

## Risk factors and characteristics associated with severe and difficult to treat asthma phenotype: an analysis of the ENFUMOSA group of patients based on the ECRHS questionnaire

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### Summary

**Background** Severe and difficult to treat asthma impairs health status and accounts for about half of asthma expenditure. In 1994, a European Network For Understanding Mechanisms of Severe Asthma (ENFUMOSA) was formed. A large group of patients from nine European countries has been selected.

**Objective** To examine the risk factors and symptoms associated with a phenotype of severe/difficult to treat asthma.

**Methods** The present report presents data assessed through the use of the European Community Respiratory Health Survey (ECRHS) Questionnaire in 148 mild–moderate controlled and 155 severe asthmatics from the ENFUMOSA group.

**Results** There is a negative association of severe asthma with reported allergy and with a family history of allergy (Odds ratio (OR) = 0.45). Sharing a bedroom before the age of five is associated with a higher risk of severe asthma (OR = 1.5) while childhood infections, play school attendance and exposure to allergens or animals are not. A larger proportion of severe asthma patients report symptoms at work (OR = 2.7) or have to change jobs (OR = 4.3) and fewer severe than mild patients are currently employed (OR = 0.39). Smoking and exposure to smoke is similar in mild and severe asthma. Dietary habits do not differ between the groups, but severe asthmatics report eating less savoury snacks and there is a trend for lower intake of sweets.

**Conclusions** Analysis of the ECRHS questionnaire in the ENFUMOSA study shows that severe asthma patients experience more symptoms and their health status is impaired by their inability to work and perhaps eat freely. Personal and maternal history of allergy is associated with mild but not severe asthma. Other than sharing a bedroom before the age of 5 years, no childhood exposure risk factors associated with severe asthma could be identified from this analysis.

**Keywords** allergy, childhood factors, clinical characteristics, diet, severe asthma, symptoms

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### Introduction

In the last decades, extensive investigation of the pathogenetic mechanisms of asthma has led to a better understanding of

the disease and to a more cognitive approach to its therapies. Today, most asthmatic patients can be adequately controlled with moderate doses of medication. Large studies have shown that in the majority of patients the combination of medications, such as inhaled steroids and  $\beta_2$ -agonists at moderate doses, manages control of asthma [1–3]. However, there still remain some asthmatics, who have persistent symptoms and frequent exacerbations despite adequate treatment [4]. These severe and difficult to treat asthma patients have impaired quality of life and account for over half of the cost of the disease [5]. Difficult asthma is currently a subject of intense research, as the risk factors and mechanisms involved in this situation are not clear.

In 1994, a European network for the understanding of the mechanism of severe asthma European Network for Understanding Mechanisms of Severe Asthma (ENFUMOSA) was formed. A large group of patients has been selected in 13 centres, in nine European countries with the participation of

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344 asthmatic patients. The first report, based on the analysis of clinical record forms, lung function and laboratory results of the patients was published some months ago and describes the clinical characteristics and risk factors associated with severe asthma in this large group [6].

The report presented here, analyses data collected through the use of the European Community Respiratory Health Survey (ECRHS) stage II Questionnaire [7, 8] in the ENFUMOSA group [6]. The questionnaire consists of 71 items covering family history of asthma and allergy, childhood exposure to risk factors, exposure in the working environment, smoking habits, dietary habits and reported allergy. The aim of this study was to examine the risk factors and symptoms associated with the phenotype of severe/difficult to treat asthma through the use of a detailed, validated and extensively used questionnaire.

## Methods

### Study design

The study was a cross-sectional multi-centre comparison between a group of patients with severe and difficult to treat asthma and a group of patients with non-severe, controlled asthma.

### Subjects

As already described in the first published study from the ENFUMOSA group of patients [6], patients aged 17–65 years with a history of wheezing, breathlessness, chest tightness or cough, starting before the age of 45 years, were recruited from outpatient clinics. All centres were instructed to enrol patients regularly seen in their clinics and not to advertise for volunteers. They had variable airways obstruction as documented during the past 5 years by at least one of the following:

- Reversibility in forced expiratory volume in 1 s ( $FEV_1$ ) of  $\geq 9\%$  predicted after four puffs of 100  $\mu$ g salbutamol dose-aerosol administered via a spacer device. Mean diurnal variation in peak expiratory flow (PEF)  $\geq 15\%$  (highest PEF–lowest PEF)/mean PEF on  $\geq 4$  days/week for at least 2 weeks.
- An increase in  $FEV_1$  of at least 400 mL after a course of prednisolone, 0.5 mg/kg/day for 14 days.
- A provocative concentration of histamine or methacholine to reduce  $FEV_1$  20% from baseline (PC20)  $< 8$  mg/mL in patients with at least a baseline  $FEV_1 \geq 80\%$  predicted.

