

# Is sensitization to *Alternaria alternata* a risk factor for severe asthma? A population-based study

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Seasonal differences in asthma mortality and hospital admission rates, with high levels of asthma in autumn, have been described in several countries. It has been suggested that fungal spores may be involved in such seasonal variations.<sup>1</sup> In a study of the effect of environmental molds on the risk of death from asthma during the pollen season, mean mold spore levels, but not tree, grass, or ragweed pollen levels, were significantly higher on the days when asthma-related deaths occurred than on the days when no deaths occurred.<sup>1</sup> In a study of 11 patients with episodes of respiratory arrest, 10 (91%) had positive skin prick test responses for *Alternaria alternata*, whereas that proportion was only 31% for the 99 matched control subjects with asthma and no history of respiratory arrest.<sup>2</sup> Thus sensitization to molds, and especially to *A alternata*, may be involved in severe exacerbations of asthma in children and young adults. It is not known whether sensitization to *A alternata* is related to severe asthma, apart from life-threatening exacerbations.

The aim of this study was to assess whether sensitization to *A alternata* was associated with asthma severity in a population of young adults.

## METHODS

Data were collected as part of the European Community Respiratory Health Survey (ECRHS; methods reported elsewhere<sup>3</sup>). Briefly, 3152 20- to 44-year-old subjects in Paris and 3774 in Montpellier were randomly selected from the electoral rolls. They completed a 9-item postal questionnaire about asthma and asthma-like symptoms. They were then invited to attend for further tests, including an extended interviewer-administered questionnaire, respiratory function testing, and skin prick tests (Phazets) for 11 common allergens; responses were considered positive if the wheal diameter was at least 3 mm greater than that for the negative control. Subjects were defined as having "current" asthma if they had had at least 1

attack or had taken asthma medication in the last 12 months. Subjects with current asthma were classified as having mild, moderate, or severe disease on the basis of the level of FEV<sub>1</sub> percent predicted, the number of asthma attacks, the number of hospital admissions for breathing problems in the last 12 months, and a history of emergency department visits for breathing problems during life according to the method described by Ronchetti et al.<sup>4</sup> Univariate associations between asthma severity and sensitization to *A alternata*, timothy grass, olive, *Dermatophagoides pteronyssinus*, *Blatta germanica*, and cat were tested with chi-square and Mantel-Haenszel trend tests. For *Cladosporium herbarum*, *Aspergillus* spp, *Parietaria judaica*, birch, and common ragweed, there were too few sensitized subjects for analysis. Multiple logistic regression models were used to test the independent associations between severe asthma and sensitization to allergens, taking confounding factors into account (SAS statistical package).

## RESULTS

Of the 1116 subjects tested (660 in Paris and 456 in Montpellier), complete skin prick test data were obtained for 1070. One hundred eight subjects were classified as having current asthma.

The mean age of the asthmatic subjects was 33.5 years, 42.6% were men, 26.2% were current smokers, and 19.6% were former smokers. Forty-three (39.8%) had mild, 44 (40.7%) had moderate, and 21 (19.4%) had severe asthma. The percent of subjects with positive skin prick test responses for *A alternata*, timothy grass, olive, *D pteronyssinus*, and cat increased with asthma severity (Fig 1), with all trend tests statistically significant. The differences between subjects with mild and severe asthma were significant for all 5 allergens. The differences between subjects with mild and moderate asthma were significant for *D pteronyssinus*, whereas the differences between subjects with moderate and severe asthma were significant for *A alternata* and were borderline ( $P = .06$ ) for olive. There was no significant association between asthma severity and sensitization to *B germanica*.

Asthma severity was not related to the patients' sex, age, smoking habits, or town of residence. The patient's mother having a history of asthma (but not the father) was more frequent in subjects with severe asthma.

Most atopic subjects were sensitized to various allergens. Of the subjects with current asthma sensitized to *A alternata*, 54% were also sensitized to timothy grass, and 45% were sensitized to *D pteronyssinus*. There were no

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These results are from a local analysis of data collected for the European Community Respiratory Health Survey. Any final international comparison may use a different form of analysis.

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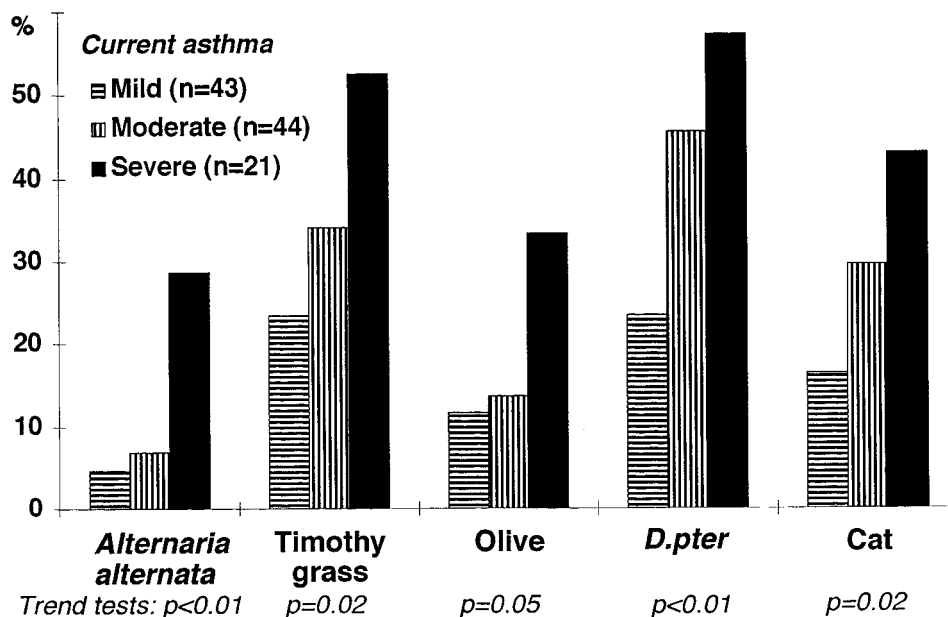


