account: gender, age (coded in tertiles as follows: 27.7–39.0, 39.1–47.2, 47.3–56.8 years), BMI (<25, 25–29.9, >=30 kg/m^2), smoking habits (non-smoker, past smoker, current smoker), and other IgE sensitization. Significance of model fit was evaluated by the likelihood ratio test. For each allergen exposure, the interactions between specific IgE levels and potential confounders were also investigated. Significance level was set at $P < 0.05$.

Table 1 Main demographic and clinical characteristics of 6391 European subjects, randomly selected and participating in ECRHS II, according to exposure to animals, pollen, and dust

	Symptoms on exposure to animals	Symptoms on exposure to pollen	Symptoms on exposure to dust
Sex			
Men	11.4% (356/3132)	27.0% (849/3144)	23.9% (748/3129)
Women	16.6% (537/3233)	32.4% (1052/3246)	31.8% (1026/3231)
	$P < 0.001$	$P < 0.001$	$P < 0.001$
Age (years, mean ± SD)			
No symptoms	43.2 ± 7.1	43.2 ± 7.1	43.3 ± 7.1
Any symptom	41.5 ± 7.1	42.6 ± 7.2	42.1 ± 7.1
	$P < 0.001$	$P = 0.002$	$P < 0.001$
BMI (kg/m^2)			
<25	15.1% (491/3242)	31.1% (1012/3254)	29.7% (961/3241)
25–29.9	12.9% (286/2209)	28.7% (637/2218)	26.5% (585/2206)
>=30	12.1% (91/749)	27.5% (207/752)	24.7% (185/748)
	$P = 0.022$	$P = 0.058$	$P = 0.005$
Smoking habits			
Never smokers	17.6% (478/2718)	33.9% (923/2726)	30.8% (837/2717)
Past smokers	13.0% (226/1732)	29.3% (510/1741)	26.5% (458/1728)
Current smokers	9.8% (187/1905)	24.2% (463/1913)	25.0% (476/1905)
	$P < 0.001$	$P < 0.001$	$P < 0.001$
Ever asthma			
No	10.2% (579/5660)	25.6% (1453/5682)	24.6% (1390/5656)
Yes	44.6% (312/700)	63.2% (444/703)	54.9% (384/699)
	$P < 0.001$	$P < 0.001$	$P < 0.001$
Nasal allergies			
No	5.5% (247/4514)	11.7%(530/4529)	18.8% (847/4510)
Yes	34.9% (641/1835)	73.8%(1360/1843)	50.2% (921/1834)
	$P < 0.001$	$P < 0.001$	$P < 0.001$
Eczema			
No	9.9% (358/3633)	25.4% (927/3651)	23.9% (866/3629)
Yes	19.6% (532/2715)	35.6% (970/2722)	33.1% (899/2714)
	$P < 0.001$	$P < 0.001$	$P < 0.001$
Other sensitizations			
No	8.8% (414/4716)	25.3%(1284/5079)	23.8% (1208/5077)
Yes	29.0% (479/1649)	47.1%(617/1311)	44.1% (566/1283)
	$P < 0.001$	$P < 0.001$	$P < 0.001$
Total IgE in kU/l (median, IQR)			
No symptoms	33.2 (14.2–81.8)	31.5 (13.3–75.3)	33 (14.1–80.9)
Any symptom	66 (29.2–165)	55.2 (22.5–134)	48.9 (19.6–123)
	$P < 0.001$	$P < 0.001$	$P < 0.001$

Qualitative variables are expressed as percent frequency (cases/total) while quantitative variables are expressed as mean ± SD for age or as median (interquartile range = IQR) for total IgE. Significance of differences was evaluated by Wilcoxon–Mann–Whitney rank-sum test for continuous variables (age and total IgE), and by Fisher's exact test for categorical variables.

Table 2 Percent prevalence of any symptom on exposure to animals, pollen, and dust, respectively, as a function of specific IgE levels to cat, timothy grass, and house dust mite

Specific IgE levels† (kU/l)	Symptoms on exposure to animals‡	Symptoms on exposure to pollen‡	Symptoms on exposure to dust‡
<0.35	9.3 (539/5801)	21.1 (1131/5349)	24.4 (1311/5364)
0.35–0.69	34.9 (52/149)	51.4 (74/144)	34.4 (83/241)
0.70–3.49	68.9 (155/225)	57.7 (188/326)	42.9 (162/378)
3.50–17.4	77.3 (116/150)	87.0 (308/354)	53.3 (131/246)
17.5–49.9	72.0 (18/25)	90.0 (135/150)	62.0 (57/92)
>=50.0	86.7 (13/15)	97.0 (64/66)	76.9 (30/39)

†IgE to cat in relation to symptoms on exposure to animals, IgE to grass in relation to symptoms on exposures to pollen, and IgE to HDM in relation to symptoms on exposure to dust.
‡Test for trend: $P < 0.001$.