The patients were non-smokers or had smoked less than 10 cigarettes a day with a total smoking history of  $\leq 5$  pack years and asthma had started before smoking. Patients had no other active acute or chronic pulmonary disorder, nor did they have any major psychiatric disease. No immunosuppressants, other than corticosteroids, were allowed.

### Severe/difficult to treat asthmatics

Severe asthma patients ( $n = 155$ ) were defined as those chronically uncontrolled by high-dose inhaled corticosteroids (ICS)  $\pm$  oral corticosteroids for at least 1 year, requiring care by an asthma specialist. Severe asthma patients were

receiving high-dose ICS (i.e. beclomethasone dipropionate or budesonide  $\geq 1600$   $\mu$ g/day or fluticasone  $\geq 800$   $\mu$ g/day) and long-acting  $\beta_2$  adrenoceptor agonists or theophylline for at least 1 year. Some patients required regular oral corticosteroids (i.e.  $\geq 5$  mg prednisolone-equivalent daily) in addition to high-dose ICS. Despite this treatment, these patients' asthma was uncontrolled, with at least one severe exacerbation requiring a course of oral steroids on top of their regular treatment in the last year. In this analysis, severe uncontrolled asthma patients from the ENFUMOSA group receiving either high-dose ICS or high-dose ICS plus regular oral steroids were studied and analysed as one group. The criteria used for severe asthma are in accordance with the ERS task force on difficult asthma position paper [9].

### Mild–moderate-controlled asthmatics

The patients ( $n = 148$ ) had chronic stable asthma without an exacerbation for at least 1 year. All patients had used ICS on a daily basis (up to 1000  $\mu$ g/day beclomethasone dipropionate or budesonide, or up to 500  $\mu$ g/day fluticasone) for more than 1 year.

### Questionnaire

At enrolment, the ECRHS stage II Questionnaire [7, 8] was interviewer administered to each patient. The questionnaire used for the analysis had been translated from the English version into the various languages of the study centres, back translated into English after its pilot use with 30 volunteers to check for comprehensibility and was then used for the ECRHS. All interviewers were trained to ask exactly the same questions, without further explanations and without interfering with the patients' answers.

The current analysis is focused on the questions regarding personal and family history of asthma and allergies, childhood exposure to allergens and infections, living conditions, dietary habits, working exposure and smoking.

### Statistical analyses

Data entry and statistical analysis was performed using the SPSS software program for windows (SPSS version 11). Demographic and other baseline characteristics were summarized using standard summary statistics (mean, SD, median for numerical data and frequencies for categorical data) for each treatment group. Numeric variables with continuous normal distribution were compared between the two groups using independent samples *t*-test; where distributions were not normal, the Mann–Whitney signed-rank test was used. Categorical variables were compared between the two groups using  $\chi^2$  with Fisher's exact test as appropriate. Odds ratios (ORs) (with 95% confidence intervals) were estimated using logistic regression with adjustment where necessary for the potentially confounding variables, age and sex. Significant differences were accepted at the 95% confidence interval level ( $P < 0.05$ ).

## Results

The clinical characteristics of all the patients are shown in Table 1. Results are based on 303 questionnaires. In the

**Table 1.** Clinical characteristics of patients

|                                | Mild-moderate asthma | Severe asthma  | P-value |
|--------------------------------|----------------------|----------------|---------|
| <i>n</i>                       | 148                  | 155            | NS      |
| Age (years)                    | 41.7 ± 14.5          | 42.8 ± 12.6    | NS      |
| Gender M/F                     | 54/94                | 32/123         | <0.001  |
| FEV <sub>1</sub> (% predicted) | 88.3 ± 17            | 71.7 ± 22      | <0.001  |
| Dose of ICS (mcg)              | 670 ± 270            | 1760 ± 680     | <0.001  |
| Dose of OCS (mg)* [ <i>n</i> ] | 0                    | 17 (4–46) [47] | <0.001  |

Data are expressed as mean ± SD.

\*Data of OCS are expressed as median (range), [*n*], = number of patients on OCS.

FEV<sub>1</sub>, forced expiratory volume in 1 s; ICS, inhaled corticosteroid; OCS, oral corticosteroid; NS, non-significant.

