Sensitisation to airborne moulds and severity of asthma: cross sectional study from European Community respiratory health survey

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Abstract

Objective To assess whether the severity of asthma is associated with sensitisation to airborne moulds rather than to other seasonal or perennial allergens.
Design Multicentre epidemiological survey in 30 centres.
Setting European Community respiratory health survey.
Participants 1132 adults aged 20-44 years with current asthma and with skin prick test results.
Main outcome measure Severity of asthma according to score based on forced expiratory volume in one second, number of asthma attacks, hospital admissions for breathing problems, and use of corticosteroids in past 12 months.
Results The frequency of sensitisation to moulds (*Alternaria alternata* or *Cladosporium herbarum*, or both) increased significantly with increasing asthma severity (odds ratio 2.34 (95% confidence interval 1.56 to 3.52) for either for severe *v* mild asthma). This association existed in all of the study areas (gathered into regions), although there were differences in the frequency of sensitisation. There was no association between asthma severity and sensitisation to pollens or cats. Sensitisation to *Dermatophagoides pteronyssinus* was also positively associated with severity. In multivariable logistic regressions including sensitisation to moulds, pollens, *D pteronyssinus*, and cats simultaneously, the odds ratios for sensitisation to moulds were 1.48 (0.97 to 2.26) for moderate *v* mild asthma and 2.16 (1.37 to 3.35) for severe *v* mild asthma ($P < 0.001$ for trend).
Conclusions Sensitisation to moulds is a powerful risk factor for severe asthma in adults. This should be taken into account in primary prevention, management, and patients' education.

Introduction

The severity of asthma varies widely between patients. Mild cases are characterised by normal lung function and patients are asymptomatic most of the time, whereas severe cases are characterised by permanently impaired lung function and frequent exacerbations. Little is known about the factors associated with severity, but the identification of such factors is necessary for management and prevention.

Sensitisation to airborne allergens might be involved in the underlying mechanisms of severity. The associations between exposure, sensitisation, and asthma have suggested that house dust mite,[1 2] animal dander,[3 4] cockroaches,[5] pollens,[6] and mould spores[7] have a causal role in development. However, the associations between sensitisation to different allergens and the severity of asthma have been poorly explored.

Sensitisation to moulds has been suggested as a risk factor for life threatening asthma.[8–10] However, the hypothesis that such sensitisation is generally associated with the severity of asthma remains to be investigated.

We used data from 1132 people with asthma from the entire dataset of the European Community respiratory health survey to assess whether the severity of asthma is associated with sensitisation to airborne moulds rather than to other seasonal or perennial allergens.

Methods

The methods of the survey have been fully described elsewhere.[11 12] Briefly, participating centres randomly selected samples of 20 to 44 year olds, who completed a short postal questionnaire about asthma and asthma-like symptoms (stage 1). At stage 2 a random subsample of responders were invited to complete a more detailed questionnaire and undergo skin prick and blood tests, assessment of lung function by spirometry, and airway challenge with methacholine.

Standardised skin prick tests were carried out with allergen coated lancets (Phazets, Pharmacia Diagnostics, Uppsala, Sweden). The allergens selected in all centres were *Alternaria alternata*, *Cladosporium herbarum*, *Phleum pratense* (timothy grass), birch, olive, *Parietaria judaica* (pellitory-of-the-wall), common ragweed (*Ambrosia artemisiifolia*), *Dermatophagoides pteronyssinus* (house dust mite), and cat. An uncoated lancet was used as the negative control. Results were regarded as positive if the mean weal diameter was at least 3 mm larger than that for the negative control.

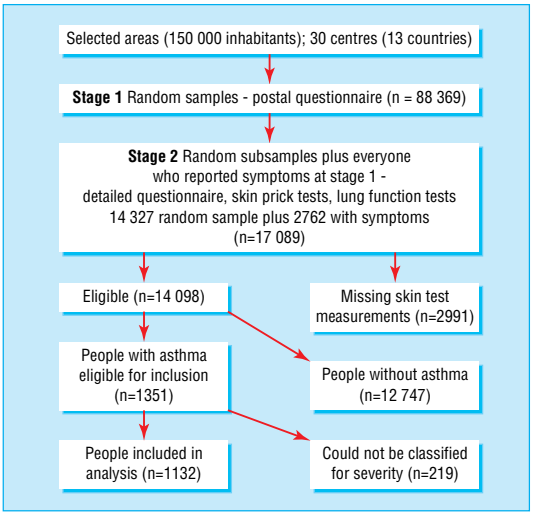

Fig 1 Study design and patients involved at each stage for 30 centres included in present analysis