To study the joint occurrence of asthmalike and oculonasal symptoms, the association between symptoms and total or specific IgE was also investigated after reclassifying exposure-related symptoms as follows: none; cough only; oculonasal, not asthmalike; asthmalike, not oculonasal; asthmalike and oculonasal. As few subjects reported 'cough only', this category was excluded from multivariable analysis. The relation between allergen-related symptoms and specific IgE levels was investigated by a multivariable multinomial logistic regression model (21), where symptoms was the response variable: 0 = no symptom (base outcome); 1 = oculonasal symptoms only; 2 = asthmalike symptoms only, 3 = both oculonasal and asthmalike symptoms. Specific IgE level (<0.35, 0.35–3.49, >=3.50 kU/l) was the explanatory variable, while sex, age (per 1 SD increase), BMI (<25, 25–29.9, >=30 kg/m^2), smoking habits (never smoker, past smoker, current smoker), and sensitization to other allergens were the potential confounders. Results were synthesized through the relative risk ratios (RRRs), adjusting standard errors for intracenter correlation.

The linear association between the sum of specific IgE and proportion of either using inhaled medicine or visiting a general practitioner for breathing problems in the last 12 months was also investigated by the nonparametric test for trend across ordered groups.

Analyses were performed with STATA statistical software, release 13 (StataCorp, College Station, TX, USA).

Results

Study population

Symptoms related to allergen exposure were more frequently reported by women, never smokers, and normoweight subjects than by men, current smokers, and obese subjects; moreover, people reporting allergen-related symptoms were slightly younger than asymptomatic subjects ($P < 0.001$) (Table 1). The prevalence of subjects reporting symptoms on specific exposure increased when a history of allergic diseases (asthma, nasal allergies, eczema) was also reported ($P < 0.001$); the increase was particularly pronounced for nasal allergies and less remarkable for eczema. In particular animal-related symptoms were rarely recounted by subjects without allergic diseases, while a large proportion of subjects suffering from allergic diseases had symptoms when exposed to pollen. The risk of allergen-related symptoms was largely increased also in subjects sensitized to allergens not related to that exposure. Total IgE were largely increased in subjects reporting allergen-related symptoms ($P < 0.001$) (Table 1).

Dose–response relation between specific IgE levels and risk of allergen-related symptoms

A clear positive relation was observed between specific IgE levels to cat, grass, and mite, and the risk of symptoms on response to animals, pollen, and dust exposure, respectively (Table 2) (test for trend with $P < 0.001$). The relation between mite sensitization and dust-related symptoms was less steep than the other two relationships considered. Pollen-related symptoms were confirmed by nearly all subjects with the highest level of specific IgE to grass. On the other hand, 24% of subjects not sensitized to mite reported dust-related symptoms, while only 9% of subjects not sensitized to cat reported animal-related symptoms.

The dose-dependent association between specific IgE levels and any allergen-related symptoms was confirmed by multivariable analysis (Table 3). The odds of pollen-related symptoms increased by 50-fold from subjects not sensitized to grass to subjects with grass IgE levels >= 17.5 kU/l, while the odds increased by fivefold when considering symptoms on dust exposure and sensitization to *D. pteronyssinus*. Also most of the other associations recorded in univariable analysis were replicated by multivariable analysis: Allergen-related symptoms were more likely in women and people sensitized to allergens not related to the considered exposure. The odds of animals or dusts related symptoms, but not pollen, decreased with advancing age and from never smokers to current smokers. Symptoms on specific exposure were no longer affected by BMI as in univariable analysis (Table 3).

A highly significant interaction ($P < 0.001$) was detected between specific IgE to cat and sensitization to other allergens: The relation between cat-specific IgE levels and animal-related symptoms was steeper in subjects not sensitized to other allergens. The same pattern was recorded when considering specific IgE to grass and symptoms on pollen exposure ($P < 0.001$); in addition, the association between grass-specific IgE and pollen-related symptoms was somewhat steeper in women than in men ($P = 0.042$).