ENFUMOSA study, 344 patients were included but no questionnaires were available for 41 patients. These are 22 severe and 19 mild patients from eight centres.

### Symptoms

The prevalence of self-reported allergy was lower in the severe/difficult to treat asthma group (OR 0.45 (0.28–0.7)) (Fig. 1a). Comparing self-reported data on allergy and data from skin prick testing (SPT) results, we found that 65% of patients who self-reported allergies also had positive SPT while 80.8% of patients with positive SPT self-reported allergies. This discrepancy was more pronounced in the severe/difficult to treat asthma group where only 56.5% of those who reported allergy had positive SPT (compared with 72.5% in the mild/moderate asthma group  $P < 0.01$ ) and 73.8% of patients with positive SPT self-reported allergies (compared with 86.1% in the mild asthma group  $P < 0.05$ ).

Both groups of patients reported cough, wheeze, shortness of breath and chest tightness after exposure to feathers and dust or pollen. However, severe asthma patients reported fewer eye (OR 0.5 (0.4–0.8)) and nose symptoms (OR 0.4 (0.3–0.7)) while more severe asthmatics reported breathing difficulties after the intake of medicines (OR 2.35 (1.38–4.1)).

With regard to seasonal prevalence, both groups reported more spring time symptoms and no differences were noted between the groups.

### Family history

There was a trend for lower prevalence of reported family history of asthma in the severe asthma group, however, this trend did not reach statistical significance (OR 0.6,  $P = 0.071$ ). The prevalence of maternal allergy (OR 0.6 (0.3–0.9),  $P < 0.01$ ) (Fig. 1a) was lower in the severe asthma group while no differences existed in paternal history of asthma or allergy or sibling history of asthma between the two groups.

### Childhood exposure

Sharing of bedroom before the age of 5 years was significantly associated with severe asthma (OR 1.5 (1.1–2.5)) (Fig. 1b). No association was found with serious respiratory tract infections or play school attendance (Fig. 1b). Reported contact with animals or exposure to dust did not differ between the groups.

### Exposure at work

Exposure to gas, fumes or dust at work did not differ between the groups. However, severe asthma patients reported that work affected their breathing (OR 2.7 (1.6–4.5)) and that they had to change jobs (OR 4.3 (2.1–7.8)). Fewer severe asthma patients were employed at the time of the study (OR 0.39 (0.24–0.7)) (Fig. 1c).

### Life style and home environment

Living conditions were similar in the two asthma groups and no differences in housing or in-house combustion were found. Ducted air heating and water damage to the building were associated with mild asthma but no differences in exposure to mouldy surfaces were reported. The intake of a particular type of food caused symptoms such as rash, diarrhoea and headache at similar rates in the two groups, however, severe asthma patients reported higher rates of breathlessness (OR 3.3 (1.4–8.9)). Severe asthma patients reported a lower intake of savoury snacks (OR 0.47 (0.27–0.79)) and there was a trend towards lower intake of sweets (OR 0.6 (0.3–1.03)) than mild asthma patients (Fig. 1d).

### Smoking

Smoking exposure was similar in the two groups: 37 (25.2%) patients in the mild asthma and 47 (30.7%) patients in the severe asthma group had a history of smoking for longer than a year. Furthermore, 38.4% of mild and 37.3% of severe asthma patients were exposed to passive smoking.

### Discussion

This analysis shows that a higher percentage of severe/difficult to treat asthmatics report respiratory symptoms after exposure to dust, animals, feathers and medications, at work and after food intake. There is a negative association of severe asthma with reported allergy and with family history of allergy. Sharing of a bedroom with a sibling before the age of 5 years is positively associated with severe asthma but childhood infections or play school attendance are not. There are no differences in living or working conditions between the groups of severe and mild asthma patients, nevertheless severe asthma patients often change or quit jobs because it affects their breathing and report eating fewer savoury snacks and sweets.

In this analysis we used the ECRHS questionnaire to collect data from the ENFUMOSA group of patients. It is true that self-reports at interview are open to bias but this questionnaire is a validated and widely used instrument that has produced comparable epidemiological data on asthma throughout the world. The ENFUMOSA study was designed with mild asthma patients as controls for the severe asthmatics and therefore, a normal control group, against which both asthma groups could be compared, is missing. However, there are some striking differences between severe and mild asthma patients.