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Table 1 Proportions (%) of participants with asthma with sensitisation to allergens tested in six regions of European Community respiratory health survey (ECRHS)

Allergen	All (n=1132)	UK and Republic of Ireland (n=205)	Northern Europe (n=264)	Central Europe (n=139)	Southern Europe (n=150)	Australia/New Zealand (n=335)	Portland (US) (n=39)	P value*
Alternaria alternata	11.9	17.6	10.2	13.7	4.7	10.5	28.2	<0.001
Cladosporium herbarum	5.8	6.8	9.9	4.3	0.7	4.5	10.3	<0.003
Timothy grass	41.3	44.4	39.4	38.1	34.0	44.8	48.7	0.18
Birch	19.4	8.8	39.8	18.0	10.0	13.1	33.3	<0.001
Olive	7.2	1.0	6.1	15.1	18.0	4.2	5.1	<0.001
Parietaria judaica	3.5	1.5	1.9	5.0	12.0	1.7	2.6	<0.001
Ragweed	2.6	2.9	3.8	3.6	2.7	0.3	7.7	0.03
Dermatophagoides pteronyssinus	47.7	58.1	23.5	48.2	34.0	67.2	41.0	<0.001
Cat	31.4	27.8	52.7	31.6	18.7	22.7	28.1	<0.001
At least 1 allergen	73.4	70.7	71.6	74.8	62.7	80.6	74.4	<0.002

*P value for overall differences among regions.

Figure 1 shows details of the study design and the numbers of participants involved at each stage.

Definitions of asthma and severity

Participants were defined as currently having asthma if they answered yes to the question"Have you ever had asthma?"and if they had had at least one asthma attack or had taken inhaled or oral corticosteroids for asthma in the past 12 months. Asthma was classified as mild, moderate, or severe according to a score derived from Ronchetti et al.[15] The overall total score ranged from 4 to 11, with levels of severity levels being mild (score 4 or 5), moderate (6), or severe (≥7).

Results

Of the 1132 people with asthma in this study, 564 (50%) had mild asthma, 333 (29%) had moderate asthma, and 235 (21%) had severe asthma. Severity was not related to age, sex, smoking, passive smoking, or parental history of asthma.

The proportion of people with mild asthma varied according to geographical area, ranging from 63% in southern Europe to 42% in Australia and New Zealand. The proportion with severe asthma was 15% in southern Europe, 17% in central Europe, 17% in northern Europe, 21% in the United Kingdom and Republic of Ireland, 28% in Australia and New Zealand, and 26% in Portland.

Over 73% of participants were sensitised to at least one allergen and 65% were sensitised to two or more. Sensitisation to moulds alone was extremely rare: nine people were sensitised to *Alternaria* only and two to *Cladosporium* only. The proportion of people with asthma with sensitisation to the various allergens varied according to the regions (table 1). Sensitisation to moulds was the lowest in southern Europe and the highest in Portland and in the United Kingdom and Republic of Ireland.

Table 2 shows that sensitisation to moulds was significantly associated with severity of asthma. For both *Alternaria* and *Cladosporium* the proportion of sensitised people increased with increasing severity ($P<0.001$ for trend). For *Alternaria* the odds ratio was 1.64 for moderate versus mild asthma and 2.05 for severe versus mild asthma. These remained unchanged in the multivariable models after we adjusted for possible confounding factors. For *Cladosporium* the odds ratio was >3 for severe versus mild asthma. When we considered sensitisation to either mould, the odds ratio was 2.34 for severe versus mild asthma ($P<0.001$). We observed similar patterns for the association between sensitisation to moulds and severity of asthma (severe versus mild asthma) in all regions (fig 2). We found no association between severity of asthma and sensitisation to pollens.