Oculonasal and/or asthmalike symptoms on specific exposure

Oculonasal symptoms were the most frequently reported symptoms, and were more frequently elicited by exposure to pollen (28.8%) or dust (25.2%) than by exposure to animals (13.1%). Of note 40% of subjects, reporting oculonasal symptoms on exposure to animals, declared also asthmalike symptoms, whereas this proportion decreased to 27% when considering symptoms on pollen exposure and further to 22%

Table 3 Determinants of symptoms on exposure to animals, pollen, and dust. The analysis was carried out on 6191 subjects of random sample only with complete information

	OR (95% CI) of symptoms on exposure to animals	OR (95% CI) of symptoms on exposure to pollen	OR (95% CI) of symptoms on exposure to dust
Sex			
Men	1	1	1
Women	2.04 (1.70–2.44)	1.60 (1.40–1.82)	1.71 (1.51–1.94)
	$P < .001$	$P < .001$	$P < .001$
Age			
27.7–39.0	1	1	1
39.1–47.2	0.90 (0.73–1.10)	1.10 (0.94–1.29)	0.84 (0.72–0.97)
47.3–56.8	0.68 (0.55–0.84)	1.07 (0.91–1.26)	0.73 (0.63–0.85)
	$P = .002$	$P = .486$	$P < .001$
BMI			
<25	1	1	1
25–29.9	1.00 (0.82–1.21)	1.06 (0.92–1.22)	1.06 (0.93–1.21)
>=30	0.95 (0.72–1.26)	1.05 (0.86–1.29)	0.95 (0.78–1.16)
	$P = .941$	$P = .726$	$P = .529$
Smoking habits			
Never smokers	1	1	1
Past smokers	0.84 (0.68–1.03)	0.97 (0.83–1.14)	0.96 (0.83–1.11)
Current smokers	0.71 (0.57–0.88)	0.85 (0.73–0.99)	0.84 (0.72–0.97)
	$P = .006$	$P = .113$	$P = .057$
Other sensitizations†			
No	1	1	1
Yes	3.12 (2.58–3.78)	1.32 (1.12–1.56)	2.02 (1.74–2.35)
	$P < .001$	$P = .001$	$P < .001$
Specific IgE levels (kU/l)‡			
<0.35	1	1	1
0.35–0.69	3.30 (2.21–4.92)	3.67 (2.57–5.23)	1.41 (1.05–1.90)
0.70–3.49	14.71 (10.52–20.56)	4.88 (3.80–6.28)	2.13 (1.68–2.70)
3.50–17.4	22.65 (14.62–35.09)	25.82 (18.33–36.36)	2.98 (2.22–4.00)
>=17.5	24.06 (10.53–54.98)	51.69 (30.40–87.90)	5.39 (3.56–8.16)
	$P < .001$	$P < .001$	$P < .001$

Adjusted OR (95% CI) and *P* values were estimated by a 2-level logistic regression model, where center was the group variable, adjusting for all variables presented in this table.

†Other sensitizations comprised sensitization to cat, grass, *D. pteronyssinus*, and *Cladosporium*, if not already included in the model.

‡IgE to cat in relation to symptoms on exposure to animals, IgE to grass in relation to symptoms on exposures to pollen, and IgE to HDM in relation to symptoms on exposure to dust.

when evaluating symptoms on dust exposure. Asthmalike symptoms without oculonasal ones were rather rare, being reported by 0.7% 0.6%, or 1.1%, respectively, after exposure to animals, pollen, or dust. Very few subjects reported cough as the only symptoms elicited by allergen exposure: 11 (0.2%) on exposure to animals, 16 (0.3%) on exposure to pollen, and 103 (1.6%) on exposure to dust. These subjects were excluded from subsequent analyses dealing with type of symptoms.

The prevalence of asthmalike symptoms among subjects reporting oculonasal symptoms progressively increased with increasing related specific IgE levels (Fig. 1). This proportion peaked to 100% in subjects with the highest IgE levels to cat when exposed to animals. Lower figures were recorded when considering subjects with the highest IgE levels to grass or mite when exposed to pollen or dust (48.4% and 48.1%, respectively).

In multivariable analysis, specific IgE level was the most important predictor of allergen-related symptoms (Table 4). The association between specific IgE levels and allergen-related symptoms was much stronger in subjects reporting both asthmalike and oculonasal symptoms. The association was particularly strong when considering levels of specific IgE to cat and symptoms on animal exposure, or levels of specific IgE to grass and pollen exposure.