Allergy is considered to be an important contributing factor for asthma [10]. In the western world a high prevalence of

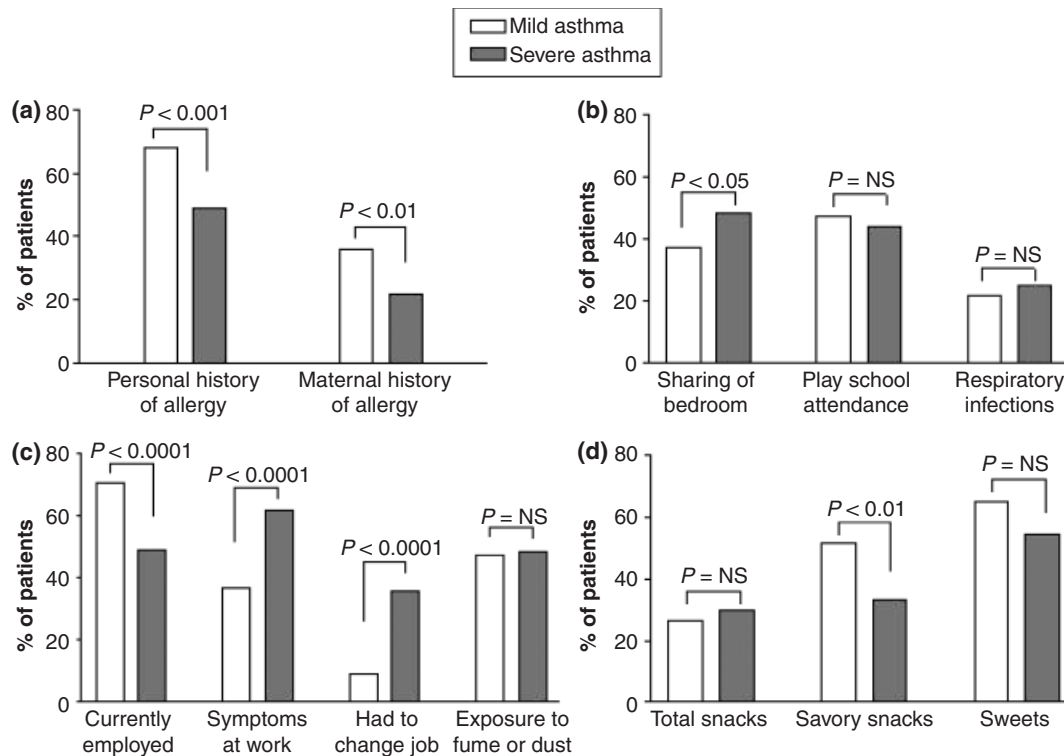


**Fig. 1.** Percentage of mild–moderate and severe asthma patients (a) with self-reported history of allergy (personal and maternal), (b) with reported sharing of bedroom with an older sibling before the age of 5 years, play school attendance and severe respiratory infections in childhood, (c) who are currently employed, report symptoms at work, had to change jobs because of breathing difficulties and who report exposure to fumes or dust at work and (d) who reported intake of snacks and specifically, savoury snacks or sweets between meals.

asthma corresponds with a high prevalence of atopy [11]. However, studies from developing countries report a high prevalence of atopy and a low prevalence of asthma [12, 13]. These studies show that, at least in some cases, asthma is not necessarily directly related to atopy. A recent review of the available epidemiological data worldwide concluded that the population attributable risk of atopy for the development of asthma is less than 50% [14], with similar results being reported for allergen exposure [15]. Moreover, in a recent editorial, Von Mutius [16] states that prevention of sensitization does not always prevent asthma. Our analysis shows a negative association of severe asthma and reported allergy. What is also evident from this study is that although severe asthma patients report fewer allergies, they experience more breathing difficulties, cough and wheeze after exposure to various stimuli. Furthermore, it seems that although patients who experience symptoms tend to attribute these to allergy, reported allergy and positive SPT match in 65% of the cases. This false attribution of symptoms to allergies is more prominent in severe asthma where about half of the patients who report allergies were tested negative. The high reported symptom rate to various stimuli in severe asthma probably reflects the impact of disease severity on everyday activity and quality of life rather than the presence of atopy.

The analysis of the ENFUMOSA Clinical Record Form (CRF) showed that a larger proportion of severe asthma patients report exacerbations in the fall [6]. The current analysis did not confirm the increased frequency of fall exacerbations. However, according to the instructions for the completion of the ECRHS questionnaire, only individuals

who report allergic symptoms after exposure to pollen should answer the question on seasonal exacerbations. Therefore, it has been answered by a subgroup of asthmatics in both groups.