Severity of asthma was positively associated with sensitisation to *D pteronyssinus* but not with sensitisation to cats. To assess the independent relations between the various allergens and severity of asthma we carried out simultaneous logistic regressions including sensitisation to moulds, pollens, *D pteronyssinus*, and cats. For moulds (*Alternaria* or *Cladosporium*,

Table 2 Associations between sensitisation to moulds and severity of asthma (% of sensitised participants by severity and odds ratios (95% confidence interval) for moderate versus mild asthma and severe versus mild asthma)

	Current asthma			
	Mild (n=564)	Moderate (n=333)	Severe (n=235)	P value for trend
Alternaria alternata				
% sensitised	8.9	13.8	16.6	<0.001
Unadjusted odds ratio	1	1.64 (1.08 to 2.52)	2.05 (1.31 to 3.21)	<0.001
Multivariate adjusted odds ratio*	1	1.61 (1.04 to 2.50)	2.03 (1.26 to 3.27)	<0.001
Cladosporium herbarum				
% sensitised	3.9	5.4	11.1	<0.001
Unadjusted odds ratio	1	1.41 (0.74 to 2.66)	3.07 (1.70 to 5.50)	<0.001
Multivariate adjusted odds ratio*	1	1.21 (0.62 to 2.36)	3.20 (1.72 to 5.94)	<0.001
Either mould				
% sensitised	10.8	15.9	22.1	<0.001
Unadjusted odds ratio	1	1.56 (1.05 to 2.32)	2.34 (1.56 to 3.52)	<0.001
Multivariate adjusted odds ratio*	1	1.48 (0.98 to 2.24)	2.34 (1.52 to 3.60)	<0.001

*Adjusted for age, sex, smoking, passive smoking, parental history of asthma, and region.

or both) the odds ratios were 1.48 (0.97 to 2.26) for moderate versus mild asthma and 2.16 (1.37 to 3.35) for severe versus mild asthma ($P < 0.001$ for trend).

The results were virtually identical when we included the number of allergens the participants were sensitised to in the models.

Discussion

Our study of asthma from large population based samples of adults living in different countries showed that the severity of asthma is associated with sensitisation to *Alternaria* and *Cladosporium* but not to pollens. As expected the severity of asthma was also associated with sensitisation to *D pteronyssinus*.

Comparison with other studies

Previous studies have shown that sensitisation or exposure to moulds is associated with death from asthma, life threatening exacerbations,[8–10] visits to emergency departments,[13] and admissions to hospital for asthma,[14] but this is the first population based study that used criteria other than healthcare attendance alone to show that sensitisation to moulds is a risk factor for severe asthma in adults.

To date, there has been little evidence that sensitisation to moulds is associated with severity of asthma. To our knowledge no population studies apart from the European Community respiratory health survey have investigated the association between severity of asthma and sensitisation to allergens in adults. In a study of the relative importance of sensitisation to individual allergens for bronchial hyperresponsiveness in the United Kingdom within the framework of the European survey, people with positive results to *Cladosporium* were considerably more responsive than those with positive results to cats or timothy grass.[15] Analysis of Spanish data showed that sensitisation to *Alternaria*, cats, and timothy grass was associated with a decrease in forced expiratory volume in one second in women.[16]

We observed a differential association between moulds and pollens and severity of asthma. Possibly the size of fungal spores allows them to reach the lower airways and also they may be inhaled by means of fragments and other amorphous bioaerosols. Pollens are larger and their effect on asthma requires exceptional situations such as thunderstorms, when pollen is concentrated by changes in air flow, grains are ruptured by osmotic shock, and each grain releases hundreds of starch granules that are small enough to be respired.[17] Other explanations for the different effects of sensitisation to moulds and to pollens are possible. Unlike pollens, moulds are present all through the year with increase in the spore counts during the autumn months. Also, the level of mould exposure is probably greater because the exposure occurs indoors rather than outdoors and people spend most of their time indoors. The severity of asthma was associated with sensitisation to airborne moulds despite the fact that sensitisation to moulds alone was extremely rare. This might suggest a synergistic or additive effect of various sensitisations in determining severity. However, this is unlikely because when the number of positive test results was taken into account in the analysis the results did not change.