The risk of allergen-related symptoms was higher in women and in people also sensitized to other allergens, and lower in current smokers. The impact of age on symptoms on specific exposure varied as a function of the allergen and symptom considered: The risk of oculonasal symptoms on exposure to animals or dust tended to decrease with age. Overweight or obesity did not affect the risk of exposure-related symptoms.

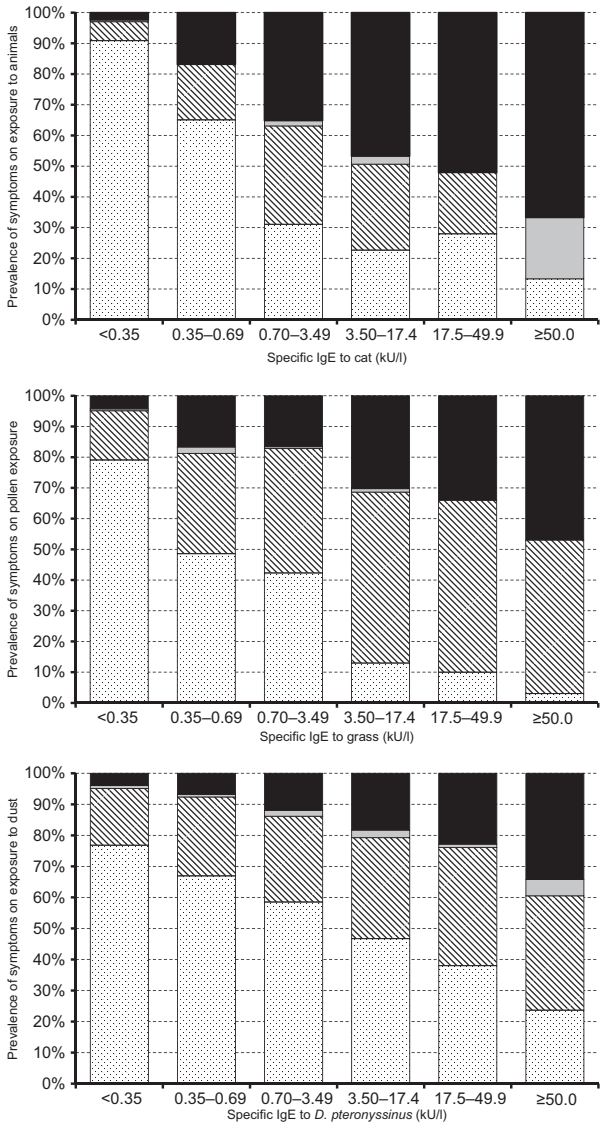

Figure 1 Specific symptoms on exposure to animals, pollen and dust as a function of IgE levels to cat, grass, and mite, respectively. Dotted area = no symptoms; dashed area = oculonasal only; grey = asthma only; black = oculonasal and asthma. Cases with cough only were excluded, as they were rather few.

Specific IgE levels and healthcare utilization

Specific IgE level was associated not only with the risk of symptoms on allergen-related exposure but also with healthcare utilization. The proportion of subjects using inhaled medicines for breathing problems in the previous year increased as a function of the sum of specific IgE levels (Fig. 2A). However, the increase was remarkable in people reporting asthmalike symptoms on animal/pollen/dust exposure, alone or in combination with oculonasal symptoms ($P < 0.001$), while being rather mild in subjects not reporting symptoms ($P = 0.002$) or reporting oculonasal symptoms but not asthmalike ones ($P < 0.001$). The proportion of people seen by a general practitioner in the previous year also increased with increasing sum of specific IgE: This trend was present in people reporting asthmalike ($P = 0.027$) or oculonasal ($P = 0.009$) symptoms on allergen-related exposure, but not in those reporting no symptoms ($P = 0.133$) (Fig. 2B). Of note, 20–25% of subjects not sensitized to any of the allergens considered, but nevertheless reporting asthmalike symptoms on allergen exposure, reported to have taken inhaled medicines or to have been seen by a general practitioner in the previous year. These percentages dropped to 5–6% in people reporting oculonasal symptoms on allergen exposure and further to 3% in people not reporting any symptom.