The negative association between a family history of asthma and severe asthma was an unexpected finding of the ENFUMOSA CRF analysis [6]. In the current analysis, although there is a similar trend, it did not reach statistical significance. In the literature, there is clear epidemiological evidence of a positive family history and asthma. The ECRHS study showed that extrinsic asthma in a parent is a strong risk factor for extrinsic asthma in the offspring (OR 4.9) [17]. Intrinsic non-allergic asthma in the parent is also a risk factor for asthma in the offspring; however, this risk is less strong (OR 1.9) [17]. The differences in ORs probably account for the negative association between family history of asthma and severe asthma in our patients: In our group of patients, there were more atopic asthmatics in the mild asthma group [6] and therefore this group has a higher risk of family history of asthma.

A large epidemiological study of asthma showed evidence of a protective effect from sharing a bedroom as a child [18] while another study showed that subjects exposed to many children at home or in day care experienced less hayfever and more asthma in adulthood [19]. In the current analysis, sharing a bedroom as a child is associated with severe asthma. This effect does not seem attributable to severe infections as comparable numbers of patients in the mild and severe groups report severe childhood infections and moreover, play school attendance is not associated with either mild or severe

asthma. It is argued that continuous infectious load rather than one severe infection may be linked to the development of asthma [20, 21]. So, although severe asthmatics do not report increased frequency of severe childhood infections, they may have been more exposed to low-grade continuous antigen load through close contact with a sibling. Further studies are needed to address the relationship between childhood infections, family size and the development of asthma.

The overall prevalence of asthma has increased over the last decades [22] and this has been largely attributed to environmental factors. Living and working conditions are similar in the two groups, there are no socio-economic differences between them and other than the association of sharing a bedroom during childhood, no risk factors for severe disease could be identified from this analysis. Although more severe asthma patients report that they had to change or leave their job because of breathing difficulties, this probably reflects the severity of disease rather than sensitization to particular agents at work, but more studies are needed to confirm this.

In the last 50 years, dietary habits have changed drastically in western societies. A hypothesis that changes in diet may be associated with the increasing prevalence of asthma has been introduced by Burney [23] and then Seaton et al. [24] and has been examined in a number of important epidemiological studies [25–32]. These studies show that increased consumption of sodium and reduced intake of vitamin C, other antioxidants and magnesium may be associated with increased risk for the development of asthma. In our study, consumption of ready-made or tinned food and carbonated drinks is similar in the two groups. Nevertheless, our data show that fewer severe asthmatics report eating savoury or sweet snacks between meals. However, this is most likely not the cause but the effect of the disease. Severe asthma patients often need oral corticosteroids and as a consequence reduced sodium intake is then encouraged. Furthermore, the CRF analysis showed that severe asthma is associated or coexists with hormonal disturbances such as diabetes. The differences in dietary habits most likely reflect these restrictions imposed by oral steroid use or concurrent endocrine problems.

As smoking is a strong risk factor for the development of chronic obstructive lung disease (COPD), a long history of smoking was an exclusion criterion for the ENFUMOSA group. Nevertheless, patients with a history of up to five pack years were included. In our group of mild smokers, no association between smoking and severe disease was found. Excluding heavy smokers is perhaps a limitation in a study examining possible factors linked with a severe asthma phenotype, it ensures, however, a clear asthma rather than COPD phenotype, especially in older patients. Furthermore, in a study of severe asthma [33], where smokers were included, only 13.5% had a smoking history greater than 10 pack years whereas 33% of severe asthma patients were current or ex-smokers, a figure not very different from the 30.7% in our study. A recent long-term asthma study showed that smoking is a risk factor for the development of respiratory symptoms but not severe decline in lung function [34], while other studies have shown that smokers with asthma are resistant to inhaled and oral corticosteroid treatment [35, 36]. The possible role of smoking in severe asthma should be examined further but severe asthma may certainly be present in the absence of smoking.

In conclusion, analysis of the ECRHS questionnaire in the ENFUMOSA group stresses the impact of disease severity on quality of life and the ability to work, indicates that severe asthma is probably associated with restrictions on dietary habits and shows differences between severe and mild asthma patients compatible with a non-atopic mechanism in severe asthma. Despite the fact that a non-allergic phenotype is associated with more difficult to control asthma, there is evidence for broadly similar immunopathology in both atopic and non-atopic variants of the disease [37]. Current knowledge clearly indicates a pivotal role for activated T lymphocytes and eosinophils but does not indicate why these patients are difficult to control with steroids. In order to better manage severe asthma, it is imperative to undertake long-term prospective studies, investigate the mechanisms and genetic background of the disease and define markers of severity and prognosis.

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