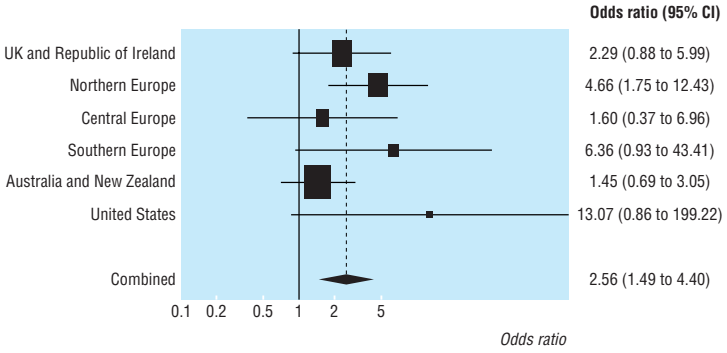

Fig 2 Multivariable adjusted odds ratios (95% confidence interval) for association of severe versus mild asthma with sensitisation to moulds (either *Alternaria alternata* or *Cladosporium herbarum*, or both) by region (adjusted within region for age, sex, smoking habits, passive smoking, and parental history of asthma) with combined odds ratio from model with region included as random effect

Our results of the associations between moulds and severity of asthma may be put together with results from studies on asthma incidence or outbreaks, where the role of moulds can be suspected for effects that were primarily attributed to other allergens. Moulds might be involved in the dramatic increase in incidence in Tucson that was initially attributed in part to a 10-fold increase in atmospheric pollen due to the widespread use of ornamental trees that produce pollen.[18] More recently, it has been suggested that moulds may have had a role in the asthma epidemics in Barcelona that were attributed to soybean.[19]

Conclusion

In conclusion, our results show that sensitisation to moulds might be involved in the severity of asthma. Given the increase of asthma and the prevalence of severe asthma in the past decades these results may be relevant for many people. Those people with asthma who are sensitised to airborne moulds should be educated to pay careful attention to symptoms and comply with treatment, particularly during the seasonal increase in mould spore counts. Patients should be encouraged to decrease exposure by avoiding indoor conditions that facilitate the growth of moulds—for example, by better ventilation and by decreasing dampness.

What is already known on this topic

Sensitisation to moulds is a known risk factor for life threatening exacerbations of asthma

It is unknown whether such sensitisation is generally associated with severity of asthma

What this study adds

The prevalence of sensitisation to moulds (*Alternaria alternata* or *Cladosporium herbarum*, or both) increased with increasing severity of asthma

In this multicentre epidemiological survey, similar patterns of results were observed in various areas of the world

Details of participating centres can be found with the long version of this paper on bmj.com

Contributions: See bmj.com

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Science commentary

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science editor, BMJ

Science commentary: Skin prick testing

Skin prick testing is conventionally used to investigate immediate type hypersensitivity to allergens in patients with rhinoconjunctivitis, contact urticaria, asthma, atopic eczema, and suspected food allergy. It is also a means of detecting allergen specific IgE and has the advantage of being relatively inexpensive, providing immediate results compared with measurement of serum allergen specific IgE by radioallergosorbent testing (RAST).

The technique used for skin prick testing involves puncturing the skin with a calibrated lancet (1 mm) held vertically, or a hypodermic needle or blood lancet at an angle of 45°, and introducing a drop of diluted allergen. All patients undergoing skin prick testing should also have a positive histamine control and negative diluent (saline) control test included. An itchy weal should develop at the histamine puncture site within 10 minutes. Test solutions are standardised to give a mean weal diameter of 6 mm. The maximum or mean diameter of the weals to various allergens should be read at 15 minutes. A weal of 3 mm or more in diameter is generally considered to represent a positive response (indicating sensitisation to the allergen). The negative control is important because it excludes the presence of dermographism, which if present makes the tests difficult to interpret.

The relevance of skin prick testing should be interpreted in the context of the patient's history. Positive results can occur in people without symptoms and, similarly, false negative results may occur. "Blanket" allergy testing (whether by skin prick testing or serological methods) can give false positive results and, particularly in the case of foods can lead to unnecessary dietary restrictions. Standardised solutions to a wide range of allergens are available commercially. For more labile allergens (such as those found in fruit and vegetables) fresh produce should be used. Skin prick tests to aeroallergens are generally considered safe, but intramuscular adrenaline should be available and full resuscitation facilities are needed when test are carried out with other allergens such as foods and natural rubber latex.