Discussion

The main results of the present study are as follows:

1 A clear positive association between specific IgE levels and the risk of respiratory allergen-related symptoms was recorded among a random sample of European adults. This pattern was replicated with three of the most common causes of allergic disorders.
2 In all three different models of allergen exposure/specific IgE levels/respiratory symptoms the proportion of subjects with both oculonasal and asthmalike symptoms largely increased with increasing specific IgE levels. Specific IgE level turned out to be the most important risk factor for allergen-related symptoms, especially for combined oculonasal and asthmalike symptoms.
3 Subjects with a higher sum of specific IgE more frequently reported to have used inhaled drugs and to have been seen by a general practitioner for breathing problems in the previous year, especially those with simultaneous oculonasal and asthmalike symptoms.

It is well known that subjects without symptoms when exposed to inhalant allergens have lower specific IgE levels than symptomatic subjects, as reported in a recent review (22). However, the positive association between specific IgE levels and the risk of symptoms on exposure has been rarely addressed.

In preschool children the risk of current wheeze significantly increased with increasing levels of specific IgE to mite, cat, and dog, suggesting that 'absolute specific IgE antibody levels offer more information than just the presence of specific IgE' (6). Interestingly a dose–response association was also found between specific IgE and clinical reactivity to food allergens in a series of allergic children and youngsters (23). Likewise, higher levels of specific IgE are also related to a larger risk of asthma exacerbation and morbidity in asthmatic children (7–9).

Studies on this topic in adults are sparse. The risk of current allergies and current hay fever increased with increasing levels of specific IgE in the NHANES 2005–2006 (10), in agreement with the present study. Also a Dutch study (24) found a similar positive association. Among adults sensitized to any of four inhalant allergens (HDM, cat, timothy grass, birch), the odds of having symptoms of asthma and/or allergy increased with increasing levels of specific IgE to any

Table 4 Influence of specific IgE levels on risk of oculonasal and/or asthmalike symptoms, elicited by exposure to related allergens

	RRRs (95% CI) of symptoms on related exposure		
	Only oculonasal symptoms	Only asthmalike symptoms	Both oculonasal and asthmalike symptoms
Exposure to animals			
IgE to cat (kU/l)			
<0.35	1	1	1
0.35–3.49	**6.24 (4.68–8.33)**	2.35 (0.96–5.76)	**15.06 (10.75–21.09)**
>=3.50	**11.37 (6.73–19.22)**	**18.75 (8.22–42.80)**	**55.26 (30.46–100.2)**
Other sensitizations			
No	1	1	1
Yes	**2.26 (1.67–3.06)**	**3.00 (1.63–5.53)**	**2.84 (2.04–3.97)**
Exposure to pollen			
IgE to grass (kU/l)			
<0.35	1	1	1
0.35–3.49	**4.24 (3.32–5.40)**	**3.54 (1.42–8.83)**	**5.65 (3.90–8.20)**
>=3.50	**25.6 (20.3–32.2)**	**8.35 (2.53–27.6)**	**49.5 (36.8–66.6)**
Other sensitizations			
No	1	1	1
Yes	**1.22 (1.07–1.40)**	0.94 (0.40–2.21)	**1.98 (1.50–2.62)**
Exposure to dust			
IgE to mite (kU/l)			
<0.35	1	1	1
0.35–3.49	**1.69 (1.36–2.09)**	1.75 (0.89–3.46)	**2.44 (1.66–3.59)**
>=3.50	**2.83 (2.08–3.83)**	**3.72 (1.54–8.98)**	**6.16 (4.80–7.89)**
Other sensitizations			
No	1	1	1
Yes	**1.73 (1.48–2.02)**	**2.11 (1.35–3.32)**	**3.34 (2.42–4.62)**

Relative risk ratios (RRRs) were computed by multinomial logistic regression, controlling also for sex, age, BMI, and smoking habits. Standard errors were adjusted for intracenter correlation.
Significant results are highlighted in bold (risk factors).

allergen (24). It should be underlined that the latter study was based on a smaller sample (n = 1904), so that both composite determinants (specific IgE levels to cat, house dust mite, timothy grass, and birch) and composite outcome (asthma attacks or asthma medication in the last 12 months, nasal allergy, symptoms on exposure to dust, pollen, or animals) had to be used in multivariable analysis. The present study, performed on a larger sample, could specifically address the association between IgE levels to each of the studied allergens, and symptoms on related exposure. Furthermore, the present study is the first to investigate asthmalike and oculonasal symptoms on allergen-related exposure, and their comorbidity, as a function of specific IgE.