FIG 1. Percent of subjects sensitized to 5 allergens among patients with mild, moderate, and severe current asthma.

TABLE I. Adjusted odds ratios (ORs) for the effect of a positive skin prick test response and mother's history of asthma on asthma severity (multiple logistic regressions)

|                            | Severe vs mild asthma |         | Severe vs moderate asthma |         |
|----------------------------|-----------------------|---------|---------------------------|---------|
|                            | OR                    | P value | OR                        | P value |
| <i>A alternata</i> *       | 10.03                 | <.02    | 5.93                      | <.03    |
| Timothy grass*             | 1.63                  | .54     | 1.87                      | .34     |
| Olive*                     | 1.88                  | .45     | 1.61                      | .53     |
| <i>D pteronyssinus</i> *   | 3.48                  | <.10    | 1.79                      | .35     |
| Cat*                       | 2.77                  | .25     | 2.43                      | .17     |
| Mother's history of asthma | 2.85                  | .38     | 2.59                      | .40     |

\*Positive response if wheal diameter was 3 mm or greater than that for the negative control.

patients sensitized to *A alternata* only. The proportion of asthmatic subjects sensitized to at least one other allergen was 76% for those sensitized to *D pteronyssinus* and 96% for those sensitized to cat. We therefore carried out multiple logistic regression analyses by including the 5 allergens associated with asthma severity and the mother's history of asthma as predictors in the statistical model. The probability of severe versus mild asthma was significantly associated with sensitization to *A alternata* and of borderline significance with *D pteronyssinus*, but it was not independently associated with sensitization to timothy grass, olive, or cat allergens (Table I). The probability of severe versus moderate asthma was associated only with sensitization to *A alternata*. Similar results were obtained when the analysis was redone, excluding the subjects admitted to hospital for breathing problems in the last 12 months.

## DISCUSSION

This population-based study provides evidence that sensitization to *A alternata* is associated with severe asthma apart from life-threatening exacerbations. Self-selection of patients for test attendance was associated with the presence of asthma but not with asthma severity.<sup>3</sup> The comparison of participant and nonparticipant subjects with asthma (from responses to the postal questionnaire) did not show any significant difference in the proportions of subjects currently taking medicine for asthma (61.3% in participants vs 63.9% in nonparticipants) or the proportion of positive responses to any of the following symptom questions referring to the last 12 months: woken by shortness of breath (39.6% vs 33.9%), wheezing (80.6% vs 72.7%), or coughing (52.2% vs 52.1%). Furthermore, self-selection of subjects with severe asthma would only have biased our results if these subjects had been conscious of the risk associated with sensitization to *A alternata*, which is unlikely.

Because there were few subjects with severe asthma, we could not study polysensitized subjects according to the number and type of other sensitizations. However, when the 5 allergens associated with severe asthma in univariate analyses were analyzed in a multiple regression model, only sensitization to *A alternata* was independently associated with severe asthma. Because mold spores are ubiquitous in outdoor air, it is difficult to investigate the effects of exposure to *A alternata*. Of the allergens implicated in asthma, house dust mites are the most studied because they occur indoors and can be accurately quantified, which is not the case for outdoor molds.

Sensitization to other molds may also be important. In our study there were too few positive skin prick test

responses for *Cladosporium herbarum* and *Aspergillus* spp to analyze the relationships between such sensitizations and asthma severity.

Because there have been no similar population studies to our knowledge, we cannot compare our results with those of other investigators. However, an Australian study<sup>5</sup> supports our view by showing that sensitization to *A tenuis* is a major risk factor for current asthma and is associated with severe bronchial hyperresponsiveness in children living in a region where the prevalence of sensitization to *Alternaria* spp is high. The authors explain their findings by the fact that fungal spores are of respirable size and have been shown to be capable of direct bronchoprovocation. Moreover, because *Alternaria* spp proliferates in decomposing vegetation, it is probably prevalent for a much longer season than pollens. Exposure to *Alternaria* allergens may also occur by means of hyphal fragments and other amorphous bioaerosols and not just by inhalation of intact spores.

The importance of sensitization to *Alternaria* spp as a

risk factor for severe asthma may be area dependent. Our results should therefore be confirmed in large populations living in various geographic locations. The consistency of such results would suggest a direct causal link between sensitization to *A alternata* and severe asthma.

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