In adults with asthma, results are less consistent: The risk of emergency department visits increased as a function of the sum of specific IgE levels to indoor allergens in asthmatics identified by the NHANES 2005–06 (9), while asthma morbidity was not affected by log-transformed IgE levels to indoor allergens in asthmatics, recruited in an American inner-city clinic (11).

The steepness of the association between specific IgE and related symptoms was the highest for pollen-related symptoms and the lowest for dust-related symptoms. The association between sensitization to *D. Pteronyssinus* and allergic symptoms was rather weak also in an English birth cohort study (6) and in the NHANES 2005–2006 (10). In the English study (6), the relation between specific IgE levels and probability of current wheeze was much steeper for specific IgE to cat than for specific IgE to mite. In NHANES (10) subjects reporting current allergies presented a much higher proportion of sensitization than subjects not reporting these conditions, as expected. However, the difference in sensitization prevalence was about 12–14% when considering sensitization to either grass or cat, but only 6–7% when considering sensitization to *D. pteronyssinus*. Indeed, respiratory symptoms on dust exposure could be elicited by a direct irritant mechanism rather than by a specific immune response.

An inverse association between smoking and symptoms on exposure was observed in the present cross-sectional study, both in univariable and multivariable analyses. Similar results were found in the NHANES 2005–2006 (10), where the prevalence of current allergies or current hay fever was associated with low serum levels of cotinine, a marker of smoke. The negative association between current smoking and symptoms on allergen exposure could be partly explained by the 'healthy smoker' effect. Subjects with allergic disorders could be less likely to start smoking and more likely to quit (25, 26). As an alternative explanation, current smokers seem to be less likely to be IgE-sensitized to cat and grass in cross-

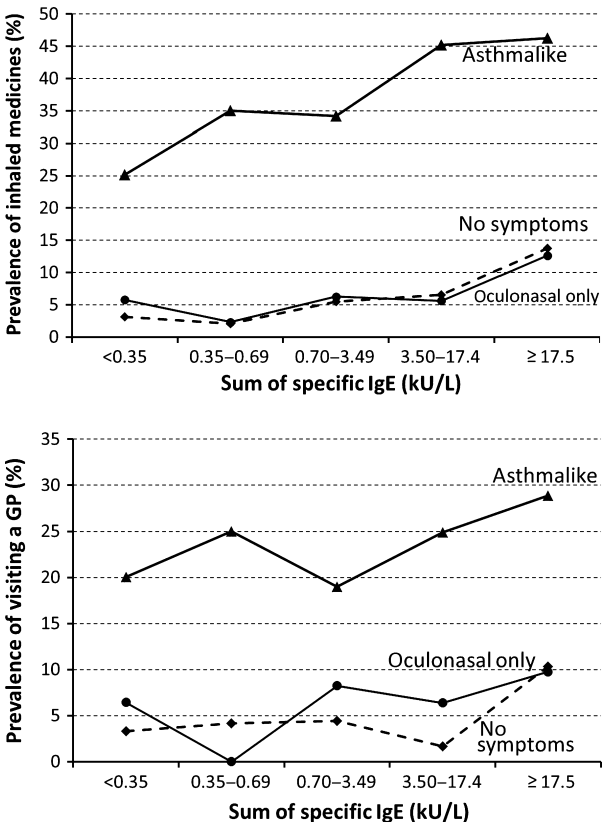

Figure 2 Prevalence of using inhaled medicines (upper panel) or visiting a general practitioner (lower panel) in the previous year, as a function of the sum of IgE to cat, grass, and mite. Asthmalike = asthmalike symptoms, with or without oculonasal ones, on exposure to animals, pollen, or dust. Oculonasal only = oculonasal symptoms on exposure, without asthmalike ones. No symptoms = no symptoms on allergen exposure.

sectional studies (26, 27) and to develop novel IgE sensitizations in longitudinal studies (28), possibly due to immunosuppressive effect of smoking.

In the present study, subjects with higher specific IgE levels were more likely to report both oculonasal and asthmalike symptoms when exposed to specific allergens. This was not unexpected, as larger amount of specific IgE are likely to be produced and released in the bloodstream, when the allergic reactions takes place in a large tract of the airways. Accordingly, both the severity of asthma and the number of suspected allergic diseases have been reported to increase with increasing specific IgE to inhaled allergens in children (29).

The present study has several strengths. All questionnaires and measurement protocols were standardized, and IgE levels were assessed at a central laboratory. The study base was a random sample of the adult general population and its size was rather large (n = 6391); indeed, only few studies, such as NHANES 2005–2006 (10), achieved a similar size. Such large sample size allowed to perform a robust statistical analysis, avoiding a priority assumption on the linearity of the association. It was possible to code specific IgE levels in three categories (<0.35, 0.35–3.49, >=3.50 kU/l), even when simultaneously considering specific allergens (cat, timothy grass, *D. pteronyssinus*) and particular/coexisting symptoms on exposure (oculonasal only, asthmalike only, both oculonasal and asthmalike).

Also some limitations must be acknowledged. The symptoms on allergen exposure were collected by a self-administered questionnaire; nonetheless, subjects with high levels of specific IgE reported not only more symptoms on allergen-related exposure but also a larger use of inhaled drugs and medical visits due to breathing problems in the current year. Questions on allergen-related symptoms were not specific for a given allergen. For instance, specific IgE to cat was compared to symptoms on exposure to animals, including cat, dog, and horse. Hence, it is possible that several subjects, not sensitized to cat, grass, or mite but nevertheless reporting symptoms on related outdoor or indoor exposure, were sensitized to other allergens, coexisting in the same environment, such as cockroach or mouse in the dusty room or pollens other than grass during pollen season. Discrepant responses were not rare: 35.5% of subjects not sensitized to any of allergens tested reported allergen-related symptoms, although these subjects, interestingly, presented higher total IgE levels (data not shown). Conversely, some sensitized individuals, especially those with low levels of specific IgE, did not report symptoms on allergen-related exposure. Indeed the cross-sectional design of the present study did not allow to investigate whether these asymptomatic subjects would have subsequently developed allergic symptoms, as suggested by Bodtger et al. (30). Furthermore, the nature of the clinical response to cat/grass differs from that to mites. The former usually give immediate and obvious allergic symptoms, which patients are more likely to report, but they could miss reactions to mite/dust, to which they are constantly exposed to some degree.

In conclusion, it is still debated whether the absolute specific IgE level offers more information about the relationship between IgE-mediated sensitization and respiratory symptoms than just the presence of specific IgE (6, 10, 24). Our results suggest that the specific IgE levels are the most important risk factor for allergic symptoms related to specific allergenic exposures in a dose-dependent manner. The clinical relevance of specific IgE levels is further supported by the higher risk of healthcare utilization in the last year by subjects reporting asthmalike symptom with or without oculonasal symptoms. This suggests that subjects with high levels of specific IgE to common environmental allergens are at higher risk for the so-called united airways disease. Additional studies in a clinical setting are necessary to confirm this epidemiological finding.

Acknowledgments

The coordinating center comprises the following members: P. Burney, project leader; S. Chinn, statistician; D. Jarvis, principal investigator; J. Knox, project coordinator; C. Luczynska, principal investigator; J. Potts, assistant statistician; and S. Arinze, data manager.

The steering committee for the ECRHS II comprises the following members: U. Ackermann-Liebrich (Switzerland), J.M. Antó (Spain), P. Burney (UK), I. Cerveri (Italy), S. Chinn (UK), R. de Marco (Italy), T. Gislason (Iceland), J. Heinrich (Germany), C. Janson (Sweden), D. Jarvis (UK), J. Knox (UK), N. Künzli (Switzerland), B. Leynaert (France), C. Luczynska (UK), F. Neukirch (France), J. Schouten (the Netherlands), J. Sunyer (Spain), C. Svanes (Norway), P. Vermeire (Belgium), and M. Wjst (Germany).

Funding

The coordination of the ECRHS II was supported by the European Commission, as part of its Quality of Life program. Funding for the individual centers is listed at http://www.ecrhs.org. The funding sources had no role in the design and conduct of the study.

Conflicts of interest

D. Jarvis has received grants from the European Union to coordinate ECRHS and to perform the Indoor study. J.M. Antó has received grants from the FIS-Health Research Fund, Spain, to support ECRHS II study in Spanish centers. The rest of the authors have declared that they have no conflict of interest.

Author contributions

Mario Olivieri conceived the study, and Giuseppe Verlato performed the statistical analysis. Mario Olivieri and Giuseppe Verlato prepared the initial draft of the manuscript. All the authors participated in the design of the study, collection and assembly of data, and interpretation of the results; revised the manuscript; and approved the final version.

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